The Anti-Apoptotic Bcl-2 Homologue: A1

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Apoptosis is an important physiological process for maintaining tissue homeostasis. Proteins of the Bcl-2 family, together with the caspase system, mitochondria, and nucleus-targeting factors, have been considered essential components of the intracellular apoptotic signaling pathways. A1, as a member of the anti-apoptotic Bcl-2 homologues, was first identified as a hematopoietic-specific early-response gene with a role in the development and differentiation of lymphoid and myeloid lineages. Recent studies have further demonstrated the important role of A1 in embryonic development and in modulating the inflammatory response in endothelial cells. A1 may function on mitochondria to delay cell death and interact with nuclear factor-κB signaling pathways. With the findings of multiple gene duplication and the expression of murine A1, as well as the difficulty of raising a specific anti-human A1 antibody to date, most of the knowledge regarding the molecular mechanisms of the biological function of A1 is not clear. This review introduces the identification of A1, the similarity of protein structure with and the functional differences of A1 from other Bcl-2 members, as well as recent progress in A1 research. Further study using conditional gene-engineered models will be helpful to clarify the exact role of A1 in cell functions and tissue development. ***(Thorac Med 2002; 17: 89-105)***

Key words: apoptosis, Bcl-2, A1, mitochondria, nuclear factor κB

Introduction: Apoptosis plays a pivotal role in tissue homeostasis

Apoptosis, or programmed cell death, is a pivotal physiological process required for the normal development and maintenance of tissue homeostasis in multicellular organisms [1]. It is known to be involved in a wide range of pathologic conditions. Inappropriate increases in apoptosis have been reported in infections by toxin-producing microorganisms, AIDS, neurogenerative disorders, neuromuscular diseases, and ischemia-reperfusion damage [2]. A decrease in apoptosis is a general characteristic of malformations, autoimmune diseases, oncogenic transformation and malignant diseases [3]. The process of apoptosis consists of three different phases: initiation, effector, and degradation [3-4]. Whereas the initiation stage depends on the type of apoptosis-inducing stimulus, the effector (which is still subject to regulation) and degradation (beyond regulation) stages supposedly are common to most apoptotic processes. Apoptosis is characterized by morphological changes such as plasma membrane blebbing, cell volume loss, perinuclear chromatin condensation, and the fragmentation of DNA at nucleosome

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intervals [5]. Several signaling pathways have been reported to be involved in apoptosis. Proteins of the B cell lymphoma (Bcl)-2 family, together with caspases, mitochondria, cytochrome C, and other nucleus-targeting proteins, including apoptosis-inducing factor (AIF), DNA fragmentation factor (DFF) and endonuclease, have been identified as essential components of the intracellular apoptotic signaling pathways [6-7].

The Bcl-2 family of proteins, including A1, constitute a critical intracellular checkpoint for apoptosis

The family of Bcl-2-related proteins constitutes one of the most biologically relevant classes of apoptosis-regulatory gene products acting at the effector stage of apoptosis. Bcl-2 family members can be subsided into two groups, based on their ability to promote or protect from cell death. The Bcl-2 gene was first found at the breakpoint of the translocation between chromosome 18 and chromosome 14 in the lymphoma cell. Under the control of the immunoglobulin heavy chain intron enhancer [8], the gene is up-regulated and hence identified as a proto-oncogene in follicular B-cell lymphoma. Bcl-2 associated protein X (Bax) was the first pro-apoptotic member of the family to be identified as a protein co-immunoprecipitating with Bcl-2 [9]. Bcl-2 and Bax are now known to belong to a growing family of apoptosis-regulatory gene products. The pro-apoptotic members of this family include Bcl-xs [10], Bax [9], Bad [11], Bak [12-14], Bik [15-16], Bid [17], and Hrk [18]. On the other side, the anti-apoptotic members of this family include Bcl-2, Bcl-xl, Bcl-w, Bfl-1, Brag-1, Mcl-1 and A1 [3, 11, 19-21]. A large number of cell-culture studies have demonstrated the ability of the Bcl-2 family members to regulate apoptosis in cells of the myeloid, lymphoid, and neuronal lineages induced by many stimuli [21]. The distribution of Bcl-2 protein in murine embryonic tissues suggested that this gene product is an important regulator of morphogenesis [22-24]. A variety of gene-engineered mice deficient for Bcl-2 [25-28], Bcl-x [27-28] and Bax [14], further substantiated that these molecules play critical roles in many organisms. In particular, an analysis of Bcl-2 and Bcl-x-deficient mice demonstrated that Bcl-2 and Bcl-x are required for the maintenance of the life span of mature and immature lymphocytes, respectively [2, 27-28].

All these Bcl-2 family members share some of the conserved sequence, called BH (Bcl-2 homology) 1, BH2, BH3, and BH4 domains [29] (Figure 1). A feature of these proteins is their ability to form homo- or heterodimers through the domains. The heterodimerization of Bcl-2 or Bcl-xl with their pro-apoptotic partners Bax, Bak, and Bcl-xs has been reported to determine the life-death decision of a cell [30]. However, mutations in Bcl-xl have been described which prevent heterodimerization with Bax or Bak but still maintain anti-apoptotic activity, suggesting that the anti-apoptotic proteins can also function independently to regulate cell survival [31]. Members of the anti-apoptotic Bcl-2 family have also been shown to regulate caspase activity [32-33]. Bcl-xl can bind to apoptosis protease-activating factor (APAF) 1 and inhibit the activation of APAF-1-dependent caspase-9 [34]. In addition, upon locating in the outer membrane of the mitochondria, Bcl-2 is able to block the release of cytochrome c, which is required for APAF-1 to activate caspase-9, and therefore the caspase cascade [35-39]. The pro-apoptotic protein Bid has been shown to be a substrate for caspase 8 [40]. The cleavage of Bid generates a C-terminal fragment of the protein (tc-Bid), resulting in the exposure of the BH3 domain and a significant change in the protein's surface hydrophobicity [41]. This could promote the translocation of tc-Bid from the cytosol to the mitochondrial membrane, and activate the mitochondrial apoptotic pathway, triggering cytochrome c release and downstream activation of effector caspases leading to cell death. In a recent study, Bcl-2 family proteins were shown to

regulate the outer mitochondrial membrane channel, and the voltage-dependent anion channel (VDAC). The pro-apoptotic proteins Bax and Bak promoted the opening of the channel, whereas the anti-apoptotic Bcl-xl closed the channel [42]. Bax was also found to be part of the complex of another mitochondrial megachannel called the permeability transition pore (PTP), which controls the cytochrome c release [43-44]. According to the report of Tsujimoto and collaborators, Bcl-2 can prevent PTP opening, thereby inhibiting the mitochondria-related apoptosis signaling pathway [45].

Bcl-2 family members may be involved in other important intracellular signaling pathways in cell cycle progression and inflammatory reactions. Bcl-2 and Bax are two of the p53-dependent genes and are able to interplay with p53-related cell cycle control [46]. According to the functional mapping study of the Bcl-2 protein in human endothelial cells, in the addition to the anti-apoptotic function, the BH2 and BH4 domains are also associated with NFκB-related anti-inflammatory mechanisms in the cells [47]. A recent study by Ferran et al. has defined a broader cytoprotective role for the anti-apoptotic genes in endothelial cells. Their study clearly demonstrates that besides protecting from apoptosis, A20, A1, Bcl-2, and Bcl-XL serve a broader cytoprotective role via inhibition of the transcription factor NF-κB [48-50]. The inhibition of NF-κB activation occurs at a level upstream of IκB degradation [51]. Importantly, both A20 and the Bcl family members were able to block the activation of NF-κB in response to TNF stimulus [52-54].

As a member of the Bcl-2 family, A1 shares many properties with Bcl-2 and Bcl-x. Like these proteins, A1 contains all the major homology domains of the Bcl-2 family [55]. Studies have shown that A1 slows cell death when transfected into cell lines [56-58], and can heterodimerize with pro-apoptotic Bax like Bcl-2 [59]. A1 suppresses the apoptosis induced by the p53 tumor suppressor protein in a manner similar to other Bcl-2 family members, such as Bcl-2, Bcl-xl [60]. Despite these characteristics, A1 is neither functionally nor structurally redundant. Differences in function between A1 and Bcl-2 have been noted. Unlike Bcl-2, A1 cooperates with the E1A antigen to provide a potent transforming capacity in vitro [61]. Murine A1 permits the myeloid differentiation to granulocytes, whereas Bcl-2 inhibits this process [56]. It has been suggested that A1 may not have the anti-porliferative capacity that has been reported for Bcl-2 [60]. Furthermore, a number of studies have suggested that A1 may have a more potent and protracted anti-apoptotic activity than either Bcl-2 or Bcl-xl. Unlike Bcl-2 and Bcl-xl, A1 activity is not modulated solitarily via dimerization with the pro-apoptotic family Bax [62]. In addition, A1 lacks the N-terminal loop of charged amino acids [63] shared by most other members. This region is protease-sensitive [64]. Deletions in this region appear to confer greater anti-apoptotic ability, and altered susceptibility to phosphorylation, and may lengthen protein biological half-life [64-65]. These differences implicate that A1 may inhibit cell death more potently than Bcl-2 or Bcl-xl, and may perform unique functions in cells.

A1 is not a redundant anti-apoptotic Bcl-2 homologue

The identification of A1

A1 was originally isolated from a cDNA library prepared from mouse bone marrow cells. Through the differential screening of a cDNA library obtained from granulocyte macrophage colony stimulating factor (GM-CSF)-stimulated murine progenitor cells, Moscinski and Prystowsky identified a series of genes expressed during early myeloid differentiation. [66-67]. Using the methods of primer extension and DNA sequencing, Lin et al. further explicated that one such novel cDNA clone, designated A1 and with sequence similarity to Bcl-2, is strongly and rapidly induced in the GM-CSF-stimulated

murine bone marrow cells. [19, 56, 67]. Later, when investigating the intracellular anti-apoptotic mechanisms triggered by pro-inflammatory cytokines and by the use of the reverse transcriptase-polymerase chain reaction (RT-PCR) and rapid amplification of cDNA ends (RACE), Karsan et al. cloned another novel gene in TNF-stimulated human endothelial cells [20]. Due to the sequence similarity to Bcl-2 and murine A1, it was designated human A1 [20].

In the process of analyzing the murine A1 gene organization, and by the use of Southern analysis, Hatakeyama et al further identified four closely-related genes for murine A1 [68]. They designated the original A1 as A1-a, and the others as A1-b, -c and -d [68]. Up to the present, it is unknown whether there is similar multiple gene duplication and expression of human A1 gene.

Nucleotide sequence and primary structure of A1

The murine A1-a gene, containing 516 nucleotides, reveals a single open reading frame (ORF) encoding a peptide of 172 amino acids. The protein deduced from the A1-a nucleotide sequence has an expected Mr of 20,024, and the expected isoelectric point of the protein is 5.05. Like Bcl-2 and Bcl-xl, A1-a contains BH1 and BH2 domains, corresponding to residules 78-97 and 132-148, respectively, for the predicted A1 amino acid sequence [19] (Figure 1). A single potential N-glycosylation site is found at residue 128. No secretion signal is evident, suggesting that A1-a is an intracellular protein [19, 56]. The murine A1-b and -d, together with A1-a, consist of two exons [68]. They have the same ORF size, and encode the BH1 and BH2 domains, which is significant for dimerization with A1 itself or other Bcl-2 family members [19, 69-70]. The A1-c gene contains 1 base pair insertion in the coding region, which results in an aberrant and truncated protein containing only BH1 domain, due to a frame-shift. With the exception of A1-c, the coding regions among A1 genes are highly conserved at >97 % at the nucleotide level, and at

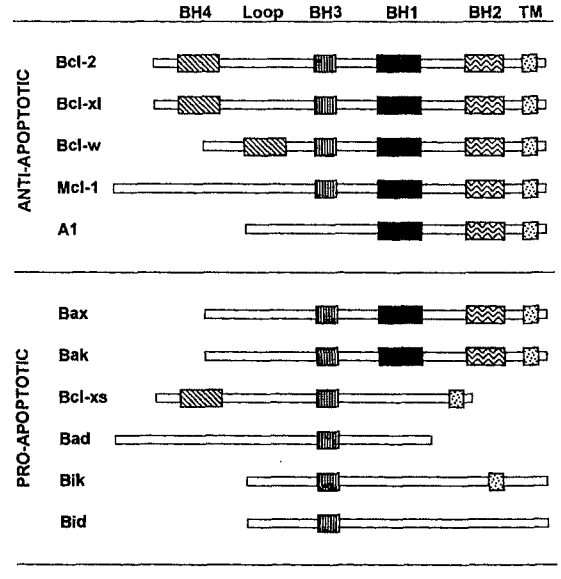

Fig. 1. Summary of Bcl-2 family members. Family members shar sequence homology at four regions, designated as BH1 throug BH4 and the Bcl-2 homology regions are indicated with simila shaded boxes,

>96 % at the amino acid level [68].

Murine A1 also shows a significant sequence relationship to Bcl-2 and Mcl-1 [19, 56]. For all three genes, there is a high similarity distributed over the corresponding carboxy-terminal regions, with a clustering of identities in similar loci within this region, suggesting a family relationship that may be indicative of shared functional features. Such features might include subcellular localization, regulation of decay, catalytic activity, or binding of other proteins or cofactors. [19]. The exon/intron structure of A1 genes is very similar to that of Bcl-2 and Bcl-x genes in which the coding region is divided into two exons (5' and 3' exons) [25, 71]. The common feature among A1, Bcl-2, Bcl-x genes is that the intron between 5' and 3' exons is intervened with the BH2 domain just after the Gly-Gly-Trp motif that is highly conserved in most of the Bcl-2 family members. The intron is extremely large (>300 kb) in the Bcl-2 gene, whereas the corresponding introns in murine A1 genes are not so large (~4.5 kbp in the A1-a gene, and 7 kbp in the A1-b and -d genes [72].

Although there is considerable homology in the coding regions of the cDNAs, human and

Figure 2. A)

1	ATG	ACA	GAC	TGT	GAA	TTT	GGA	TAT	ATT	TAC	AGG	CTG	36
1	MET	Thr	Asp	Cys	Glu	Phe	Gly	Tyr	Ile	Tyr	Arg	Leu	12
37	GCT	CAG	GAC	TAT	CTG	CAG	TGC	GTC	CTA	CAG	ATA	CCA	72
13	Ala	Gln	Asp	Tyr	Leu	Gln	Cys	Val	Leu	Gln	Ile	Pro	24
73	CAA	CCT	GGA	TCA	GGT	CCA	AGC	AAA	ACG	TCC	AGA	GTG	108
25	Gln	Pro	Gly	Ser	Gly	Pro	Ser	Lys	Thr	Ser	Arg	Val	36
109	CTA	CAA	AAT	GTT	GCG	TTC	TCA	GTC	CAA	AAA	GAA	GTG	144
37	Leu	Gln	Asn	Val	Ala	Phe	Ser	val	Gln	Lys	Glu	Val	48
145	GAA	AAG	AAT	CTG	AAG	TCA	TGC	TTG	GAC	AAT	GTT	AAT	180
49	Glu	Lys	Asn	Leu	Lys	Ser	Cys	Leu	Asp	Asn	Val	Asn	60
181	GTT	GTG	TCC	GTA	GAC	ACT	GCC	AGA	ACA	CTA	TTC	AAC	216
61	Val	Val	Ser	Val	Asp	Thr	Ala	Arg	Thr	Leu	Phe	Asn	72
217	CAA	GTG	ATG	GAA	AAG	GAG	TTT	GAA	GAC	GGC	ATC	ATT	252
73	Gln	Val	Met	Glu	Lys	Glu	Phe	Glu	Asp	Gly	Ile	Ile	84
253	AAC	TGG	GGA	AGA	ATT	GTA	ACC	ATA	TTT	GCA	TTT	GAA	288
85	Asn	Trp	Gly	Arg	Ile	Val	Thr	Ile	Phe	Ala	Phe	Glu	96
289	GGT	ATT	CTC	ATC	AAG	AAA	CTT	CTA	CGA	CAG	CAA	ATT	324
97	Gly	Ile	Leu	Ile	Lys	Lys	Leu	Leu	Arg	Gln	Gln	Ile	108
325	GCC	CCG	GAT	GTG	GAT	ACC	TAT	AAG	GAG	ATT	TCA	TAT	360
109	Ala	Pro	Asp	Val	Asp	Thr	Tyr	Lys	Glu	Ile	Ser	Tyr	120
361	TTT	GTT	GCG	GAG	TTC	ATA	ATG	AAT	AAC	ACA	GGA	GAA	396
121	Phe	Val	Ala	Glu	Phe	Ile	Met	Asn	Asn	Thr	Gly	Glu	136
397	TGG	ATA	AGG	CAA	AAC	GGA	GGC	TGG	GAA	AAT	GGC	TTT	432
137	Trp	Ile	Arg	Gln	Asn	Gly	Gly	Trp	Glu	Asn	Gly	Phe	144
433	GTA	AAG	AAG	TTT	GAA	CCT	AAA	TCT	GGC	TGG	ATG	ACT	468
145	Val	Lys	Lys	Phe	Glu	Pro	Lys	Ser	Gly	Trp	Met	Thr	156
469	TTT	CTA	GAA	GTT	ACA	GGA	AAG	ATC	TGT	GAA	ATG	CTA	504
157	Phe	Leu	Glu	Val	Thr	Gly	Lys	Ile	Cys	Glu	Met	Leu	168
505	TCT	CTC	CTG	AAG	CAA	TAC	TGT	TGA					528
169	Ser	Leu	Leu	Lys	Gln	Tyr	Cys	Stop					175

Figure 2. B)

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Hu A1  M T D C E F G Y I Y R L A Q D Y L Q C V L Q I P Q P G S G P S K T S R  35
MuA1   M A E S E L M H I H S L A E H Y L Q Y V L Q V P A F E S A P S Q A C R  35
         • • •   • • •   • •     • •       •       •   • • •   •     • • •

Hu A1  V L Q N V A F S V Q K E V E K N L K S C L D N V N V V S V D T A R T L  70
MuA1   V L Q R V A F S V Q K E V E K N L K S Y L D D F H V E S I D T A R I I  70
           •                               •     • • •   •   •       • •

Hu A1  F N Q V M E K E F E D G I I N W G R I V T I F A F E G I L I K K L L R  105
MuA1   F N Q V M E K E F E D G I I N W G R I V T I F A F G G V L L K K L P Q  105
                                                   •   •           • •

Hu A1  Q Q I A P D V D T Y K E I S Y F V A E F I M N N T G E W I R Q N G G W  140
MuA1   E Q I A L D V C A Y K Q V S S F V A E F I M N N T G E W I R Q N G G W  140
       •     •   • •   • •   •

Hu A1  E N G F V K K F E P K S G W M T F L E V T G K I C E M L S L L K Q Y C  175
MuA1   E D G F I K K F E P K S G W L T F L Q M T G Q I W E M L F L L K        172
         •   •               •     • •   •   •     •
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Figure 2. C)

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A1     • • • • • M T D C E • • • • • F G Y I • Y R L A Q • • • D Y L Q C V L  21
Bcl-2  M A H A G R T G Y D N R E I V M K Y I H Y K L S Q R G Y E W D A G D V  35

A1     Q I P Q P G S P S K T • • • • • • • • • • • • • • • • • • • • • • • • • • 32
Bcl-2  G A A P P G A A P A P G I F S S Q P G H T P H P A A S R D P V A R T S  70

A1     • • • • • • • • • • • • • • • • • S R V L Q N V A F S V Q K E V E K N L  51
Bcl-2  P L Q T P A A P G A A A G P A L S P V P P V V H L A L R Q A G D D F S  105

A1     K S C L D N V N V V S V D • • • • • • T A R T L F N Q V M E K E F E D  80
Bcl-2  R R Y R G D F A E M S S Q L H L T P F T A R G R F A T V V E E L F R D  140

A1     G I I N W G R I V T I F A F E G I L I K K L L R Q Q I A P D V D T Y K  115
Bcl-2  G • V N W G R I V A F F E F G G V M C V E S V N R E M S P L V D • • •  171

A1     E I S Y F V A E F I M N N T G E W I R Q N G G W E N G F V K K F E P •  149
Bcl-2  N I A L W M T E Y L N R H L H T W I Q D N G G W D • A F V E L Y G P S  205

A1     • • • • • K S G W M T F • • • • • L E V T G K I C E M L S L L K Q Y C  175
Bcl-2  M R P L F D F S W L S L K T L L S L A L V G A C I T L G A Y L S H K •  239
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Fig. 2. A) Nucleotide and deduced amino acid sequences of human A1. B) Alignment of human A1 and murine A1. There is 72 % identity of human A1 with murine A1. Dots denote the different amino acids in peptide sequences. C) Alignment of human A1 and Bcl-2. There is 29 % identity of A1 with Bcl2. Gaps were inserted to maximize alignment.

mouse A1 sequences diverge in the untranslated region [19-20]. Compared with murine A1 protein, human A1 is 3 amino acids longer. Similar to murine A1, human A1 has a single potential N-linked glycosylation site at residue 128, and lacks a secretory signal sequence. In addition, the BH1 and BH2 domains and a segment at the amino-terminus that has been shown to be essential for Bcl-2 function and dimerization [72, 73] are well conserved. In contrast to most other members of the Bcl-2 family, hydrophobicity plots suggest that human A1 lacks a hydrophobic C terminus [58]. Overall, human A1 has 29% homology to human Bcl-2, with greater homology in the carboxyl region of the proteins, and has 72% identity with murine A1 [20] (Figure 2).

Localization of A1

Murine A1 has been reported to be hematopoietic specific [19], and is expressed in several cell lineages, including T-helper cells, macrophages, and cells of the neutrophilic lineage which are distributed in the thymus, spleen, and bone marrow [19, 74]. According to the study by Hatakeyama et al., murine A1-a, -b, and -d genes are expressed specifically in organs containing many neutrophils. In the neutrophils, A1-a, -b, and -d transcripts were detected at a comparable level [68]. Human A1 is clearly not restricted to hematopoietic cells, as suggested for murine A1. In addition to being identified in endothelial cells, human A1 is also expressed in cultured smooth muscle cells, and has a widespread tissue distribution, including the heart, lung, small intestine, colon, pancreas and testis [58]. It is unclear, at present, whether this widespread tissue distribution is related to the presence of endothelial, smooth muscle, or hematopoietic cells, or to other cell types present in these organs [20].

Furthermore, by the use of semi-quantitative RT-PCR and in situ hybridization, A1 demonstrated restricted multiple tissue distribution during murine embryonic development [57]. In the embryo, A1 was detected first at embryonic day 11.5 in liver, brain, and limbs. At 13.5 of gestation, A1 expression was identified in the central nervous system, liver, perichondrium, and digital zones of developing limbs. In the central nervous system of 15.5-day embryos, A1 was expressed at high levels in the ventricular zone and cortical plate of the brain cortex. The expression of A1 was retained in many adult tissues [57].

In human myeloerythroid leukemia cell line K562 transfected with pcDNA3-FLAG-A1, confocal microscopy showed that the A1 protein was localized to the cytoplasm in a pattern similar to that of Bcl-2, suggesting the possible localization of A1 to the membranes of mitochondria, and to the perinuclear envelope and endoplasmic reticulum [57, 75-76]. Interestingly, in murine neutrophils, by the use of immunohistochemistry, it was reported that the A1 protein was translocated from the cytoplasm to the nucleoplasm during the course of apoptosis [74]. To date, there is no report regarding the role of the possible nuclear translocation of A1.

The biological functions of A1

A1 is an early-response gene

A1 is an early-response gene with the characteristic features of expression, including: the onset of mRNA accumulation within approximately 1 h of stimulation; a return to basal levels of expression within several hours (transient induction); and inducibility in the absence of protein synthesis [19, 40, 70]. Its expression is associated with a variety of stimuli and occurs in several hemopoietic cell types. In murine, A1 gene expression is rapidly and transiently induced in bone marrows by GM-CSF and in macrophages in response to either LPS or GM-CSF. [19]. Based on the findings of a wide distribution of A1 in hematopoietic tissues, including the bone marrow, spleen, and thymus [67], the A1 product could conceivably function to mediate the regulation of tissue-specific genes

in response to various agents. Plausible targets of such regulation would include genes encoding cytokines and cell surface proteins that are induced late, following stimulation, and that are important in the development of hematopoietic cells [19, 67].

A1 and B lymphocyte development

B cell survival and life span is influenced by members of the Bcl-2 family to different degrees at different stages of development [30, 55, 77-78]. In mice, Bcl-2 and/or Bcl-xL protect germinal center B cells from programmed cell death [79]. Also, Bcl-xl expression, following engagement of the B cell antigen receptor, protects B cells from Fas-induced apoptosis [19, 80]. Similarly, Tomayko recently showed that A1 mRNA is expressed at low levels throughout B cell development in the bone marrow and periphery, but is up-regulated as cells enter the long-lived mature B cell pool [81], suggesting A1 is necessary to allow B cell survival following activation [82].

In the cell line study, Knodel et al showed that the levels of A1 determine the checkpoint between the death and survival of Blimp-1 (B lymphocyte-induced maturation protein 1)-expressing immature WEHI 231 murine B lymphoma cells at different stages of differentiation [83]. The study of Matthias et al., also suggests that high levels of A1 expression may characterize the checkpoint for the survival of Blimp-1-expressing cells, and that Blimp-1-expressing and Ig-secreting plasma cells may enter a long-lived pool following up-regulation of A1 [83]. Furthermore, it was reported that CD40-stimulated A1 expression permits WEHI 231 cells to survive in the presence of anti-IgM anti-bodies, and suggests a protective role for A1 in the antigen receptor-mediated apoptosis in B cells. CD40-induced A1 expression renders immature B cells resistant to antigen receptor-induced cell death. A1 up-regulation during the transition from the immature to the mature stage of B cell differentiation can be further stimulated by CD40, and appears to be crucial for cell survival in most stages of B cell maturation [84].

A1 and T lymphocyte development

Gene products of the Bcl-2 family are pivotal in establishing thresholds of susceptibility to programmed cell death among developing T cell subsets [85]. The anti-apoptotic members Bcl-2 and Bcl-xl are developmentally regulated in T cells, and overexpression of either can yield increased numbers of particular thymocyte subpopulations and mature T cells [86-88]. Further, thymocytes that overexpress either Bcl-2 or Bcl-xl survive longer in vitro, and better resist γ-irradiation- or corticosteroid-induced death [86-90].

A1 is modulated at critical points in T cell differentiation, most likely via receptor-associated singling pathways [28, 91]. A1 mRNA is expressed at high levels in thymic T cells, and is found at highest levels among CD4/CD8 double-positive thymocytes [91]. It is down-regulated in CD4/CD8 single-positive thymocytes and expressed at ~25-fold lower levels among single-positive peripheral T cell populations. These data suggest A1 is important in maintaining the viability of double-positive thymocytes awaiting positive selection. Although A1 expression is not dependent on TCR-MHC interactions, it can be transiently up-regulated following TCR engagement in single-positive thymocytes [92-93]. All these data lead to the speculation that A1 plays a critical role in thymocyte development and function to preserve mature peripheral T cells upon receptor engagement [91, 94]

A1 and myeloid cell development

Studies have shown that A1 prolongs precursor cell survival and permits myeloid differentiation. A1 is induced during the neutrophilic differentiation driven by G-CSF and GM-CSF in murine bone marrow cell lineage, indicating that A1 is related to myeloid precursor cell development [19]. According to the report of

Lin et al, the over-expression of Bcl-2, but not A1, abolishes myeloperoxidase expression in transfects of murine myeloid precursor cell lines, suggesting that early events in myeloid differentiation are inhibited by Bcl-2 over-expression, but not by A1. [56]. With stable transfection of A1 into an interleukin-3 (IL-3)-dependent murine myeloid precursor cell line, 32D c13 leads to a retardation of IL-3 withdrawal-induced cell death similar to that observed with the transfection of Bcl-2. However, unlike Bcl-2, which is down-regulated during terminal myeloid differentiation, A1 expression permits the accumulation of differentiated myeloid cells both before and after IL-3 withdrawal. The appearance of the A1 message during the G-CSF-driven neutrophilic differentiation of 32D cl3 cells substantiates an important role in myeloid development. These studies imply that A1 and Bcl2 proteins have distinct roles that may be related to the divergent regulation of their expression during myeloid differentiation [56, 95, 96]. A1 is constitutively expressed in murine neutrophils [19, 74], and the expression of murine A1 can be induced in activated macrophages and neutrophils during the course of an acute inflammatory response [74]. All these findings have further demonstrated that A1 is a potent anti-apoptotic regulator in mature macrophages and neutrophils.

In human myeloerythroid leukemia cell line K562 cells, the expression of A1 was associated with the retardation of apoptotic cell death induced by actinomycin D and cycloheximide, as well as by okadaic acid [97]. Additionally, Chuang et al showed the progressive A1 mRNA accumulation in human promyelocytic cell line HL60 during all-trans retinoic acid-driven neutrophilic differentiation, and the presence of A1 mRNA in resting mature neutrophils, suggesting that A1 also has an important role in neutrophilic development and in modulating mature neutrophil survival in humans [98]. The finding that human A1 can be up-regulated in neutrophils stimulated by G-CSF and LPS, agonists that promote neutrophil survival, further implicates the vital role of A1 in regulating the survival of activated neutrophils as well as forming a possible cross-talk between apoptosis mechanisms and cytokine- or endotoxin-related signaling pathways [98].

A1 and embryonic development

A1 functions to protect against cell death during embryonic development [57]. The expression of A1 was especially intense in the ventricular zone of the wall of the neural tube, where neuroblasts undergo proliferation and differentiation [57]. In addition, the data of Carrio et al. that showed A1 was also up-regulated in the digital zones during digit formation [57, 99]. A1 expression was prominent in the perichondrium of the digits, suggesting an important role in the survival of chondrocytes and the remodeling of the digits. Interestingly, A1 was absent in the interdigital spaces of developing limbs and in the intermediate region of the developing brain cortex, two sites associated with extensive cell death [57]. The finding that A1 was observed in more differentiated cells and absent in sites associated with extensive cell death suggests an important and a regulatory roles of this gene in selection and differentiation process during embryonic development and morphogenesis.

A1 and endothelial cells

Human A1 is rapidly induced by PMA in human umbilical vein endothelial cells (HUVEC), in a human dermal microvascular cell line (HMEC-1), and in vascular smooth muscle cells, and confers protection against apoptosis [58]. Unlike hematopoietic cells, human A1 is not induced by endothelial growth factors, fibroblast growth factor (bFGF), or vascular endothelial growth factor (VEGF), but rather by pro-inflammatory cytokines, suggesting a role in inflammation, and a cell-type specific function of A1. Human A1 can be induced in endothelial cells during the early stage of stimulation by tumor necrosis factor (TNF)-α and interleukin (IL)-1β. Additionally, in the late stage of

endothelial cell/monocyte co-cultures, A1 can be up-regulated in endothelial cells via monocyte adherence and PECAM-1 (CD31) engagement [100-101]. All these data point to a regulatory role for A1 in protecting endothelial cells against death and damage in inflammation.

Study of gene-engineered mice: A1a knock-out and EuA1a transgenic mice

To understand the physiological importance of A1, Hatakeyama S et al created mice lacking A1 subtype, -a [68]. There was no embryonic lethality. The spontaneous apoptosis of the peripheral blood neutrophils of nullizygous A1-$a^{-/-}$ mice was enhanced compared with that of either wild-type mice or heterozygous mutants (A1-$a^{+/-}$ mice). The prolongation of neutrophil survival induced by lipopolysaccharide treatment in vitro, and the transendothelial migration of neutrophils in vivo observed in wild-type mice were abolished in both A1-$a^{-/-}$ and A1-$a^{+/-}$ mice. But in their study, the extent of the tumor necrosis factor-induced acceleration of neutrophil apoptosis was not different among A1-$a^{-/-}$, A1-$a^{+/-}$, and wild-type mice [68, 102]. These results suggest that A1-a is not only involved in the inhibition of certain types of neutrophil apoptosis, but also has a role in modulating neutrophil chemotaxis in inflammation.

In the study of Willerford et al., transgenic mice overexpressing A1-a under the control of an Eμ enhancer were constructed to investigate the function of A1 in lymphoid development [103]. Their data showed the Eμ-A1 transgene led to an expansion of pro-B cells in lymphopoiesis, suggesting that A1 impaired the progression of lymphoid precursors to pre-B cells. Compared with nontransgenic controls, the thymocytes and peripheral lymphocytes from transgenic animals survived better ex vivo, and the thymocytes were more tolerant toward death-inducing stimuli, including γ-irradiation and dexamethasone. The mutation of the DNA-dependent protein kinase catalytic subunit in severe complex immuno-deficient (SCID) mice leads to impaired V(D)J recombination and the failure of T and B cell development [2]. The Eμ-Bcl-2 transgenes expressed in SCID B-lineage cells lead to the rescue of pre-B cell development [104]. Unlike Bcl-2, A1 was not able to rescue the pro- to pre- B cell transition in SCID mice, indicating that anti-apoptotic Bcl-2 homologues interact differentially with intracellular pathways which affect cell fate in lymphoid cells [103, 105].

The molecular mechanisms of the A1 function

In contrast to Bcl-2 and Bcl-xl, the molecular mechanisms of the A1 function have not been well-studied [30, 106]. Most of the reports have come from the studies of endothelial cells. The study of Karsen et al. previously revealed that the induction of A1 in response to TNF or LPS was dependent on NF-κB activation, a finding that has subsequently been confirmed by others [17, 58, 82, 107-109]. A human mesangial endothelial line (HMEC) that constitutively expresses an inhibitor of NF-κB, HMEC-Flag-IκB mutant, does not up-regulate A1 following TNF stimulation [108]. Co-transduction of the HMEC-Flag-IκB-mutant cell line with A1, protects endothelial cells from death [31]. Although the degree of caspase 8 cleavage is similar whether A1 is expressed or not, interestingly, caspase 3 activation is slightly delayed in A1-expressing cells [110-111]. Other studies show that A1 functions at the mitochondria to delay endothelial apoptosis in response to tumor necrosis factor [111-112]. A1 is able to prevent mitochondrial depolarization, and inhibits the release of cytochrome c and the activation of caspase 9 [113]. A1 is also able to prevent the cleavage of BID and subsequent mitochondrial activation, as well as the cleavage of Poly [ADP-ribose] Polymerase (PARP) and subsequent DNA fragmentation in this model [43, 111, 114]. Taken with the mitochondrial localization of A1, the above findings suggest that A1 can prevent mitochondrial events of apoptosis but not the direct activation of caspase 3 by caspase 8 [115]. Using the human

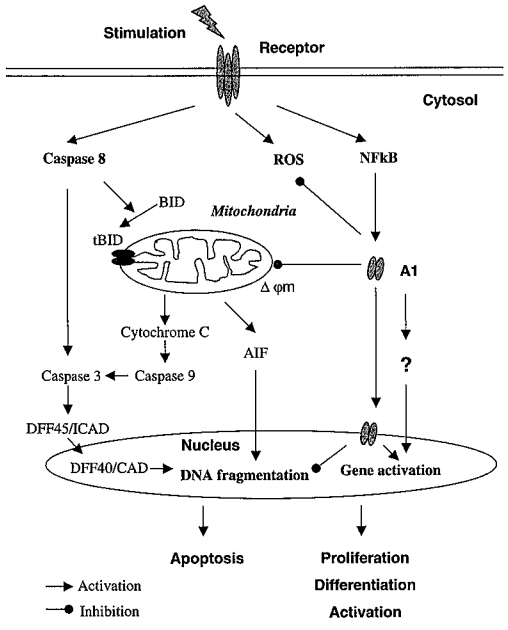

Fig. 3. A model for the cytoprotective effect of A1 in stimulated cells. A1 may function on mitochondria and interact with intracellular oxidative metabolisms to prevent cell apoptosis. Furthermore, A1, as an early response gene, may translocate to nucleus, and trigger other biological functions including cell cycle progression and proliferation. NFkB, nuclear factor kappa-B; AIF, apoptosis-inducing factor; DFF45/ICAD, DNA fragmentation factor 45 / Inhibitor of Caspase-3 activated DNase I (45kDa in non-apoptotic cells); DFF40/CAD, DNA fragmentation factor 40 / Caspase-3 activated DNase I (40 kDa in apoptotic cells); ROS, reactive oxygen species.

promyelocytic cell line HL60 transfected with human A1 as a model, Liu et al further demonstrated that overexpression of A1 conferred a cytoprotective capacity against exogenous hydrogen peroxide- and peroxynitrite-triggered cell death, suggesting that A1 may also function on intracellular oxidative metabolisms to alleviate the toxic effect of reactive oxygen species [116-118]. The cytoprotective effect of A1 may provide enhanced survival capacity to cells in inflammatory situations (Figure 3).

Future study

As an anti-apoptotic Bcl-2 homologue, A1 has an important role in regulating the hematopoiesis of lymphoid and myeloid lineages, as well as embryonic development. Recent studies have further extended the scope of the A1 function in modulating cell proliferation, transformation and inflammatory responses. Although the function and complicated network of the Bcl-2 family proteins are under intensive investigation, in contrast to other members of this family, the knowledge of the function of A1 is still limited. Many of the observations are not conclusive and the generality or the specificity of the A1 function in different cell types are mainly not well known. Additionally, the exact intracellular localization and the molecular mechanisms of A1 also remain unclear to date. With the limitation of the specificity and sensitivity of anti-murine A1-subtype antibodies due to the extreme similarity between them, as well as the difficulty in producing anti-human A1 antibody till present, conditional gene targeting experiments will be able to provide important information regarding the precise role of this gene with respect to cell survival and proliferation, cell transformation, hematopoiesis, as well as inflammation.

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B 細胞淋巴瘤相關蛋白：A1

劉劍英　郭漢彬

細胞生理死亡在維持組織生理平衡上具有重要角色。Bcl-2 蛋白質群和 Caspase 胨系統、粒腺體、以及以細胞核為標的之細胞生理死亡因子群已經被認為是細胞內細胞生理死亡傳訊路徑的基本組成。A1 為抗細胞生理死亡 Bcl-2 同類蛋白之一員，最初被認為是具血球生成系統專一性的早發反應性基因，與淋巴系和骨髓系血球生成及分化有關。最近的研究更進一步的發現 A1 對胚胎發育具有重要角色並可能調控血管內皮細胞之發炎反應。A1 可能做用於粒腺體而延緩細胞死亡，並且與核因子 NF-κB 有交互作用。隨著在鼠類發現多重基因表現以及至今仍無法製造出抗人類 A1 蛋白之專一抗體、大部份與 A1 有關之生物機能的分子機轉仍不明白。這篇文獻回顧介紹了 A1 基因的發現、A1 蛋白與其它 Bcl-2 蛋白結構的相似處和生物機能的相異處、以及有關 A1 研究最近的進展。以條件調控基因表現為模式的研究將有助於進一步闡明 A1 在組織發展和細胞生物學上的確切功能。 ***(胸腔醫學 2002; 17: 89-105)***

關鍵詞：細胞生理死亡，Bcl-2 蛋白質群，A1，粒腺體，核因子 NF-κB

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The Role of Noninvasive Positive Pressure Ventilation in Hypoxemic Respiratory Failure —A Review of the Literature

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Noninvasive positive pressure ventilation (NIPPV) was first adopted in the 1930's for use on patients with respiratory failure. It did not gain popularity until the 1980's when a number of small reports came out in favor of its use in primarily hypercapnic failure and post-extubation patients. Its benefit in hypoxemic respiratory failure is still controversial. We reviewed randomized trials published since 1995 on the use of NIPPV in patients with hypoxemic respiratory failure.Of the eight randomized trials published since 1995, six reported a significant decrease in the endotracheal intubation (ETI) rate with NIPPV use. However, one of the six trials had a large proportion of COPD patients and did not show a decrease in the ETI rate when the COPD patients were excluded from the analysis. Of the two that did not show a decrease in the ETI rate, one had a small sample size, and the other was done on emergency room patients. Two of the eight studies also reported a decrease in the mortality rate. In conclusion, NIPPV is probably helpful in patients with hypoxemic respiratory failure as well, but not to such a marked extent as with hypercapnic respiratory failure. ***(Thorac Med 2002; 17: 106-113)***

Introduction

Chronic Noninvasive positive pressure ventilation (NIPPV) is a mode of mechanical ventilation that seems attractive for many reasons. Ideally speaking, it may provide physicians the control and assurance of mechanical ventilation without the concomitant disadvantages of the invasive nature of endotracheal intubation [1]. Moreover, it can improve patient comfort, preserve the airway defense mechanisms, preserve speech, allow swallowing, and provide physicians greater flexibility in instituting and removing mechanical ventilation [2]. Despite the many theoretical advantages associated with NIPPV, it has not been in widespread use until the last decade even though it was first conceived in the 1930's.Even with the gradual acceptance of NIPPV as an established method for treating hypercapnic respiratory failure in recent years [3-4], the use of NIPPV in hypoxemic respiratory failure remains highly controversial. In the following text we will review the medical literature published in the last decade exploring the use of NIPPV in hypoxemic respiratory failure.

Historical background

The origin of noninvasive positive pressure

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ventilation probably goes back thousands of years to the early days of man. The Book of Genesis, Chapter Two, paragraph seven, records the following text: "and the Lord God formed man of the dust of the ground, and breathed into his nostrils the breath of life, and man become a living soul." In the 1930's, Barach reported a series of studies involving continuous positive airway pressure (CPAP) delivery through a facemask [5-7]. His patient population consisted mainly of patients with pulmonary edema and other forms of respiratory failure. However, in the 1960's, the endotracheal tube (ETT) became accepted as the exclusive interface to deliver mechanical tidal breaths. Studies utilizing noninvasive ventilation then became extinct in the literature. In the late 1970's, CPAP via a mask was introduced into clinical practice to improve oxygen exchange in hypoxemic acute respiratory failure (ARF) [8-11]. In the early 1980's, intermittent positive pressure ventilation (IPPV) was used on patients with neuromuscular diseases and chronic COPD [12]. Finally in the 1990's, larger trials began to be conducted investigating the effects of noninvasive ventilation (NIV) and IPPV in patients with ARF. Of these trials, the majority (>70%) was conducted with patients with hypercapnic failure. Only the minority investigated the effects of NIV and IPPV on hypoxemic respiratory failure.

Recent data

Despite the emerging interest in utilizing NIPPV in acute respiratory failure, many of the studies conducted during this period were of a small size and not randomized. Therefore, their conclusions are more difficult to evaluate. A meta-analysis conducted by Keenan, SP, and published in *Critical Care Medicine*, searched MEDLINE records from 1966 to September 1995 to examine the use of NIPPV in acute respiratory failure [13]. Out of the two hundred and twelve initially selected studies, only seven published and unpublished, randomized, controlled trials fulfilled the selection criteria and were included in the meta-analysis. The study populations were from France, Greece, the United Kingdom, and the United States. Four out of the seven studies included only COPD patients, two were of mixed population, and one excluded COPD patients. Five out of the seven trials supplied information on mortality, and showed a strong survival benefit in the NIPPV group, with an odds ratio of 0.29.The one trial that excluded COPD patients (Wysocki *et al.*, 1995) found a weaker trend but no significant difference in survival between the NIPPV and the control group, with an odds ratio of 0.67.Five of the seven trials evaluated the effect of NIPPV on the need for endotracheal intubation in acute respiratory failure. Overall, they showed a strong effect favoring NIPPV, with an odds ratio of 0.20.For non-COPD patients, there was a trend, but no significant benefit, favoring NIPPV, with an odds ratio of 0.77.

In reviewing the literature on the application of NIPPV in hypoxemic respiratory failure, the major studies published since 1990 are listed in Table 1.Wysocki *et al.* conducted a prospective, randomized, controlled trial with forty-one patients who had acute respiratory failure not related to COPD [14]. He randomized twenty-one patients to NIPSV (noninvasive pressure support ventilation) plus conventional therapy, and twenty patients to conventional therapy alone. The NIPSV in his study was delivered with a facemask connected to a ventilator in the PS/PEEP mode. He found that the rate of endotracheal intubation (ETI) and the mortality rate were not significantly different between the NIPSV and the conventional groups (62 vs. 70% for ETI and 33 vs. 50% for mortality, respectively). By further analysis, NIPSV was shown to have produced a significant reduction in the ETI rate (36 vs. 100%) and the mortality rate (9 vs. 66%) in patients with $PaCO_2$ > 45 mmHg (N = 17). The top two diagnoses causing acute respiratory failure, which comprised more than 70% of the study population in Wysocki's study, were pneumonia and cardiogenic pulmonary

Table 1 Major Studies on NIPPV Published Between 1991 and 2000

Study (year)	Case Number	Hypercapnic Failure	Hypoxemic Failure	Vent mode	% Success
Pennock (1991)	29	8	21	BiPAP	76
Wysocki (1993)	17	6	11	PSV	47
Pennock (1994)	110	(32)	60	BiPAP	80
Tognet (1994)	15	–	15	PSV	40
Wysocki (1995)*	21	–	21	CPAP/PSV	62
Kramer (1995)*	31	–	–	BiPAP	69
Sacchetti (1995)	22	–	22	BiPAP	91
Pollack (1995)	50	24	26	BiPAP	43
Meduri (1996)	158	92	49	CPAP/PSV	65
Mehta (1997)*	27	–	–	BiPAP	93
Wood (1998)*	27	–	–	BiPAP	56
Antonelli (1998)*	64	–	64	CPAP/PSV	69
Alsous (1999)	56	25	31	BiPAP	63
Confalonieri (1999)*	56	25	31	CPAP/PSV	79
Antonelli (2000)*	40	–	40	CPAP/PSV	80
Martin (2000)*	61	29	32	BiPAP	72

* randomized studies

edema in both the NIPSV and conventional groups. Overall, his study showed a trend, but no statistical significance, favoring the use of NIPSV in hypoxemic patients. This result may be related to the lack of statistical power in his study caused by the small sample size.

Kramer *et al.* published a prospective, randomized trial of NIPPV in 1995, in *American Journal of Respiratory and Critical Care Medicin* [15]. Thirty-one patients, all with acute respiratory failure, were included in the final analysis. Twelve out of the fifteen patients in the control group, and eleven of the sixteen patients in the NIPPV group had COPD; while had COPD. In this study, NIPPV was administered via nasal masks connected to BiPAP machines; the resulting data were not analyzed based on hypoxemic/ hypercapnic categories. The analysis showed that the ETI rate was reduced from 73% in the control group to 31% in the NIPPV group, with statistical significance. The mortality rate was similar in both groups.

In 1996, Meduri *et al.* published in *Chest* a large-sized, prospective, nonrandomized study, based in a medical ICU, with N = 158 [16]. Forty-one patients in his study had hypoxemic failure; fifty-two had hypercapnic failure; twenty-two had hypercapnic "insufficiency"; seventeen patients were categorized as "others"; and twenty-six patients had advanced illnesses and refused intubation. NIPPV was used as first-line treatment in all not-yet-intubated patients with respiratory insufficiency admitted to the medical ICU. Mechanical ventilators were connected to face masks in the CPAP/PSV or SIMV mode. In the conclusion, 65% of all not-yet-intubated patients avoided ETI, excluding the Do-Not-Intubate patients, and 66% of hypoxemic patients avoided ETI. The mortality rate was 16% in all patients and 22% in the hypoxemic subgroup. The three leading causes of hypoxemia were pneumonia with AIDS, pneumonia without AIDS, and pulmonary edema.

Mehta *et al.*, in 1997, published a

randomized, controlled, double-blind trial of patients with acute pulmonary edema (N = 27) [17], in *Critical Care Medicine.* Thirteen patients were randomized to nasal CPAP, and fourteen to nasal BiPAP. A surprising result came out of the study: the myocardial infarction rate was found to be higher in the BiPAP group (71%) compared with both the CPAP group (31%) and the historically matched controls (38%). Both the BiPAP and the CPAP groups had reduced intubation rates in relation to the historical controls (7% in BiPAP, 8% in CPAP, and 33% in controls). No differences were noted in mortality rates between the two groups. The differences in the myocardial infarction rates were postulated to be related to two factors. The first was the baseline population differences between the BiPAP and CPAP groups that were present at the beginning of the study. The second contributing factor was the higher initial mean intrathoracic pressure in the BiPAP group that would have had a negative impact on patients with insufficient cardiac reserve. There was the possibility that a relative decrease in myocardial perfusion in the BiPAP group could have extended the areas of incipient infarction.

A prospective, randomized, controlled study published in *Chest,* in 1998, was conducted by Wood *et al.* [18] among patients with acute respiratory distress presenting to the emergency department. Sixteen patients were randomized to conventional therapy plus NIPPV, and eleven were randomized to conventional therapy alone. NIPPV was administered via BiPAP connected to nasal masks with or without chin straps. The data were not analyzed according to hypoxemic/ hypercapnic categories. The result showed that 56% of the NIPPV group and 55% of the control group had avoided ETI. There were no statistical differences in either the ETI rates or the mortality rates between the two groups.

Antonelli *et al.* published another prospective, randomized trial with sixty-four patients, in *the New England Journal of Medicine* in 1998 [19]. He randomized patients with hypoxemic respiratory failure to either endotracheal intubation or face masks connected to mechanical ventilators. He found that 31% of the patients in the noninvasive group eventually required endotracheal intubation (69% success in avoiding ETI). More patients in the conventional ventilation group had serious complications compared to the NIPPV group (66% vs. 38%, p = 0.02), and 53% of the conventional ventilation group and 72% of the noninvasive ventilation group survived their ICU stay. However, the conventional ventilation group had significantly lower arterial pHs at the beginning of the trial (7.37 vs. 7.45). It is not clear whether this baseline difference played a role in the more favorable result in the NIPPV group.

A study published by Confalonieri *et al.* in *the American Journal of Respiratory and Critical Care Medicine,* in 1999, analyzed fifty-six patients with severe community-acquired pneumonia [20]. This was a multicenter, prospective, randomized trial. Twenty-three patients had COPD while thirty-three did not. Patients were randomized to either Venturi masks or NIPPV through face masks. They found that the use of NIPPV was associated with a significant reduction in the need for endotracheal intubation (21% vs. 50%; p = 0.03). The mortality rates were similar in both groups. However, if the patients with COPD were excluded from the analysis, there was no significant reduction in the intubation rates in the NIPPV group.

Antonelli *et al.* published another prospective, randomized trial in *JAMA* in 2000 [21]. He recruited forty patients who were recipients of solid organ transplantations and who had acute hypoxemic respiratory failure. Twenty were randomized to NIPPV, and twenty were randomized to standard treatment with supplemental oxygen. NIPPV was administered by facemasks connected to mechanical ventilators. The rationale for studying the use of NIPPV on transplant recipients was the following: the immunosuppressive drugs used on transplant patients make them more susceptible to the morbidity and mortality associated with pulmonary infections. Nosocomial pneumonia is a frequent

Table 2 Summarized Conclusions from Randomized Studies on NIPPV

Study (year)	↓ ETI rate	↓ Mortality	Note
Wysocki (1995)	No	No	Sample size small
Kramer (1995)	Yes	No	Predominantly COPD patients
Mehta (1997)	Yes	No	• MI rate increased • All pulmonary edema patients
Wood (1998)	No	No	• Nasal mask • All emergency room patients
Antonelli (1998)	Yes	Yes	• Baseline pH lower in NIPPV group • Control is ETI
Confalonieri (1999)	(Yes)	No	No change in ETI rate if COPD patients excluded
Antonelli (2000)	Yes	Yes	All solid organ transplant patients
Martin (2000)	Yes	No	No specific criteria for ETI

complication of mechanical ventilation with an endotracheal tube. It was postulated that transplant patients might be a group more sensitive to the favorable effects of NIPPV, if there were any. In this study, the average days after transplantation to the onset of respiratory failure were twenty-three and twenty-two in the NIPPV and control groups, respectively. The types of transplants received by the study population in descending order were liver, kidney, and lung, in both groups. The top three causes of acute respiratory failure in both groups were ARDS, mucous plugging/atelectasis, and cardiogenic pulmonary edema. In the conclusion, the need for ETI was 20% and 70% in the NIPPV and control groups, respectively, with statistical significance. The ICU mortality rate was reduced from 50% in the control group to 20% in the NIPPV group ($p = 0.05$). There was no statistical difference in the hospital mortality rates.

Martin *et al.* published a prospective, randomized controlled trial in *the American Journal of Respiratory and Critical Care Medicin,e* in 2000 [22].He analyzed the data of thirty-two patients with hypoxemic respiratory failure and twenty-nine patients with hypercapnic respiratory failure, a total of sixty-one patients. The patients were randomized into either NIPPV or usual medical care. The pathophysiology of the study population included COPD (23 patients), non-COPD-related pulmonary disease (29 patients), neuromuscular disease (6 patients), and post-extubation (3 patients). At the conclusion of the study, 28% of the NIPPV patients and 59% of the usual medical care patients required intubation. In further analysis, the patients with hypoxemic failure in the NIPPV group had a significantly lower ETI rate than those in the usual medical care group (7.46 intubations vs. 22.64 intubations per 100 ICU days, $p = 0.026$). They found no differences in the ICU mortality rates. However, there were no specific criteria for ETI in this study, and so, there was potential clinician bias in the decision to intubate.

Summary

The major conclusions of the above-mentioned studies are summarized in Table 2.Six of the eight studies concluded that NIPPV decreases the endotracheal intubation rate. However, one of them showed no decrease if COPD patients were excluded from the analysis; another study consisted of predominantly COPD patients. Of the two negative studies, one might not have had enough statistical power. In terms of the impact on mortality rate, only two of the eight studies showed a decrease in mortality with the use of NIPPV.

In conclusion, acute respiratory failure in COPD patients is generally due to upper respiratory tract infections. Therefore, aggressive treatment of the airway inflammation combined with respiratory muscle rest usually results in improvement in a few days. The use of NIPPV is known to be beneficial in COPD patients. It probably acts preferentially by improving respiratory muscle strength. Hypoxemic failure from other causes, on the other hand, tends to require more prolonged mechanical support. The poorer response rate with pneumonia may be due to several factors. Patients with infectious pulmonary processes usually have difficulty handling their secretions. They also tend to have high levels of ventilatory requirements, which often cannot be satisfied with NIPPV. The reduced lung compliance common in pneumonia and ARDS patients also mandates higher levels of pressure. All of the above factors may contribute to the higher failure rates of NIPPV use in hypoxemic respiratory failure caused by pneumonia [23].

In general, nasal masks are more comfortable for patients on NIPPV. They also facilitate speech and swallowing. Facemasks are superior to nasal masks for severely dyspneic patients in terms of improving oxygenation, since dyspneic patients are often mouth-breathers. Mouth breathing in patients wearing nasal masks may decrease the efficacy of NIPPV due to the loss of pressure via the mouth. Therefore, in severely dyspneic patients and in patients unable to comply with nasal breathing, full facemasks are preferred. However, there are certain contraindications to the use of NIPPV. One should keep them in mind and elect other methods of oxygenation such as endotracheal intubation if any of these contraindications are suspected. They include: respiratory arrest, hemodynamic instability, upper airway obstruction, facial trauma, inability to clear secretions, altered level of consciousness, need for airway protection, inability to cooperate, inability to fit the mask properly, and uncontrolled arrhythmia.

In conclusion, NIPPV has been shown to have a positive effect in decreasing the endotracheal intubation rate and the ICU mortality rate of acute hypercapnic respiratory failure patients. NIPPV has also been shown to decrease the endotracheal intubation rate in pulmonary edema. However, the myocardial infarction rate may increase in patients with pulmonary edema on NIPPV without a concomitant rise in the morality rate. The effect of NIPPV in acute hypoxemic respiratory failure seems to be positive, based on the existing randomized trials to date. However, the benefit of NIPPV in hypoxemic respiratory failure is not as great as in acute hypercapnic failure. No single physiologic parameter predicts the success of NIPPV use in preventing endotracheal intubation in any particular case of hypoxemic respiratory failure. In view of the minor side effects of the device and the potential benefit, we recommend a trial of NIPPV in all patients with hypoxemic respiratory failure prior to endotracheal intubation, as long as there are no contraindications.

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非侵襲性陽壓呼吸輔助於缺氧性呼吸衰竭之運用

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非侵襲性陽壓呼吸輔助(NPPV)有許多理論上的益處，包括避免氣管內管插入所引起之併發症、增進病患的舒適度、保留呼吸道天然的保衛機轉、說話能力、以及吞嚥能力。自 1935 年起便有報告提出持續性陽壓呼吸輔助(CPAP)於肺水腫之病患治療上之益助。在 1970 年代更有持續性陽壓以及間歇性陽壓呼吸輔助(IPPV)運用於缺氧性呼吸衰竭以及神經肌肉性及慢性阻塞性肺病之報告出爐。在 1980 年代開始有較大型隨機試驗探討非侵襲性陽壓呼吸輔助在高二氧化碳以及缺氧性呼吸衰竭之運用。以目前已出版之報告來評估，非侵襲性陽壓呼吸輔助在高二氧化碳性呼吸衰竭病患之治療有一定的助益。在缺氧性呼吸衰竭之治療上，由於人數較少，可參考資料較不齊全。自 1990 年起，才陸續有著重於缺氧性呼吸衰竭與非侵襲性陽壓呼吸輔助之研究。研究證明，非侵襲性陽壓呼吸輔助再缺氧性呼吸衰竭的治療上亦佔了一席之地。 ***(胸腔醫學 2002; 17: 106-113)***

關鍵詞：非侵襲性陽壓呼吸輔助，呼吸衰竭，缺氧

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呼吸胸腔科門診病患藥物吸入技術衛教成效

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目的：評估呼吸胸腔科門診病患使用定量噴霧劑（MDI）及乾粉吸入劑（DPI）藥物吸入技術衛教之成效。

病患及設置：針對本院呼吸胸腔科曾接受過定量噴霧劑（MDI）或乾粉吸入劑（DPI）藥物吸入衛教之門診病患，由專職呼吸治療師進行藥物吸入技巧評估及修正衛教。

措施及測量：利用一份病患正確使用各種吸入藥物方法及再次檢視修正的評估表（如附件一），作為176位門診病患藥物吸入技術的評估工具，並對病患使用之不同藥物吸入形式（MDI或DPI）分別作評估。

結果：經由此評估表之統計結果發現，病患正確吸藥的技巧與年齡、首次諮詢對象、吸入藥物種類有明顯關係，但經由衛教後，病患吸藥技巧可立即獲得改善。

結論：於評估門診病患藥物吸入技巧時，常可見到病患不當的吸藥技巧[1-2]，進而影響病情的改善，但大多數的病患皆可經由衛教學習正確的藥物吸入技巧[3]，由專人給予正確的衛教對病患而言是有益的。

（胸腔醫學 2002; 17: 114-119）

關鍵詞：定量噴霧劑，乾粉吸入劑，藥物吸入技術衛教，專職呼吸治療師

前　言

在呼吸胸腔科門診常見病患使用定量噴霧劑（MDI）或乾粉吸入劑（DPI），來做為治療氣喘及慢性阻塞性肺疾病[1，4]。病患是否能夠正確使用吸入性藥物，關係著患者病情變化及改善程度。根據研究顯示，不當的藥物吸入技術，會導致藥物沉積在肺部的藥量減少、用藥次數的增加及呼吸道阻塞難以控制[3,5-6]。

在本院開辦呼吸治療衛教門診之前，病患之藥物諮詢來源多為醫師、護理人員或藥師，但是病患藥物使用方式錯誤者大有人在。此篇研究報告是評估病患由各諮詢對象衛教後，成效是否不同，以及接受專職呼吸治療師再次修正衛教後，其吸藥技巧是否有顯著改善。

病患族群

此份評估統計期間是由2001年4月至2001年8月，總共176位病患，其中包含氣喘病患:男性47人（26.7%），女性72人（40.9%）。另有慢性阻塞性肺疾病病患;男性46人（26.1%），女性11人（6.3%）。依其藥物型式分類：使用定量噴霧劑（MDI）男性55人（60.4%），平均年齡分布在62±14歲;女性36人（39.6%），平均年齡分布在52±16歲。另使用乾粉吸入劑（DPI）男性38人（44.7%），平均年齡分布在53±16歲;女性47人（55.3%），平均年齡分布在54±14歲。

方　法

針對本院呼吸胸腔科曾接受過定量噴霧劑（MDI）或乾粉吸入劑（DPI）藥物吸入衛教之門診病患，由醫師開立使用吸入藥物醫囑（MDI或DPI），並由專職呼吸治療師收集病患基本資料:年齡、性別、診斷、第一次藥物諮詢對象、吸入藥物種類、劑量、頻率及首次衛教日期等。根據門診病患吸入藥物使用方法及再次檢視修正評估表之評估項目，依其不同藥物型式進行吸入技巧評估，並修正其錯誤技巧，預約病患下次回診日（2-4周後），再次評估修正後的藥物吸入技巧。

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表一 MDI 衛教前後錯誤步驟百分比

MDI 衛教前後錯誤步驟百分比				
步驟	第一次評估個案數	第一次評估百分比	第二次評估個案數	第二次評估百分比
1.打開蓋子接上吸入輔助器	9	10%	0	0.00%
2.垂直上下搖動噴霧液罐	17	18.70%	0	0.00%
3.用嘴吐完氣	48	52.70%	10	10.90%
4.將吸入輔助器含住並閉緊嘴唇	4	4.40%	0	0.00%
5.按壓噴霧器一次	21	23.10%	3	3%
6.持續吸飽氣	26	28.60%	4	4.40%
7.閉氣 5-10 秒	31	34.10%	9	9.90%
8.於 20—30 秒後再吸入下一劑	67	73.60%	43	47.30%
9.吸入第二劑前再次搖動噴霧液罐	33	36.30%	17	18.70%
10.能正確使用藥物劑量	5	5.50%	0	0%
11.辨別剩藥及過期	16	17.60%	1	1.10%

表二 DPI 衛教前後錯誤步驟百分比

DPI衛教前後錯誤步驟百分比				
步驟	第一次評估個案數	第一次評估百分比	第二次評估個案數	第二次評估百分比
1.上藥	34	40%	10	11.80%
2.用嘴吐完氣	41	48.20%	16	18.80%
3.含住藥瓶快速用力深吸氣	19	22.40%	4	4.80%
4.閉氣十秒	24	28.20%	6	7.00%
5.正確使用藥物劑量	5	5.90%	0	0%
6.辨別剩藥及過期	14	16.50%	2	2.40%
7.吸完藥後正確漱口	26	30.60%	3	3.50%

評估結果

經由此份評估表之統計結果發現，定量噴霧劑（MDI）使用病患常見的錯誤吸藥技巧百分比由高至低為:(1)未於 20－30 秒後再吸入下一劑，佔 73.6%，修正後仍為 47.3%。(2)吸藥前未先吐完氣，佔 52.7%，修正後為 10.9%。(3)吸入第二劑前未再次搖動噴霧液罐，佔 36.6%，修正後為 18.7%。(4)未閉氣 5－10 秒，佔 34.1%，修正後為 9.9%。(5)未持續吸飽氣，佔 28.6%，修正後為 4.4%。(6)吸入前連續按壓噴霧器數次，佔 23.1%，修正後為 3%。(7)吸藥前未搖動噴霧液罐，佔 18.7%，修正後為 0%。(8)未能辨別剩藥及過期，佔 17.6%，修正後為 1.1%。(9)未接上吸入輔助器，佔 10%，修正後為 0%。(10)未能正確使用藥物劑量，佔 5.5%，修正後為 0%。(11)未將吸入輔助器含住並閉緊嘴唇，佔 4.4%，修正後為 0%。（表一）

在使用乾粉吸入劑（DPI）方面，常見的吸藥錯誤步驟百分比為：(1)吸藥前未先吐完氣，佔 48.2%，修正後為 18.8%。(2)未能正確上藥，佔 40%，修正後為 11.8%。(3)吸完藥後未漱口，佔 30.6%，修正後為 3.5%。(4)未閉氣 5-10 秒，佔 28.2%，修正後為 7%。(5)吸藥時未能快速用力深吸氣，佔 22.4%，修正後為 4.8%。(6)未能辨別剩藥及過期，佔 16.5%，修正後為 2.4%。(7)未能正確使用藥物劑量，佔 5.9%，修正後為 0%。（表二）

為了分析修正衛教對個案的吸藥技術是否有明顯改善，採用配對 T 檢定（paired-ttest）分別檢定使用 MDI 及 DPI 患者之吸藥技巧，MDIt 值=9.87（$p<0.001$），DPIt 值=9.69（$p<0.001$），證明由專職呼吸治療師第二次修正衛教後，不論是使用 MDI 或 DPI 的病患其衛教前後吸藥技巧有顯著差異。又以配對 T 檢定（paired-ttest）分析衛教後所有病患在 MDI 及 DPI 各個吸藥步驟錯誤百分比是否明顯改善，得到 MDIt 值=5.98（$p<0.001$），DPIt 值=6.32（$p<0.001$），顯示衛教前後所有病患在 MDI 及 DPI 各個吸藥步驟錯誤百分比有顯著差異。

在統計 MDI 首次諮詢對象衛教情形方面，諮詢對象為專職呼吸治療師者，佔總諮詢個案數的 76.9%;諮

表三 MDI 藥物首次諮詢對象分布 （*各組與專職呼吸治療師組的比較）

MDI藥物首次諮詢對象分布							
諮詢對象	個案數	各首次諮詢對象佔總衛教人數之百分比	總錯誤步驟次數平均值	總錯誤步驟次數標準差	總錯誤步驟次數標準誤	t值*	p值*
專職呼吸治療師	70	76.90%	2.06	1.32	0.16		
醫師	7	7.70%	6.43	1.99	0.75	7.93	<0.001
藥師	10	11.00%	6.2	2.25	0.71	5.68	<0.001
護理人員	4	4.40%	6.5	1.29	0.65	6.54	<0.001
總計	91	100%					

表四 DPI 藥物首次諮詢對象分布 （*各組與專職呼吸治療師組的比較）

DPI藥物首次諮詢對象分布							
諮詢對象	個案數	各首次諮詢對象佔總衛教人數之百分比	總錯誤步驟次數平均值	總錯誤步驟次數標準差	總錯誤步驟次數標準誤	t值*	p值*
專職呼吸治療師	69	81.20%	1.29	1.25	0.15		
醫師	5	5.90%	4.00	1.87	0.84	4.54	<0.001
藥師	7	8.20%	4.57	1.27	0.48	6.62	<0.001
護理人員	4	4.70%	5.00	1.41	0.71	5.73	<0.001
總計	85	100%					

詢對象為醫師者，佔總諮詢個案數的 7.7%;諮詢對象為藥師者，佔總諮詢個案數的 11%;諮詢對象為護理人員者，佔總諮詢個案數的 4.4%。而以兩組樣本 t 檢定法分別檢定專職呼吸治療師對醫師、藥師、護理人員之衛教成效的差異，則其結果皆達統計上顯著差異。（表三）

在統計 DPI 首次諮詢對象衛教情形方面，諮詢對象為專職呼吸治療師者，佔總諮詢個案數的 81.2%;諮詢對象為醫師者，佔總諮詢個案數的 5.9%；諮詢對象為藥師者，佔總諮詢個案數的 8.2%;諮詢對象為護理人員者，佔總諮詢個案數的 4.7%。而以兩組樣本 t 檢定法分別檢定專職呼吸治療師對醫師、藥師、護理人員之衛教成效的差異，則其結果亦皆達統計上顯著差異。（表四）

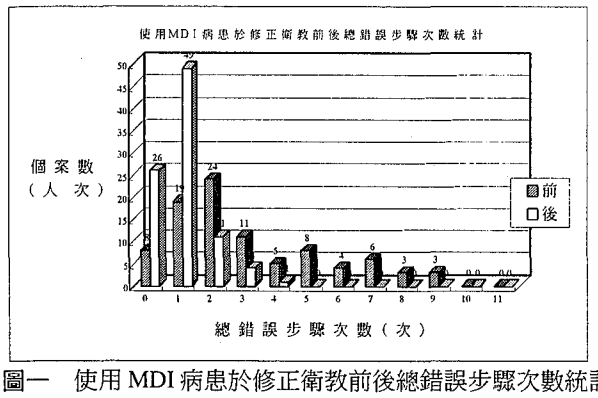
以上結果得知，雖然個案的抽樣分布不均，導致選取個案中首次諮詢對象為專職呼吸治療師者佔大多數，然不論使用 MDI 或 DPI，由專職呼吸治療師衛教者，其錯誤吸藥技巧比例皆較低。相較之下，首次諮詢對象非專職呼吸治療師者，雖衛教的個案數不多，但錯誤吸藥的比例卻相當高。

在評估 MDI 修正衛教前患者藥物使用步驟錯誤項目大於等於 5 項者共有 24 位，於修正衛教後再評估，則所有病患皆可達到錯誤步驟低於 4 項。在評估 DPI 修正衛教前患者藥物使用步驟錯誤項目大於等於 4 項者共有 18 位，於修正衛教後再評估，則所有病患皆可達到錯誤步驟低於 3 項。（圖一、圖二）以 Wilcoxon sign rank test 檢定病患於 MDI 或 DPI 之修正衛教前後總錯誤步驟次數是否有顯著差異，結果發現無論是 MDI 或 DPI 均未達統計上顯著差異。

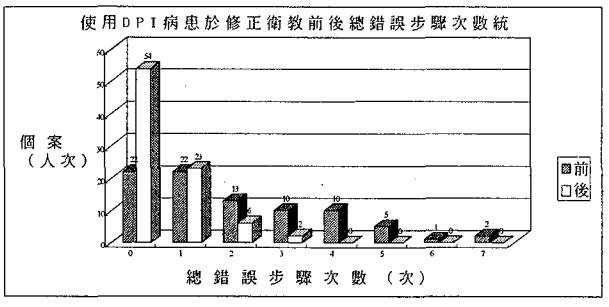
討 論

根據研究顯示，以平均 8 分鐘的衛教，幾乎所有的病患皆能正確執行藥物吸入步驟，但隨著時間的過去，卻發現病患正確吸藥的比例也逐漸下降[3]。另有研究指出衛教過程中病患群中年紀較大者，手部力氣不足，及理解能力較差者較易發生不當的吸藥技巧[7-9]，在本評估計畫中我們亦遭遇到同樣的困難，此類族群病患經由反覆評估及衛教後仍有部分病患吸藥技巧不正確，但我們在衛教經驗中發現，若於衛教過程中有病患家屬陪同參與，則可幫助此類病患族群強化吸藥技巧，提高衛教成效。但本研究並未深究此因素對衛教結果的影響，有待進一步探討。

此篇評估報告中，顯現病患首次諮詢對象亦關係著病患是否正確執行藥物吸入技巧，由非專職人員進行初次衛教的個案，其錯誤吸藥技巧的比例相對較高，部分探討健康照護者對 MDI 使用之知識與技巧之研究指



圖一　使用 MDI 病患於修正衛教前後總錯誤步驟次數統計



圖二　使用 DPI 病患於修正衛教前後總錯誤步驟次數統計

出，多數醫療專業人員，如醫師、護理人員、藥師及呼吸治療師皆缺乏正式吸入性藥物之訓練，故不精通正確之吸入性藥物使用技巧[2,10-11]，詳究此次評估結果，亦不排除上述因素，其他可能因素為：(1)追蹤時間太短:本研究只針對病患接受衛教後 2-4 周給予再次評估，有研究指出隨著時間的過去，病患正確吸藥的比例也逐漸下降[3]，因此我們認為應針對衛教後再次評估的時間點深入探討，可作為病患追蹤衛教的參考。(2)抽樣樣本數太少:雖在個別比較不同諮詢對象之衛教成效時達統計上之顯著差異，但在以 Wilcoxon sign rank test 檢定病患於 MDI 或 DPI 之修正衛教前後總錯誤步驟次數的結果未達統計上顯著差異，若增加個案數或許會有不同的結果。(3)其他醫護人員無充裕的時間好好衛教病患所造成。但經由專職呼吸治療師再次修正病患的錯誤吸藥技巧及給予衛教，仍可改善其錯誤吸藥技巧。為加速達到控制病情的目標，持續追蹤病患藥物吸入技術是必要的[6-7,12]。

本研究肯定在繁忙的門診中，設立門診衛教室，由專職的呼吸治療師執行衛教，可以改善病患的吸藥技術進而控制病情。因此設立專職的衛教室值得推廣。

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附件一、門診病患吸入藥物使用方法及再次檢視修正評估表

姓名：_____ 病歷號：_____ 年齡：_____ 性別：□男 □女

診斷：□Asthma □COPD

◆第一次檢視及修正日期：_____年_____月_____日

◆第二次檢視及修正日期：_____年_____月_____日

◆第一次藥物諮詢：□醫師 □呼吸治療師 □藥師 □護理人員

◆第二次藥物諮詢：□醫師 □呼吸治療師 □藥師 □護理人員

藥物吸入技術評估：

□MDI: □Atrovent □Berotec □Serevent

1. □ □打開蓋子接上吸入輔助器
2. □ □垂直上下搖動噴霧液罐
3. □ □用嘴吐完氣(吐氣至 RV 或 FRC)
4. □ □將吸入輔助器含住並閉緊嘴唇
5. □ □按壓噴霧器一次
6. □ □持續由口吸氣至 TLC
7. □ □閉氣 5-10 秒
8. □ □於 20-30 秒後再吸入下一劑
9. □ □吸入第二劑前再次搖動噴霧液罐
10. □ □能正確使用藥物劑量
11. □ □辨別剩藥及過期

DPI:□Pulmicort

1. □ □轉藥時垂直拿正 右旋再左轉,有嘎聲
2. □ □用嘴吐完氣
3. □ □含住藥瓶快速用力深吸氣
4. □ □閉氣 10 秒
5. □ □能正確使用藥物劑量
6. □ □辨別剩藥及過期
7. □ □吸完藥後漱口

DPI: □Flixotide

1. □ □將上藥扳手扳到底,有喀聲
2. □ □ 用嘴吐完氣
3. □ □含住藥瓶快速用力深吸氣
4. □ □閉氣 10 秒
5. □ □能正確使用藥物劑量
6. □ □辨別剩藥及過期
7. □ □吸完藥後漱口

♦下次回診日期：_____年_____月_____日

Evaluation of the Effectiveness of Inhaler Technique Education in the Respiratory Outpatient Department

Chao-Chien Wu, Chiung-Chu Chen, Mei-Lien Tu, Young-Fa Lai*

Background: Inhaler therapy【metered-dose inhaler (MDI) or dry-powder inhaler (DPI)】is the primary method of managing asthma and chronic obstructive pulmonary disease (COPD). The proper technique of using the inhaler can control the disease. This study was undertaken to evaluate the effectiveness of inhaler technique education by different primary consultants, and to evaluate the impact of inhaler technique reeducation by the special respiratory therapist.

Patients and Setting: 176 outpatients were included, with 55 males (aged 62 ±14 years) [mean ± standard deviation], and 36 females (aged 52 ± 16 years) using MDI, and 38 males (aged 53 ± 16 years), and 47 females (aged 54 ± 14 years) using DPI for their asthma or COPD. All patients had received some instruction on the technique of using the MDI or DPI from doctors, nurses, or pharmacists.

Interventions and Measurements: A checklist on the technique of using the MDI and DPI was used to evaluate the properness of inhaler usage by a special respiratory therapist. Patients with an incorrect technique were given reeducation, and reevaluated by the special respiratory therapist 2 to 4 weeks later.

Results: Incorrect inhaler technique is very common among these patients. To test the difference in the inhaler technique before and after the reeducation by the special respiratory therapist, the two-paired t test was used. These results showed there was a significant difference in the technique of using the inhaler before and after the reeducation, no matter whether the inhaler was a MDI ($t=9.87$ $p<0.001$) or DPI ($t=9.69$ $p<0.001$). We also found the effectiveness of education regarding inhaler usage differed among the technique from various primary consultants.

Conclusions: Most patients had a more correct inhaler technique after education by the special respiratory therapist. We strongly recommend that every hospital have a special program for patient inhaler technique education. ***(Thorac Med 2001; 17: 114-119)***

Key Words: metered-dose inhaler (MDI), dry-powder inhaler (DPI), inhaler technique education, special respiratory therapist.

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Clinical Characteristics of Patients with Coexisting Bronchogenic Carcinoma and Pulmonary Tuberculosis

Wei-Chieh Lin, Yuan-Chih Chu, Chiung-Zuei Chen, Cheng-Hung Lee, Chang-Wen Chen

Several previous studies have demonstrated a higher incidence of lung cancer in patients with pulmonary tuberculosis than in the general population. There has also been evidence that lung cancer patients with coexisting pulmonary tuberculosis may have a poor prognosis. Unfortunately, the early diagnosis of carcinoma in patients with tuberculosis is difficult because bronchogenic carcinoma often masquerades the changes in pulmonary tuberculosis in their radiographic manifestations. Besides, the signs and symptoms of both diseases are frequently non-specific. We retrospectively reviewed the medical records of 26 patients with coexisting bronchogenic carcinoma and pulmonary tuberculosis who were diagnosed between 1989 and 2001. In order to determine whether there is a difference in the clinical and radiological features, the patients who were initially suspected of having carcinoma were compared with those who were not. Most of our patients were elderly and male chronic cigarette smokers. Squamous cell carcinoma was most common histologically, and accounted for 50% of these cases. The patients who were not initially suspected of lung cancer had a significantly higher incidence of sputum positive for acid-fast bacilli ($p < 0.05$), and a more frequent occurrence of lung cancer and pulmonary tuberculosis appearing in the same lung ($p < 0.05$). Both obviously contributed to a delay in the diagnosis of carcinoma. The majority had been in an advanced stage at the time of diagnosis of carcinoma, and only 3 of our patients had lesions amenable to adequate resection. We concluded that the early diagnosis of coexisting bronchogenic carcinoma and pulmonary tuberculosis is difficult, particularly if the sputum is positive for acid-fast bacilli. Only a high level of suspicion and the close surveillance of high-risk patients with pulmonary tuberculosis offer an early opportunity to diagnose and consequently improve the prognosis of this coexisting disease.
(Thorac Med 2002; 17: 120-127)

Key words: pulmonary tuberculosis, bronchogenic carcinoma, squamous cell carcinoma

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Introduction

The incidence of tuberculosis remains high, although morbidity and mortality from tuberculosis have decreased in recent decades [1]. This means that most tuberculosis patients could live long enough to reach the cancer age. Furthermore, the incidence of lung cancer has increased progressively [2]. In patients with pulmonary tuberculosis, particularly, there is a higher incidence of lung cancer than in the general population [3-4]. Several previous studies have indicated an increased incidence of coexisting bronchogenic carcinoma and pulmonary tuberculosis [5-7]. There has also been evidence that lung cancer patients with coexisting pulmonary tuberculosis are associated with a poor prognosis [8]. Difficulties and delays in the diagnosis of these coexisting diseases might contribute to the poor prognosis. Both clinical and radiographic findings have been proposed as a basis for suspecting carcinoma in patients with coexisting pulmonary tuberculosis [5-7]. However, information regarding the comparison of patients in whom the diagnosis of carcinoma was suspected initially with those in whom the diagnosis of carcinoma was delayed is scarce. We therefore undertook this retrospective study to determine whether there is a difference in the clinical and radiological manifestations between the two groups.

Materials and Methods

From June 1989 to April 2001, 1274 patients with pulmonary tuberculosis were admitted to the National Cheng Kung University Hospital, a tertiary referral medical center in southern Taiwan. Of these, 26 have eventually been shown to have coexisting lung carcinoma. Their medical records were analyzed retrospectively for this report.

The diagnosis of carcinoma in these patients was proven histologically by a cytological examination of the sputum, a bronchoscopic, lymph node, thoracoscopic or mediastinoscopic biopsy, and surgical resection. The lung cancer cell types were classified according to the criteria of WHO/IASLC (World Health Organization/ International Association for the Study of Lung Cancer) histologic classification. The staging of the lung cancer was made based on TNM descriptors [9]. Tuberculosis was proven by sputum smears and cultures, and by the histologic examination of the pleural biopsy or surgically resected specimens.

To analyze the clinical and radiographical features, patients were divided into two groups: those in whom carcinoma was suspected at the first consultation and pulmonary tuberculosis was an incidental finding or developed later (Group 1), and those in whom pulmonary tuberculosis was diagnosed first, then intercurrent bronchogenic carcinoma was suspected and later confirmed because of the roentgenographic progression of the parenchymal disease despite anti-tuberculous therapy (Group 2).

The demographic data included age, sex, smoking history, and the time interval of the delay in diagnosis of the cancer. Smokers were defined as those who have or had smoked cigarettes for a period of 6 months or longer. The time interval of the delay in the diagnosis of cancer was defined as the time elapsed from the first presentation of the patients to the time of diagnosis of carcinoma.

Initial chest radiographs taken at our hospital or other hospitals were available for analysis by at least two of the authors. The characteristics of the initial chest radiographs, including upper lung infiltrates, pleural reaction (either fluid or seeding), atelectasis, cavitation, unilateral hilar or parenchymal enlargement, and location of the lesions, were recorded and analyzed.

Data are presented as a mean±SD. The clinical and radiological characteristics of the two groups were compared with the use of the Student's t-test, chi-square test, or Fisher's exact test, as appropriate. A p value < 0.05 was

Table 1. Clinical characteristics of 26 patients with coexisting lung cancer and pulmonary tuberculosis

	Group 1	Group 2	Total	*P* value
Patient number	17	9	26	
Mean±SD age (range)	64.9±7.6 (48–77)	66.8±7.1 (27–87)	65.6±11.4 (27–87)	NS
Gender (male/female)	16/1	7/2	23/3	NS
Smoker (%)	15 (88.2)	5 (55.6)	20 (76.9)	NS
Cell type of lung cancer (%)				
Squamous cell cancer	8 (47.0)	5 (55.6)	13 (50.0)	NS
Adenocarcinoma	5 (29.4)	1 (11.1)	6 (23.1)	
Large cell cancer	0 (0.0)	1 (11.1)	1 (3.8)	
Small cell cancer	2 (11.8)	0 (0.0)	2 (7.7)	
Unspecified	2 (11.8)	2 (22.2)	4 (15.4)	
Lung cancer staging (%)				
I, II, IIIa	3 (17.6)	1 (11.1)	4 (15.4)	
IIIb, IV#	14 (82.4)	7 (77.8)	21 (80.8)	NS
Unknown	0 (0.0)	1 (11.1)*	1 (3.8)*	
Initial positive sputum for acid-fast bacilli (%)	5 (29.4)	8 (88.9)	13 (50)	$P < 0.05$

Group 1, the diagnosis of lung cancer was suspected at the fist time of presentation; **Group 2,** only pulmonary tuberculosis was considered at the first time; # Two patients of small cell lung cancer were extensive stage, who were incorporated into advance stage (IIIb, IV); * One patient died before completely staging; NS = not statistically significant differences.

considered significant. The SPSS for Windows software package was used for statistical analysis.

Results

During the period of our study, the incidence of lung cancer in tuberculosis patients was approximately 2% (26/1274) at our hospital. Their mean age was 65.6±11.4 years (27–87 years), and the male to female ratio was 23:3. There were 17 patients in Group 1 in which the diagnosis of lung cancer was suspected on the initial roentgenographic examination (aged 64.9±7.6 years, range 48–77 years). In Group 2 with the remaining 9 patients, the radiographs were considered to represent only a reactivation of the pulmonary tuberculosis (mean±SD age 66.8±17.1 years, range 27–87 years). There was no difference in age between the two groups. Fifteen of 17 patients in Group 1 and 5 of 9 patients in Group 2 were smokers ($p > 0.05$) (Table 1).

All of our patients had received sputum examinations for acid-fast bacilli at either our hospital or other hospitals. There were 13 (50%) patients whose initial sputum smears were positive for acid-fast bacilli. A more frequent initial positive sputum smear for acid-fast bacilli was found in Group 2 than in Group 1 (88.9% vs 29.4%, $p < 0.05$) (Table 1). The pulmonary tuberculosis of 3 patients was proven by the histologic examination of surgically resected specimens; pleural biopsy was used for diagnosing tuberculosis in one patient; and 8 patients developed active pulmonary tuberculosis after chemotherapy and radiotherapy.

The diagnosis of carcinoma was known at the time of hospital admission in 8 patients. In the remaining 18 patients, lung cancer was diagnosed during the admission period. The diagnosis of carcinoma was proven histologically by sputum cytology in 4 of 22 patients, bronchoscopic brushing or biopsy in 10 of 15, pleural biopsy in 2 of 3, pleural fluid cytology in 3 of 6,

Table 2. Radiological characteristics of initial chest radiographs

	Group 1 (n = 17)	Group 2 (n = 9)	*P* value
Location of lung cancer*			
RUL	8	3	
RML	0	2	
RLL	2	1	
(B6)		(1)	
LUL	3	0	
LLL	4	3	
(B6)	(1)	(2)	
RMB	1	0	
LMB	0	1	
Upper lobe or B6	12	6	NS
Location of main TB lesion			
Upper lung field	9	8	NS
Lower lung field	1	1	
Not obvious§	7	0	
Location of lung cancer and TB#(%)			
Ipsilateral	8(47.0)	9(100.0)	$P < 0.05$
(same lobe)	(5)	(4)	
Contralateral	2	0	
Not sure§	7	0	
Characteristics of initial chest radiographs (%)			
Pleural reaction	7 (41.2)	2 (22.2)	NS
Atelectasis	4 (23.5)	2 (22.2)	NS
Cavitary lesions	2 (11.8)	0 (0.0)	NS
Unilateral hilar or paratracheal enlargement	7 (41.2)	2 (22.2)	NS

*: Chest radiographs showed alveolar filling in bilateral lower lobes in one patient with adenocarcinoma and two similar size of masses in RUL and LLL in another patient; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; B6, superior segment of lower lobe; LUL, left upper lobe; LLL, left lower lobe; RMB, right main brochus; LMB, left middle bronchus; §: no suspecting TB lesions could be identified in initial chest radiographs; #: Ipsilateral, the lung cancer and TB located in same hemithorax; contralateral, the lung cancer and TB located in opposite hemithorax.

mediastinoscopic biopsy in 1 of 1, thoracoscopic biopsy in 2 of 2, scalene node biopsy in 2 of 2, and lung biopsy in 5 of 5. The distribution of the histologic classifications of the lung cancers are shown in Table 1. Squamous cell carcinoma was the most common, histologically. Twenty-one of 26 patients were in an advanced stage (stage IIIb, IV) at the time of diagnosis of carcinoma. There were no statistically significant differences in the distribution of cancer staging between Group 1 and Group 2 (Table 1). The time interval of delay in the diagnosis of carcinoma in Group 2 varied from 1 to 6 months (mean ± SD 4.6 ± 2.0 months).

Both lung cancer and pulmonary tuberculosis have a higher incidence of upper lobe involvement. In 17 patients, the cancer was located on the same side as the main pulmonary tuberculosis lesion. Group 2 had a more frequent occurrence of both lesions appearing in the ipsilateral lung than Group 1 ($p < 0.05$) (Table 2). Radiographic appearances, including pleural

reaction, atelectasis, cavitation, and unilateral hilar or paratracheal enlargement in Group 1 were not significantly different from Group 2. There was also no difference in the numbers of patients, in either group, who had their cancer and main tuberculosis lesions in the upper lobes or superior segment of the lower lobes (Table 2).

Discussion

Our results showed that the incidence of lung carcinoma in tuberculosis patients was approximately 2% in our hospital during the period of study. This high incidence was compatible with previous reports [10], and may be partially attributable to the higher number of older male smokers among our patients. Others have also reported that coexistent tuberculosis and carcinoma of the lung was overwhelmingly a disease of older men [11-12].

The relationship between pulmonary tuberculosis and bronchogenic carcinoma remains unclear. In our series, there was a high incidence of squamous cell carcinoma. Thirteen of 26 patients had active pulmonary tuberculosis at the time of the diagnosis of carcinoma. Our finding that there was no correlation between tuberculosis activity and tumor cell type was similar to that of previous reports in which squamous cell carcinoma predominated as well [6-8, 13-14]. Many investigators have suggested that chronic pulmonary inflammatory disease and fibrosis predisposes the patient to pulmonary neoplasm [7,15]. However, scar cancer, in which several authors have found a high incidence of bronchiolòalveolar cell carcinoma [15-16], was less common in our patients. The high percentage of male smokers may have contributed to this high incidence of squamous cell carcinoma [17]. Another important finding was that there was no difference in cancer cell type, whether the diagnosis of lung carcinoma was suspected initially or not.

Eight patients developed active pulmonary tuberculosis after chemotherapy and radiotherapy in our series. Carcinoma of the lung may have reactivated an old primary tuberculosis lesion by breaking into the old tuberculosis foci [18]. Lung carcinoma could also cause a tuberculous reactivation because of the consequent debility, cachexia, and compromised cellular immunity [19]. In the same way, inactive tuberculosis may be activated by the radiotherapy and chemotherapy used to treat the neoplasm.

We have noticed that the patients in Group 2 had a significantly higher incidence of positive sputum for acid-fast bacilli. As a result, there had been a delay of an average of 4.6 months in the diagnosis of carcinoma. In general, if acid-fast bacilli are demonstrated in the sputum of a patient with a roentgenographic opacity and other features of pulmonary tuberculosis, the tendency is to make a diagnosis of active pulmonary tuberculosis and to treat the patients accordingly.

Only 4 of our patients were in the early stage of carcinoma, and their lesions were amenable to adequate resection. Three of them had a suspected lung cancer initially. The other 22 patients were treated with chemotherapy, radiotherapy, or only supportive therapy because of advanced disease. Twelve of our patients who had maintained follow-up at our hospital died within one year. Chen et al has reported on 17 of 31 patients who were in advanced stages of carcinoma and concluded that survival is poor in lung cancer patients with active pulmonary tuberculosis, as compared with those without tuberculosis [8]. Many factors may have contributed to the poor prognosis of our patients. They often were of an advanced age and had associated pulmonary insufficiency. Recognition of the coexisting malignancy frequently was late in the course of the disease, and the resectability rate was very low. The lower socio-economic class of these patients may have had a great effect on their prognosis, since people of this socio-economic status are less accustomed to seeking medical resources or often refuse to accept diagnostic and therapeutic procedures.

The early diagnosis of coexisting carcinoma

in tuberculosis patients can lead to early surgical resection and good survival. But we found that early diagnosis by means of chest radiographs is disappointing. Both pulmonary tuberculosis and bronchogenic carcinoma have a well-known predilection for the upper lobes, as in our study, which compounds the difficulty in diagnosis since the carcinoma may be superimposed upon the tuberculosis. We found that the patients in whom the diagnosis of carcinoma was not suspected initially had a significantly higher incidence of malignant lesions appearing in the same lung as the tuberculosis lesion. Furthermore, there is no statistically significant difference in radiographic findings, whether the diagnosis of lung cancer is suspected initially or not. Numerous radiographic criteria, however, have been proposed as a basis for suspecting carcinoma in patients with coexisting tuberculosis [1, 6-7], such as the progressive enlargement of the existing lesions under adequate anti- tuberculosis drug therapy, the development of new infiltrates or nodules, superior sulcus infiltrates, unilateral hilar and paratracheal enlargement, thick-walled cavities with irregular lining, segmental or lobar atelectasis, unilateral effusion, osseous involvement, and paralysis of the diaphragm. Bronchogenic carcinoma also frequently mimics the appearance of pulmonary tuberculosis. In our study, Group 2 demonstrated that bronchogenic carcinoma might appear as irregular infiltrates, or as calcified spots in the tumor lesion, or the tumor might be obscured by extensive old tuberculosis lesions, which often mislead physicians into making a diagnosis of pulmonary tuberculosis. Chest CT (computerized tomography) is a more sensitive imaging study to identify tumor lesions than is the chest radiograph. Unfortunately, no patients in Group 2 undertook a chest CT initially, and this led to a delay in recognizing the superimposed carcinoma. The main reason for this oversight is that physicians tend to consider only one disease process at a time. Thus, we strongly suggest that a high degree of suspicion of the possibility of lung cancer should be kept in mind in high-risk patients who are over 50 years old, chronic cigarette smokers, and tuberculosis patients. As soon as the possibility is suspected, a detailed evaluation for carcinoma is indicated. In addition to chest radiographs, an imaging study, such as CT or MRI (magnetic resonance imaging), should be arranged, if available. Repeated sputum cytology has been suggested as a valuable diagnostic tool [6, 13]. Biopsies of the scalene node, pleura, and lung are also very helpful in diagnosing superimposed carcinoma. In cases in which the diagnosis of tuberculosis is not clear-cut, an aggressive diagnostic procedure such as bronchoscopy, thoracoscopy, mediastinoscopy, or thoracotomy should be undertaken to rule out coexisting carcinoma.

In conclusion, the diagnosis of bronchogenic carcinoma superimposed on pulmonary tuberculosis is difficult, particularly if the sputum is positive for acid-fast bacilli. Radiologically, both lung cancer and tuberculosis tend to occur in the upper lung field, and lung cancer usually masquerades as tuberculosis. Clinically, the signs and symptoms of both diseases are frequently non-specific and overlapping. However, physicians caring for patients with pulmonary tuberculosis should strongly consider the possibility of coexisting bronchogenic carcinoma in any adult, and particularly in the smoker who is over 50 years of age. Only a higher level of suspicion and close surveillance of these patients can afford an early opportunity to diagnose and consequently improve the prognosis of this coexisting disease.

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合併有肺癌和肺結核的病人之臨床研究

林偉傑 朱遠志 陳炯睿 李政宏 陳昌文

先前有許多研究顯示，肺結核的病人肺癌的發生率比一般人高，而且這些同時具有肺結核與肺癌的病人的預後也較差。不幸的是，要早期診斷出這些病人是困難的，因為在影像學上肺癌的表現常與肺結核類似，在症狀和病徵上，兩者也皆不具特異性。所以我們回顧性研究 26 位從 1989 至 2001 年間在本院診斷出同時具有肺癌和肺結核的病人。結果顯示，大多數的病人是男性且長期抽煙的老年人，組織學上以鱗狀上皮細胞癌佔 50%為大多數。我們把這些病人分成兩組：一開始即被懷疑有肺癌的病人和僅肺結核被懷疑的病人。我們發現那些一開始不被懷疑有肺癌的病人，其痰液 acid-fast bacilli 呈陽性反應的比例比另一組高 ($p < 0.05$)，而且肺癌和肺結核居於同側肺的比例也比另一組高 ($p < 0.05$)。這兩點很明顯延誤肺癌的診斷。大多數我們的病人癌症被診斷出來已經是末期了，而且僅有三位可以接受手術治療。結論是，要早期診斷出同時合併有肺癌和肺結核的病人是困難的，尤其是當痰液呈陽性 acid-fast bacilli 時。唯有靠臨床醫師對高危險群的肺結核病人保持高度的警覺性，才能提早診斷出合併的肺癌，並改善其預後。 ***(胸腔醫學 2002; 17: 120-127)***

關鍵詞：肺結核，肺癌，鱗狀上皮細胞癌

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Pulmonary Actinomycosis Extension From Lung to Retroperitoneum—A Case Report

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Thoracic actinomycosis is an uncommon bacterial infection characterized by its ability to spread to contiguous tissues without regard to normal anatomic barriers. Together with the reduction of its incidence, the clinical presentation has changed markedly over the past decade. Nowadays, extensive destruction of the chest wall is rarely seen. We report a patient who was admitted with a soft tissue mass on the left lateral chest wall. Radiography and CT scans of the chest showed lower left lobe consolidation with fluid collection and extension to the pleura, chest wall, and retroperitoneum. Pulmonary actinomycosis was confirmed by operation and pathology. Treatment consisted of surgical resection, drainage, and antibiotics. ***(Thorac Med 2002; 17: 128-132)***

Key words: Pulmonary actinomycosis, chest CT, retroperitoneal abscess

Introduction

Actinomycosis is an uncommon infectious disease, usually affecting the cervicofacial, pleuropulmonary, or abdominal region. Pulmonary actinomycosis represents around 20 percent of all observed cases of actinomycosis [1-2], and is caused mainly by *Actinomyces israelii*, which is a normal inhabitant of the oropharynx.

Before the advent of antibiotics, actinomycosis was the most commonly diagnosed "fungal" disease of the lungs, presenting a fairly typical picture of extensive destruction of the chest wall with discharging sinuses [3]. This advanced stage is rarely seen now. In fact, the clinical presentation of actinomycosis has changed greatly, and the incidence of thoracic involvement has declined markedly [3-4].

We described a case of pulmonary actinomycosis presenting with direct extension from the lower left lung to the retroperitoneal space.

Case Report

A 51-year-old male was diagnosed with schizophrenia 25 years ago, and is living in a mental health institution with antipsychotic drug control. He presented with a mass formation, measuring about 10 cm x 10cm, on his left lateral chest wall, of about 3 months' duration. The mass

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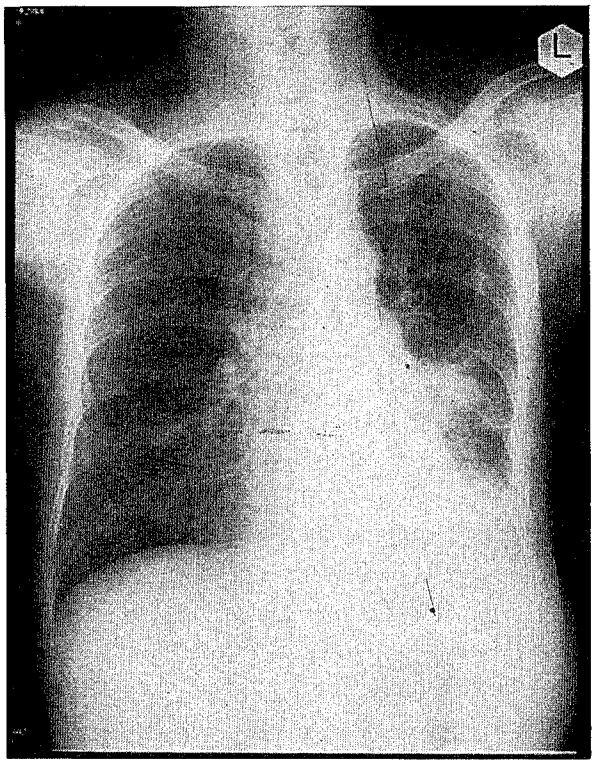


Fig. 1. Chest radiograph PA shows infiltrates in the lower left lung, with a contiguous chest wall soft tissue mass.

was fixed, soft, and non-tender, with no surface erythema. The patient denied the presence of cough, chest pain, or fever.

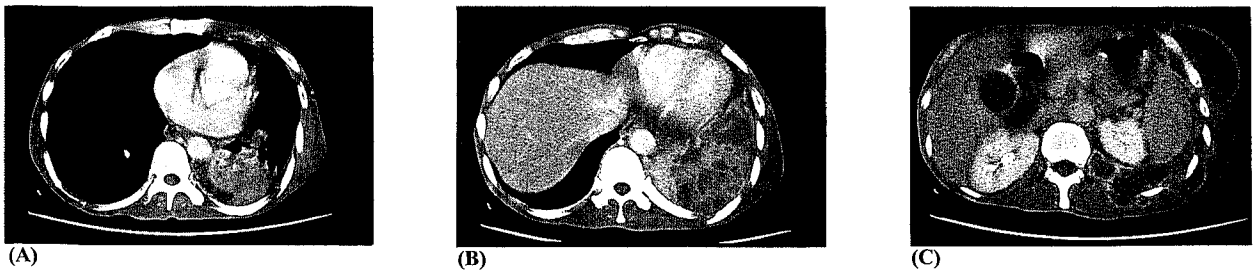
The laboratory investigation showed WBC: 17200/ul with band form 44%, and segment form 39%; a hemoglobin level of 10.3 g/dl and a platelet count of 37600/ul.

A standard chest roentgenogram showed heterogeneous air space lesions in the lower left lung field in association with a bulging soft tissue mass in the contiguous chest wall (Figure. 1). The computerized tomography of the chest and abdomen revealed a consolidation of the lower left lobe with minimal fluid collection, and multiloculated lesions with fluid content at the left lateral and posterior chest wall, which extended to the left retroperitoneal space, with anterior displacement of the left kidney and spleen, but without invasion to the peritoneal cavity (Figure. 2). Percutaneous needle aspiration was performed, and pus was obtained. Gram stains showed neutrophils and gram-positive bacilli.

He was underwent an exploratory thoracotomy, with a wedge resection of the lower left lobe and drainage of the pus in the pleura, subcutaneous tissue of the left lateral chest, and retroperitoneal space. The pathologic report from the surgical specimens showed acute suppurative inflammation with purulent exudates, infected granulation tissue formation, foamy cell aggregation, and actinomyces with sulfur granules formation (Figure. 3). The culture grew *Fusobacterium nucleatum* and Actinomyces species. Postoperatively, high-dose aqua penicillin (18,000,000 U/day) was administered for one month, and continued in a oral form after discharge.

Discussion

Actinomycosis is usually caused by *Actinomyces isralii*, a filamentous, Gram-positive, rod-shaped organism, which is a commensal inhabitant of the oropharyngeal and gastrointestinal tract. It is believed that pulmonary actinomycosis enters the thorax via the bronchial tree, through



(A) (B) (C)

Fig. 2. Enhanced CT scan demonstrates air-space consolidation in the lower left lung field, with minimal pleura effusion (A), a multiloculated abscess formation (B), and invasion to the retroperitoneum and chest wall, and compression to the left kidney and spleen (C).

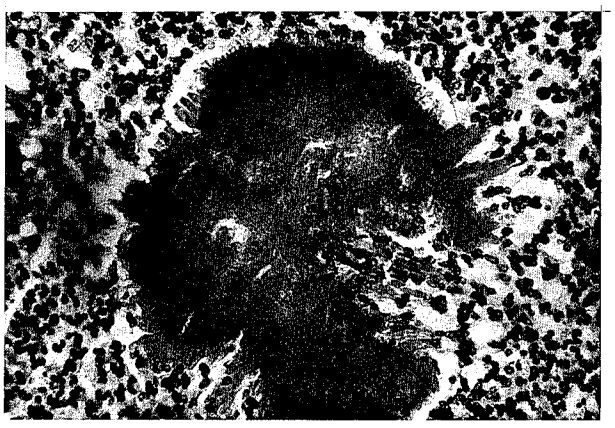


Fig. 3. Actinomycotic sulfur granules surrounded by inflammatory cells (hematoxylin-eosin stain, x400)

the aspiration of contaminated secretions from the oropharynx. Pulmonary actinomycosis produces an acute and chronic inflammatory reaction characterized by abscess formation, draining sinus tracts formation, and dense scarring. This disease, having no respect for anatomical boundaries, may involve the pleuraand the chest wall, and may extend through the diaphragm into the liver [5], the neck soft tissue causing Pancoast's syndrome [6], and the mediastinum causing pericarditis [7]. Retroperitoneal actinomycosis has also been reported masquerading as an inflammatory tumor after an unresolved lower left lobe pneumonia, post-antibiotic treatment [4], or after a traumatic event [8]. In our case, the lower left lobe of the lung was infected with actinomyces presenting as consolidation and abscess formation. The actinomyced extended to the pleural space and the chest wall's subcutaneous and retroperitoneal spaces. It is rare that the classical appearance of draining sinuses did not present in this patient with a huge abscess formation in the chest wall.

Actinomycotic lesions often contain other bacteria, especially *Actinobacillus actinomycetemcomitans* [9]. Although the role, if any, of this organism in the production of disease is unclear, it has been hypothesized that it may enhance the pathogenicity of Actinomyces by lowering oxygen tension or inhibiting phagocytosis [10]. *Bacteroides fragilis*, Peptostreptococcus sp, and *Mycobacterium tuberculosis* werehave also been identified [11]. *Fusobacterium nucleatum* was found in our culture in combination with Actinomyces and this anaerobic bacterium, perhaps, had the effect proposed above.

The radiographic findings reported by Flynn and Felson are a mass lesion, chronic alveolar infiltrates, pulmonary fibrosis, cavitation, transgression of an interlobar fissure, pleural effusion, chest wall involvement, soft tissue swelling, bony destruction, and pulmonary osteoarthropathy [12]. The CT findings were characterized by a peripherally located mass or nodule, and consolidation with adjacent pleural thickening, with lower lobe predominance; the findings may be multifocal, may cross fissures, and often demonstrate cavitations or areas with low attenuation due to abscess formation [11,13].

The treatment of choice for pulmonary actinomycosis is long-term antibiotic therapy with penicillin. Yew et al. used short-course therapy with imipenem-cilastatin for four weeks in eight cases, and the outcome was favorable [14]. Clinical improvement has been reported with isoniazid and rifampin [15], ciprofloxacin [16], and ceftriaxone [17] in case reports, but the optimal duration of treatment and its efficacy merit further investigation. Surgery provides, in some cases, the best method to achieve diagnosis and ultimate treatment [18]; the surgical drainage of the abscess and empyema, as well as the excision of the sinus tracts, are also helpful, and antibiotic coverage should be added soon after the operation [19].

In conclusion, we describe herein a case of pulmonary actinomycosis with a very unusual presentation. The disease appears to have started from the lower left lobe of the lung, and extended to the contiguous chest wall and retroperitoneal space, with only the presentation of a huge chest wall abscess without sinus tract formation. The culture yielded *Fusobacterium nucleatum* in combination with Actinomyces.

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肺部放線菌病從肺部蔓延到後腹腔—病例報告

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肺部放線菌病是個少見的細菌感染，它的特徵是擴散到週邊組織而不遵守解剖構造。現今不但發生率逐漸的減少而且嚴重的個案更是越來越少。本病例為 51 歲的男性病人因為左側胸部腫塊住院，胸部 X 光及電腦斷層掃描顯現出左下葉實質化而有多房性膿瘍，病灶擴散到肋膜、胸壁及後腹腔。經手術後病理診斷為放線菌感染。病人的治療包括左下葉部份切除、膿瘍引流及青黴素抗生素使用。***(胸腔醫學 2002; 17: 128-132)***

關鍵詞：肺部放線菌，胸部電腦斷層掃描，後腹腔膿瘍

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Ectopic Spleen in Thorax—A Case Report

Chia-Man Chou, Cheng-Yen Chuang, Chou-Ming Yeh, Chung-Ping Hsu, Chih-Yi Chen

Splenic ectopia is a rare condition following splenectomy or splenic trauma, and is diffucult to diagnose preoperatively. Thoracic ectopic spleen has never been reported in the past. We report a 53-year-old male who received a splenectomy twenty years ago. Thoracic ectopic spleen was noted as an incidental finding recently and surgical intervention was performed with satisfactory results. ***(Thorac Med 2002; 17: 133-136)***

Key words: ectopic spleen, thoracic, splenectomy

Introduction

Ectopic spleen or splenosis is defined as an autotransplantation of splenic tissue after splenic rupture [1]. The incidence is rare, ranging from 0.2% to 17% following splenectomies in past reports [2-3]. It is always asymptomatic and is diagnosed as an incidental finding; the diagnosis is almost never suspected preoperatively [4]. Several diagnostic tools, including ultrasonography, computerized tomography, and even additional scintography, are helpful [5-6]. If a patient who had undergone splenectomy in the past was found to have incidentaloma, ectopic spleen should be listed in the differential diagnosis and a further survey should be done.

Case Report

This 53-year-old male was a victim of TB pleurisy with complete anti-TB medication for 6 months 10 years ago. He had been involved in a traffic accident, and abdominal blunt injury and splenic rupture was diagnosed. An emergency splenectomy was done at another local hospital at that time, and no other operative findings, such as diaphragmatic hernia or chest trauma, were mentioned. He had been rather well in the following years.

The patient received a health check-up at a local hospital recently, and a nodular lesion in the lower left lung field was incidentally found on the chest X-ray. Thereafter, he visited our hospital for further evaluations. The chest X-ray showed a well-defined opacity in the left retrocardial area, with pleural change and a blunting of the left costophrenic angle (Figure 1). Computerized tomography of the chest revealed a well-defined soft tissue mass in the mediastinum of the lower left lung field (Figure 2). A mediastinal tumor originating from the pulmonary parenchyma was suspected.

A mini-thoracotomy to remove the mediastinal tumor was performed, and a well-encapsulated homogenous brown tumor, measuring 3x2.6x2.4 cm3, was excised. Ectopic spleen was then proved by histology (Figure 3).

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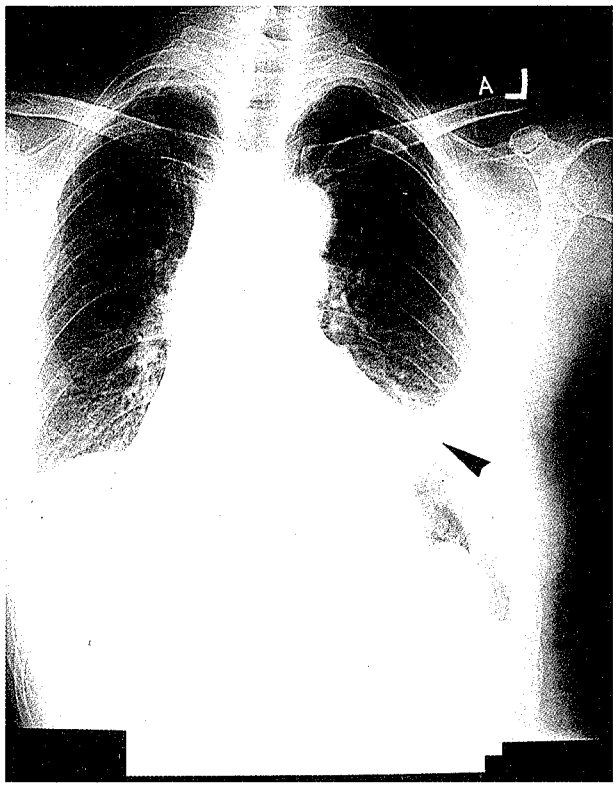

Fig. 1. Chest X-ray shows a well-efined opacity over the left retrocardial area (arrow) with a C-P angle blunting.

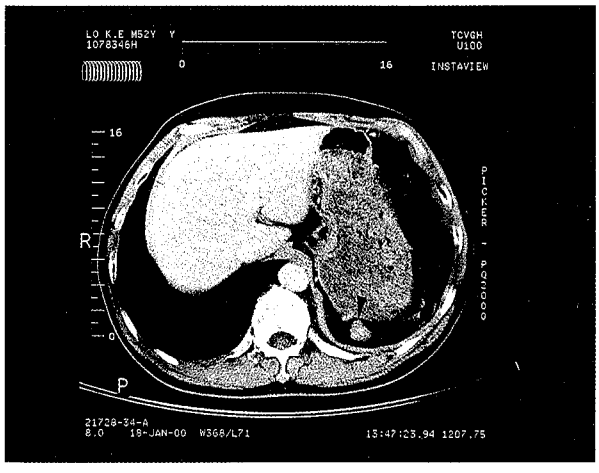

Fig. 2. Chest CT reveals a well-defined soft tissue mass in the mediastinum of the lower left lung field.

The postoperative recovery was uneven and the patient was discharged 5 days after the operation. The patient was doing well at the 18-month follow up.

Discussion

Fig. 3. The ectopic spleen consists of the characteristic features of the spleen: a homogenous dark-red mass, the "red-pulp", that is interrupted by elongated, oval, gray-white islands, ie "white-pulps". H and E stain (×400)

The spleen develops in the upper left quadrant, from the mesenchymal cells in the dorsal mesogastrium near the gastric fundus (Gordon *et al.* 1977). The position of the spleen is relatively constant and fixed (Gordon *et al.* 1977). Some theorist have suggested that wandering spleen results from defective supporting structures, such as the lienogastric, lienorenal, or phrenicocolic ligaments [6-7].

Splenic ectopia or splenosis is a rare condition [8-9] and is defined as an autotransplantation of splenic tissue after a rupture of the spleen [1]. Splenosis is associated with splenectomy or splenic trauma, and occurs frequently after a traumatic lesion of the spleen, and rarely after selective splenectomy for hematological reasons [1]. The incidence of splenic ectopia has ranged from 0.2% to 17% in past reports [2-3]. Pugh in 1946 reported a frequency of 0.2% in 1003 splenectomies at the Mayo Clinic between 1904 and 1945 [2]. A report from Uganda presented 17% of all splenectomies [3]. Ectopic spleen occurs 13 to 20 times more frequently in males, with ages ranging from 20 to 40 years old [10-11]. The clinical munifestation of ectopic spleen is always asymptomatic, and it is diagnosed as an incidental finding [4]. The diagnosis is difficult and is almost never suspected preoperatively [4]. Our patient was a 53 year-old male who also presented ectopic

spleen as an incidental finding. Several investigative diagnostic tools are helpful in the diagnosis of ectopic spleen, including ultrasonography, arteriography, computerized tomography, and even additional scintography. Scintography is valuable in the evaluation of splenic function, since the abnormally positioned spleen will uptake radionuclides. In addition, other reports have favored heat- damaged radioisotope-labelled erythrocytes and suggested that they are superior to using isotope-labelled colloid [1].

Ectopic spleen is located commonly in the peritoneal cavity, retroperitoneum, or scrotal region, due to an abnormality in the embryonic development process [8], but has never been reported in the pleural cavity. If a patient had ever undergone a splenectomy with incidentaloma noted, ectopic spleen should be listed in the differential diagnosis and a further survey should be done.

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位於胸腔之異位脾—病例報告

周佳滿　莊政諺　葉周明　徐中平　陳志毅

異位脾為一罕見疾病，常發生於脾臟切除手術後或脾臟外傷之病人，且一般術前很難正確診斷，但就我們所知，文獻上未曾報告位於肋膜腔中。報告一 53 歲男性病例，於 20 年前曾接受脾臟切除手術，肋膜腔異位脾經手術後確定診斷。 ***(胸腔醫學 2002; 17: 133-136)***

關鍵詞：異位脾，肋膜腔，脾臟切除手術

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Endobronchial Actinomycosis with Nontuberculous Mycobacterial Colonization—A Case Report and Literature Review

Bor-Yiing Jiang, Wen-Bin Shieh, Tung-Jung Huang, Chung-Chin Hua, Teng-Ren Yu

Actinomycosis is a chronic granulomatous disease caused by the fungus *Actinomyces israelii*, and is characterized by suppuration, abscess formation, and eventually the development of multiple drainage sinuses. The number of lesions that mimic actinomycosis of the lung is extensive. We report a case of a 60-year-old women who presented with chronic cough and profuse sputum. The sputum acid-fast stain showed positive (one plus) and the culture yielded nontuberculous mycobacterium. Fiberoptic bronchoscopy revealed an endobronchial tumor with stenotic bronchus. Histologic examination of the biopsy specimen demonstrated *Actinomyces* infection. There was a clinical response to penicillin therapy. ***(Thorac Med 2002; 17: 137-142)***

Key words: endobronchial actinomycosis, nontuberculous mycobacterium, bronchogenic carcinoma

Introduction

Pulmonary actinomycosis is an indolent, infectious pulmonary disease caused by *Actinomyces*, an anaerobic or microaerophilic fungus which may form mycelia [1-2]. There are a number of lesions that mimic endobronchial actinomycosis, such as tuberculosis or malignancy [3-9]. We report a case of endobronchial actinomycosis with suspected nontuberculous mycobacterial colonization.

Case Report

A 60-year-old female patient had a history of nasopharyngeal cancer and received a complete course of radiotherapy 32 years ago, with no recurrence till now. She also had a history of post-tuberculous bronchiectasis and was admitted to our Chest ward 12 years ago (June 1990). At that time, due to a segmental atelectasis of the lower left lobe, a bronchoscopic examination was performed. It revealed 3 polypoid hypervascularity nodules over the orifice of the lower left lobe, whitish material on the medial side of the lower left lobe, and a near occlusion of the lumen. A biopsy was performed, and the pathologic findings were acute and chronic inflammation; the patient was treated with three combined antituberculous agents for 9 months. After that discharge, she had chronic

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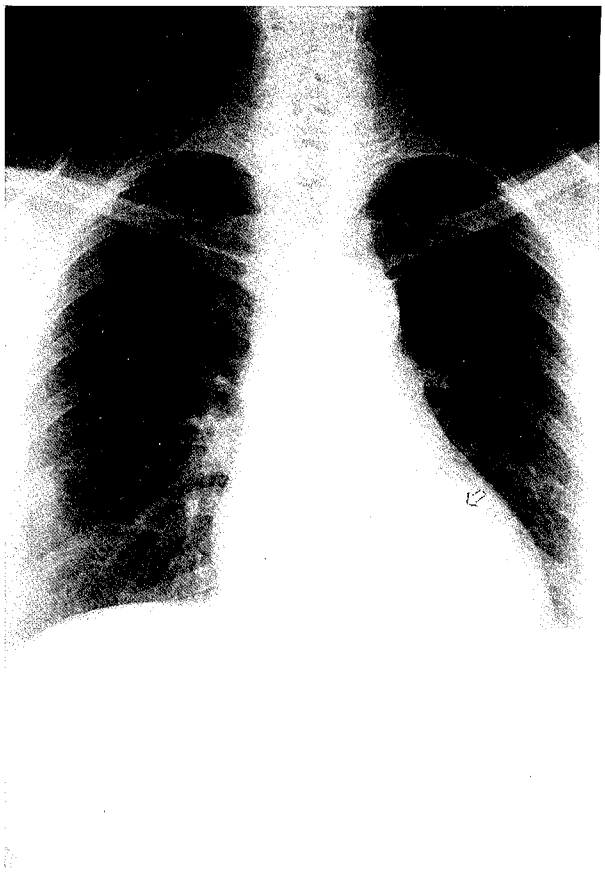

Fig. 1A. The posteroanterior X-ray film of the chest revealed infiltration and a patchy density in the lower left lobe (arrow).

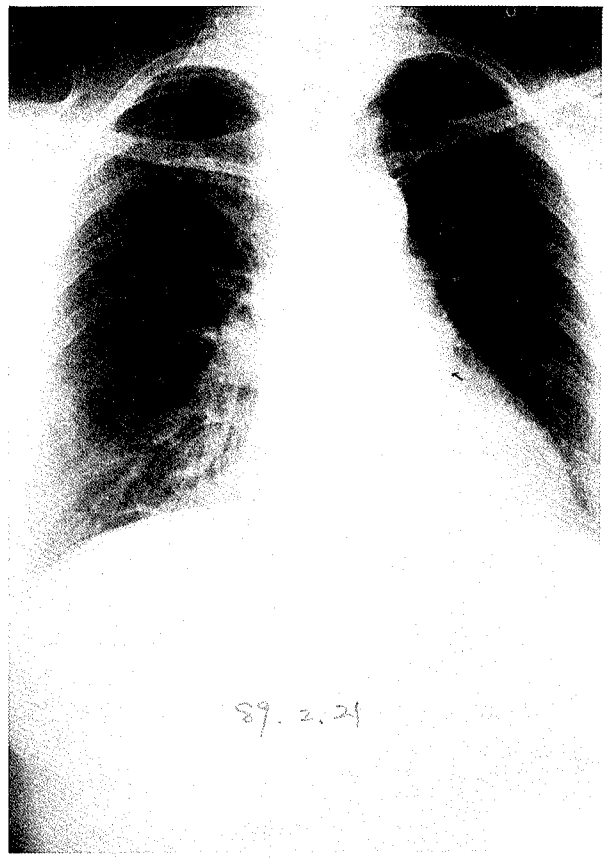

Fig. 1B. The follow-up posteroanterior X-ray film of the chest showed a marked resolution of the pulmonary lesions.

cough, dyspnea, and tachypnea intermittently for about 8 years, and underwent regular management at a hospital in Ilan. Due to a progression of the cough, dyspnea, and profuse sputum, she visited our chest outpatient department on November 22, 1999. The chest film (Figure 1A) revealed infiltration and a patchy density in the lower left lobe. Therefore, she was admitted for further evaluation.

On admission, the vital signs were body temperature 36.5 °C, pulse rate 84/minute, and respiratory rate 22/minute. Physical examination showed mild stridor and bilateral lung field wheezing on auscultation. Laboratory findings revealed: blood urea nitrogen 10 mg/dl, creatinine 0.4 mg/dl, serum protein 6.4 g/dl, globulin 2.9 g/dl, calcium 7.9 mg/dl, and alkaline phosphatase 68 u/L. The leukocyte count was 7600/mm^3 (57.9% neutrophils, 1.6% eosinophils, 4.7% monocytes), hemoglobin was 10.9 mg/mm^3 (MCV 88.4 fl, MCH 28.2 pg, MCHC 31.9 g/dl), and platelet count was 301,000/mm^3. Chest computerized tomography (Figure 2) revealed a lower left lobe collapse with bronchiectasis; coexisting bronchial cancer was highly suspected. Bronchoscopy showed that the lower left lobe was occluded by a tumor mass which had a whitish irregular surface, bled upon touching, and was firm in consistency. A forceps biopsy was performed, and the pathologic findings were numerous sulfur granules denoting colonies of *Actinomyces* (Figure 3). The sputum smear acid-fast stain showed positive (one plus) and the culture result was nontuberculous mycobacterium. She was administered with intravenous aqueous penicillin (3 million U q6h) for 3 weeks, followed by oral penicillin-V (500 mg tid) for 12 weeks, for the endobronchial actinomycosis, and was

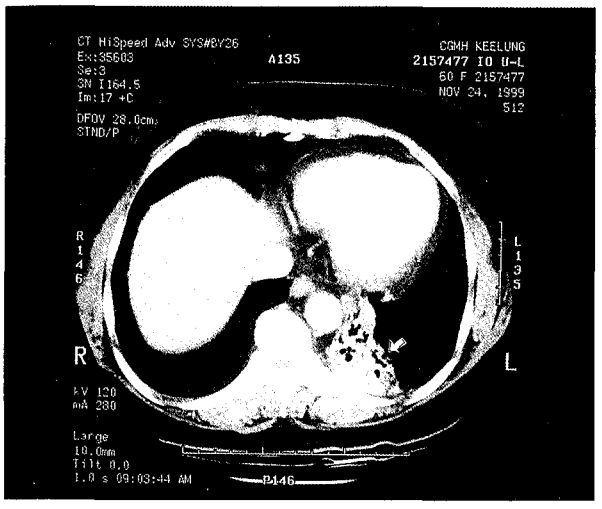

Fig. 2. The computerized tomographic scan of the chest revealed a lower left lobe collapse with bronchiectasis and a suspected tumor (arrow).

also treated initially with four combined anti-tuberculous agents (Isoniazid, Rifampin, Ethambutal and Pyrazinamide) for the mycobacteriosis. After treatment, the pulmonary lesions on the follow-up chest film (Figure. 1B) normalized.

Discussion

Actinomycosis is an infectious disease caused by the *Actinomyces israelii* fungus. The organisms are not highly virulent and are found normally in the human oropharynx; the disease is more commonly found in patients with poor oral hygiene [10], or foreign body aspiration [11-13] (Table 1). This patient with nasopharyngeal cancer who underwent a complete course of radiotherapy was probably at high risk for this disease.

The manifestation of pulmonary actinomycosis is usually an insidious onset with cough, sputum, fever, and weight loss. Hemoptysis and pleuritic pain may occur. The clinical course may resemble pulmonary tuberculosis, lung abscess, or poorly responding pneumonia [10]. In this case of post-tuberculous bronchiectasis with chronic cough and profuse sputum, a tuberculosis reactivation was suspected initially. Therefore, we sent sputum for a mycobacterial smear/culture,

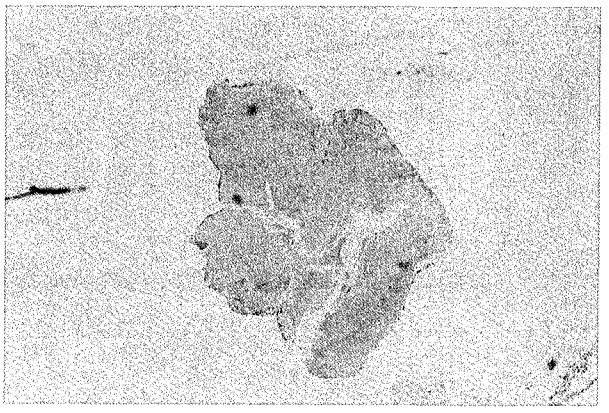

Fig. 3. "Sulfur Granules" (arrow) surrounded by neutrophils in a bronchial biopsy specimen.

and the sputum acid-fast stain showed one-plus positive. This was highly compatible with tuberculosis reactivation, hence treatment with anti-tuberculous agents was given.

The rare case of endobronchial actinomycosis may simulate bronchogenic carcinoma (Table 1). Endobronchial actinomycosis is also an uncommon cause of hemoptysis, and may show a tumor occluding the large bronchi [14]. A review of 13 cases in the English literature found that the lower lung field is usually involved, but with no predominant lobe; however, it is interesting to note that no involvement of the upper lobes has ever been reported. Chest radiography revealed obstructive pneumonia or infiltrates in most cases. Pulmonary actinomycosis is often difficult to diagnose using simpler means, and most cases of pulmonary actinomycosis are diagnosed by transbronchial biopsy or open lung biopsy [6]. The bronchoscopic findings usually reveal a yellow-white or reddish mass. However, in this case, a bronchial tumor of the lower left lobe was highly suspected from the findings on chest radiography and chest computerized tomography. A bronchoscopic examination was then performed, and a polypoid tumor mass nearly occluding the lower left lobe was found. The pathologic examination demonstrated sulfur granules denoting *Actinomyces*. This patient was then treated with penicillin for 15 weeks. Penicillin remains the main drug of choice despite the many other effective drugs available. If penicillin treatment fails, or with allergic patients,

Table 1. Literature review of endobronchial actinomycosis

Author	Case No.	Age	Sex	Predisposing factor	Location	CXR	Appearance	Treatment	Outcome
Miracco C, et al (1988)	1		Male	Aspiration of contaminated material		Normal	A large mass occluding the middle lobe bronchus		
Julia G, et al (1991)	2	58		Foreign body aspiration (chicken bone)					
Ariel I, et al (1991)	3	59	Female	Dental procedure Bronchial lipoma	LLL	Segmental infiltrate	Yellow white mass	Medical (Penicillin G)	Complete resolution
	4	43	Male	Poor oral hygiene	RLL & RML	Consolidation	Irregular red polypoid mass	Medical (Penicillin G + Metronidazole)	Complete resolution
	5	69	Male		RML	Infiltrate	Soft yellow mass		
	6	62	Male		RLL	Diffuse infiltrate with pleural involvement Round shadow in the hilum	Irregular firm infiltrative raised lesion	Gentamicin for sputum culture (Klebsiella organisms)	Expired
	7	40	Male		LLL	Interstitial infiltrate	Fixed smooth whitish tumor	Lobectomy	
Lau KY (1991)	8	60	Male		LLL	Infiltrate	A friable, necrotic mass	Medical (penicillin)	Complete resolution
Dicpinigaitis PV, et al (1992)	9	66	Male	Foreign body aspiration (chicken bone) NIDDM Carious teeth & dental procedure	RLL & RML	Postobstructive pneumonia	A large, pearly gray, slightly friable, polypoid mass	Remove foreign body Medical (IV penicillin then oral penicillin VK)	Gradual resolution
Dalhoff K, et al (1994)	10	57	Male	Nil	RLL	Atelectasis Ipsilateral tracheal deviation	Yellow-white mass	Medical (Cefotaxime + clindamycin then change to amoxycillin/clavulanate)	Complete resolution
Hashimoto A, et al (1996)	11	63	Male		Right lower lung field	Obstructive pneumonia	A mass in the right basal bronchus	Medical (penicillin)	Complete resolution
Lee SH, et al (1999)	12	70	Female	Poor oral hygiene	RLL	Volume loss & focal consolidation	A reddish, polypoid, and slightly friable lesion	Medical (IV penicillin then oral ampicillin)	Symptom improve
2000 CGMH, Keelung	13	60	Female	Nasopharyngeal carcinoma s/p radiotherapy	LLL	Collapse	A yellow-white polypoid mass	Medical (Penicillin G then oral Penicillin V)	Symptom improve

sulfonamides or other alternate antibiotics (including clindamycin, tetracycline, erythromycin, carbencillin, gentamicin, and chloramphenicol, etc.) are effective [6, 10]. Most cases respond well to medical treatment.

Both bronchogenic carcinoma and pulmonary tuberculosis may co-exist with pulmonary actinomycosis [1, 15]. The co-existence of pulmonary actinomycosis and pulmonary tuberculosis is rare. According to previous reviews in the English literature, 1.6% to 2.4% (2 of 85 cases, and 2 of 125 cases) of pulmonary tuberculosis is complicated with pulmonary actinomycosis [1, 4]. The presence of actinomycosis did not influence the course of the pulmonary tuberculosis [3]. The infrequency of tuberculosis-actinomycosis cases may be due to the anaerobic metabolism of the *Actinomyces*, which inhibits the growth of tuberculous bacilli [5]. The co-existence of pulmonary actinomycosis with pulmonary tuberculosis should be kept in mind [4]. However, a coexisting nontuberculous mycobacterial infection is not known to have occurred. The sputum examination of this case only showed one time and one plus of acid-fast bacilli, and the nontuberculous mycobacterium culture suggested the probability of the colonization of this microorganism due to underlying bronchiectasis and bronchial obstruction.

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支氣管放線菌症合併肺部非結核性分枝桿菌症—病例報告及文獻回顧

姜伯穎　謝文斌　黃東榮　花仲涇　游騰仁

放線菌症是由以色列放線菌所引起的慢性肉芽腫疾病，它具有化膿、膿瘍形成或甚至形成多個引流瘻管。有多種疾病疑似肺部放線菌症。我們報告一位以慢性咳嗽併多量痰液的六十歲女性。痰液抗酸性塗片為陽性且培養結果為非結核分枝桿菌。光纖支氣管鏡檢查顯示支氣管性腫瘤併支氣管狹窄。切片生檢組織學檢查證實為放線菌感染且對青黴素靜脈給藥有效。 ***(胸腔醫學 2002; 17: 137-142)***

關鍵詞：支氣管放線菌症，非結核性分枝旱菌症，支氣管性癌

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Single Lung Transplantation for Pulmonary Langerhans' Cell Histiocytosis—A Case Report

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Pulmonary Langerhans' cell histiocytosis (LCH) is a diffuse, smoking-related, interstitial lung disease characterized pathologically by bronchiolocentric inflammation, cyst formation, and widespread intrinsic vascular abnormalities. Despite spontaneous remissions sometimes occurring, the clinical status progressively worsens, and lung transplantation offers a therapeutic option in a few cases. The present case is a 28-year-old man who underwent right single lung transplantation (SLT) for end-stage pulmonary Langerhans' cell histiocytosis. He survived the SLT. Postoperative recovery was uneventful, and his respiratory function improved significantly after 6 months of follow-up. ***(Thorac Med 2002; 17: 143-148)***

Key words: pulmonary Langerhans' cell histiocytosis, single lung transplantation

Introduction

Langerhans' cell histiocytosis (LCH) is a heterogeneous group of conditions of unknown etiology characterized by an abnormal proliferation of antigen-presenting cells of bone marrow derivation known as Langerhans'cells [1]. Lung involvement is most commonly seen in young adults, many of whom are cigarette smokers [2]. Pathologically, pulmonary LCH consists of destructive granulomatous lesions containing Langerhans' cells which cause bronchiolocentric inflammation, cyst formation, and diffuse fibrostic changes [1]. The clinical course of pulmonary LCG is unpredictable. It may either spontaneously regress, or it may progress to pulmonary fibrosis and honeycombed lung. In addition, severe pulmonary hypertension in pulmonary LCH may occur because of proliferative vasculopathy involving muscular arteries and veins, with prominent venular involvement [3].

As there is no definitive treatment, pulmonary LCH has recently been added to the list of indications for lung transplantation [2, 4-5]. We herein report on a patient with end-stage pulmonary LCH and severe secondary pulmonary hypertension who underwent successful right SLT.

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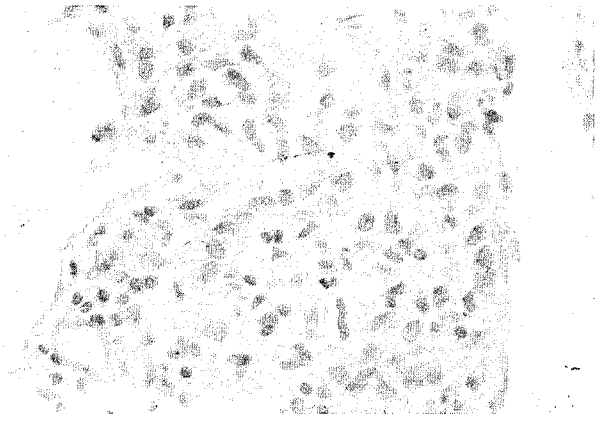

Fig. 1. Lung biopsy showing a diffuse thickened alveolar septum containing inflammatory infiltrates and some scattered Langerhans' cells (H&E stain, original magnification, x20).

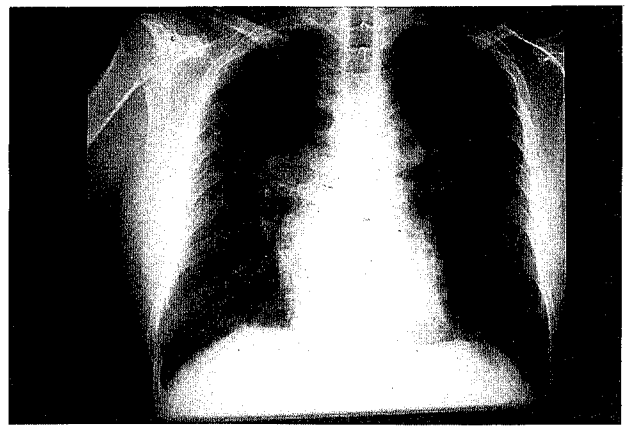

Fig. 2. Chest radiograph revealing a diffuse, bilateral reticulonodular pattern and a bulging appearance in the pulmonary trunk.

Case Report

A 28-year-old man with a 10-pack-a-year history of smoking was diagnosed in 1998 with pulmonary LCH which was based on an open lung biopsy in 1999 (Figure 1). Since 1998, he had repeatedly suffered bilateral pneumothorax treated by chest intubation and intrapleural tetracycline instillation. His pulmonary function test in August 2000 showed a vital capacity of 2.53 L (53% of predicted) and forced expiratory volume in 1 second of 1.56 L (38.1% of predicted). The chest radiograph revealed a diffuse, bilateral reticulonodular pattern and a bulging appearance in the pulmonary trunk (Figure 2). A high-resolution chest computerized tomography (CT) scan revealed a diffuse reticular pattern with cystic lesions in both lungs (Figure 3). A quantitative lung perfusion scan demonstrated a right-to-left perfusion ratio of 48%: 52%. The Tc99m-DTPA alveolar clearance rate showed a rapid alveolar clearance of the radiotracer with a T1/2 of 48 and 52 min (reference value: 75-113 min, SD., 19 min) for the right and left lungs, respectively, indicating impaired alveolar-capillary membrane integrity. Subsequent cardiac catheterization showed an enlarged right ventricle and pulmonary artery pressure of 85/60 (70) mmHg. In addition, nuclear ventriculography showed a right ventricular ejection fraction of 28%. Noninvasive positive pressure ventilation was utilized due to the severe dyspnea and hypoxemia 3 days after this admission, on April 2001.

One week after admission, a 39-year-old female donor became available. The donor had sustained severe cranial trauma and was declared brain dead. The patient then underwent a right SLT. The right lung was chosen because the donated left lung had severe contusions. During the operation, the pulmonary artery pressure was 117/68 (85) mmHg. A cardiopulmonary bypass was initially instituted with a single 21 Fr. cannular in the right femoral vein and right femoral artery. A right SLT was performed using standard methods [6]. After the patient had been easily weaned from the cardiopulmonary bypass, the pulmonary artery pressures decreased to

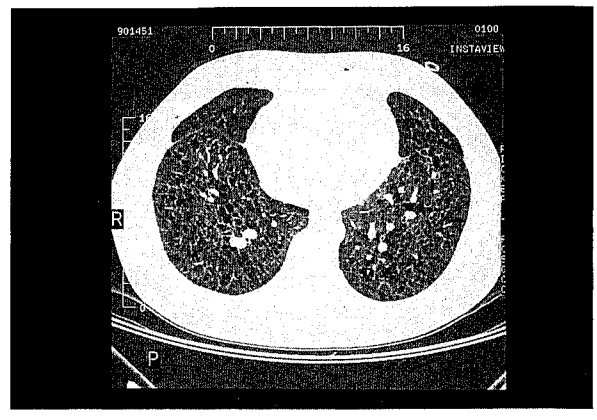

Fig. 3. High-resolution chest CT scan revealing a diffuse reticular pattern in both lungs with multiple thin-walled cystic lesions.

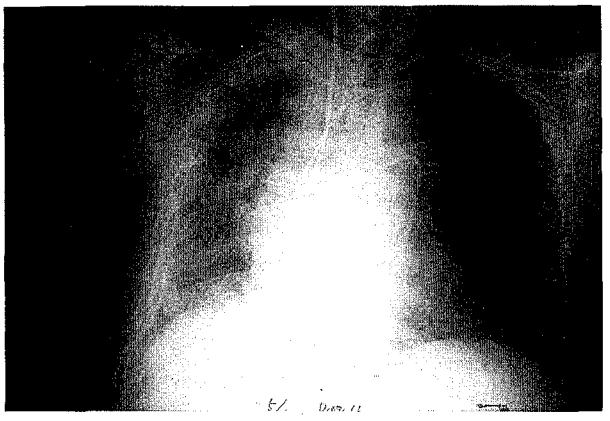

Fig. 4. Chest radiograph revealing diffuse fluffy infiltrates in the right lung field.

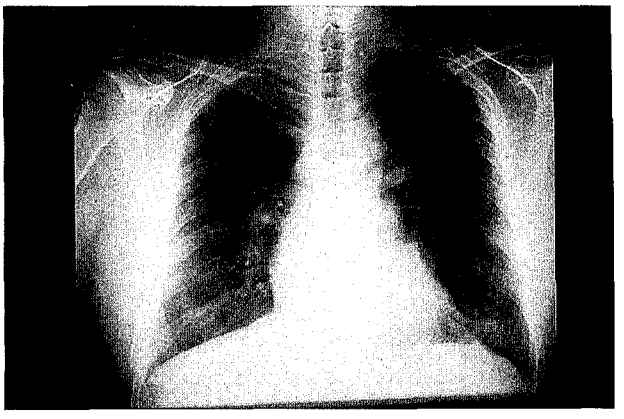

Fig. 5. Chest radiograph revealing that the right transplanted lung fields were within normal limits.

53/36 (43) mmHg. The bypass time was 97 min. The ischemic time for the transplanted lung was 392 min.

Heavy sedation and paralysis, using a continuous infusion of midazolam and atracurium besylate for the maintenance of hemodynamic and gas-exchange stability, were mandatory during the first 2 days after transplantation while the patient was in the intensive care unit (ICU). The subsequent recovery was almost uneventful, except for an acute pulmonary edema revealed by chest radiography (Figure 4) on day 2 after the transplantation. The edema was successfully treated with diuretic agents. On day 5 after the transplantation, pulmonary artery pressure was 32/22 (26) mmHg. The patient was discharged from the ICU 7 days postoperatively. He received our routine immunosuppression regimen, including pre-SLT: azathioprine (2 mg/kg) and intraoperative 1 g methylprednisolone after vascular anastomosis; and post-SLT: equine anti-human thymocyte globulin (2 mg/kg) administered for 5 days, followed by prednisone (1 mg/kg/day). Cyclosporine A (adjusted to a whole blood level of 250-350 ng/ml) and azathioprine were administered intravenously in the immediate post-SLT period, and the patient was converted to the oral formulation as tolerated. Antimicrobial prophylaxis included vancomycin and tienam for 5 days. Cytomegalovirus prophylaxis with gancyclovir was instituted.

Bronchoscopy with a transbronchial lung biopsy at 1 week and again at 3 weeks after transplantation showed no sign of rejection. The bronchial anastomosis was noted to be healing well. Eleven days after the operation, a perfusion lung scan showed 92% perfusion to the transplanted lung and 8% to the native left lung.

The patient was discharged on postoperative day 29. Six months after transplantation, the result of the 6-min walk test was 440 m; the pulmonary function test showed a vital capacity of 3.19 L (68% of predicted) and forced expiratory volume in 1 second of 2.52 L (63.4% of predicted); the chest radiograph was within normal limits (Figure 5). Also, nuclear ventriculography showed a right ventricular ejection fraction of 38%.

Discussion

Since the first successful SLT reported by Cooper *et al.* in 1983 [7], 11, 148 transplantations have been reported to the International Lung Transplant Registry, among which, 58% were SLTs. The overall survival is above 80% at 6 months after lung transplantation (bilateral or single), according to the registry [8].

Pulmonary LCH results from the local accumulation of Langerhans' cells which leads to the formation of a destructive form of interstitial lung disease characterized by a diffuse bilateral reticulonodular radiographic appearance and unique pathologic features [1, 5, 9]. The clinical

course of pulmonary LCH is variable and difficult to predict, and ranges from spontaneous remission to progressive respiratory insufficiency and death [10]. Although the presence of a systemic disease has traditionally been considered a contraindication to lung transplantation, recent reports have suggested lung transplantation for the end-stage lung involvement of lymphangioleiomyomatosis [11], sarcoidosis [12], systemic vasculitis [13], and pulmonary LCH [2, 4-5]

Our patient was an ideal candidate considering his age and motivation. In spite of having end-stage lung disease caused by pulmonary LCG, pulmonary hypertension which progressively deteriorated during the preceding year, and a level of function consistent with the criteria, he was judged to be a suitable candidate for lung transplantation [6]. In addition to the characteristic bronchiolocentric inflammation with aggregates of Langerhans' cells, other inflammatory cells, and fibrosis, the cause of pulmonary hypertension can be explained by the facts of widespread vascular abnormalities with proliferative vasculopathy involving muscular arteries and veins with prominent venular involvement found in a majority of cases [3, 9].

Technically, SLT can be a therapeutic option for end-stage lung disease with pulmonary hypertension [14-15], but it has also been one of the most difficult procedures in lung transplantation. Regarding the use of bypass in this patient during operation, it has been mentioned that bypass has rarely been needed in recipients with obstructive lung disease and has been required in 17 to 41% of patients with restrictive lung disease, but patients with severe pulmonary hypertension are more likely to need a bypass [6]. The theoretical basis of SLT for pulmonary hypertension was based on earlier animal models, which suggested that the pulmonary vasculature after SLT can support the entire cardiac output without an increase in pulmonary arterial pressures [16]. After the operation, pulmonary edema, which fortunately was adequately treated with diuretics and sedation, was noted in this patient. The mechanism for the observed pulmonary edema is not known, but may be related to increased pulmonary capillary permeability, high unilateral blood flow, and a loss of lymphatic drainage. We confirmed the dramatic immediate improvement in pulmonary artery pressure, as well as the improvement in functional class after SLT in this patient, as previous reports have demonstrated [17-19]. Although the advantages of SLT over heart-lung or bilateral lung transplantation are based on in its technical simplicity and the more efficient utilization of a restricted donor pool, SLT for patients with pulmonary hypertension results in lower functional recovery and higher graft-related mortality than do heart-lung and bilateral lung transplantation, as recently suggested by Bando et al. [15]. In addition, significant improvement in right ventricular function has been observed in patients with chronic pulmonary thromboembolic disease and pulmonary hypertension following pulmonary thromoboendarterectomy [20], which was also demonstrated in this patient.

Clinically, most patients with pulmonary LCG have a history of smoking. It is interesting to find that recurrence after lung transplantation has been reported in patients who resumed smoking [2, 5].

In conclusion, a 28-year-old man with end-stage lung disease and secondary pulmonary hypertension due to pulmonary LCH underwent an SLT with excellent pulmonary and right heart function results that persisted beyond 6 months of follow-up. SLT offers a palliative choice for selected patients with end-stage lung disease.

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單肺移植治療肺部 Langerhans'細胞組織細胞增生症—病例報告

陳品儒 杭良文* 林智一** 李秉純*** 黃信哲 施志勳 許南榮

肺部 Langerhans'細胞組織細胞增生症是一瀰漫性，和抽煙病史有關的間質性肺疾，病理上的特徵是細小支氣管有向心性發炎，形成囊泡，以及廣泛性的內因性血管病變。雖然有時會自動緩解，對一些臨床上會逐漸惡化的病例，肺臟移植可以做為治療上的選擇。在此，我們報告一 28 歲男性病例，因為末期的肺部 Langerhans'細胞組織細胞增生症而實施右側單肺移植手術。他手術後存活，平安恢復，經 6 個月追蹤後，肺部功能有顯著改善。 ***(胸腔醫學 2002; 17: 143-148)***

關鍵詞：肺部 Langerhans'細胞組織細胞增生症，單肺移植

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Endobronchial Tuberculosis—A Case Report

Wee Jee Koon, Mei Li Wu*, Ming Pin Wu*, Min Cheng Su**

A 24-year-old female had suffered from chronic cough and dyspnea for five months. She was treated as bronchial asthma though there was no previous history of this condition. Serial chest radiographs within a five-month period had demonstrated no definite lesion. Physical examination revealed localized wheezing in the left hemithorax. However, two sputum examinations did not reveal acid-fast bacilli. Fiberoptic bronchoscopy revealed a stenotic left main bronchus with caseous material obstructing the common orifice of the upper left lobar bronchus. An endobronchial polypoid lesion leading to the total occlusion of the left lingular bronchus was identified. Sputum collected from the bronchoscopic examination demonstrated acid-fast bacilli, and the bronchoscopic biopsy confirmed the diagnosis of endobronchial tuberculosis (EBTB). An antituberculosis regimen was administered for this actively caseating subtype of endobronchial tuberculosis. A follow-up bronchoscopy six months after antituberculosis chemotherapy demonstrated a resolution of the caseous material, and only a slightly stenotic change in the orifice of the left main bronchus. The patient was found to be free of localized wheezes upon physical examination. ***(Thorac Med 2002; 17: 149-153)***

Key words: endobronchial tuberculosis (EBTB), actively caseating subtype

Introduction

Endobronchial tuberculosis (EBTB) is a highly infectious disease. There is a higher incidence among females, and in the main bronchus [1]. Cough is the most common complaint, and is seen in 97% of cases [1]. The diagnosis of EBTB is frequently delayed until the onset of serious bronchial stenosis, with resultant atelectasis and bronchiectasis [6]. Bronchoscopy is the method of choice for an early and accurate diagnosis. Early diagnosis with prompt treatment, before the formation of fibrosis, would be necessary to prevent the complications of endobronchial tuberculosis, such as bronchostenosis [9].

Case Report

A 24-year-old female had suffered from chronic cough and dyspnea for five months. She denied any systemic diseases or previous history of bronchial asthma. She was treated as bronchial asthma with an inhaled corticosteroid and inhaled bronchodilator, but in vain. Serial chest radiographs within a five-month period had

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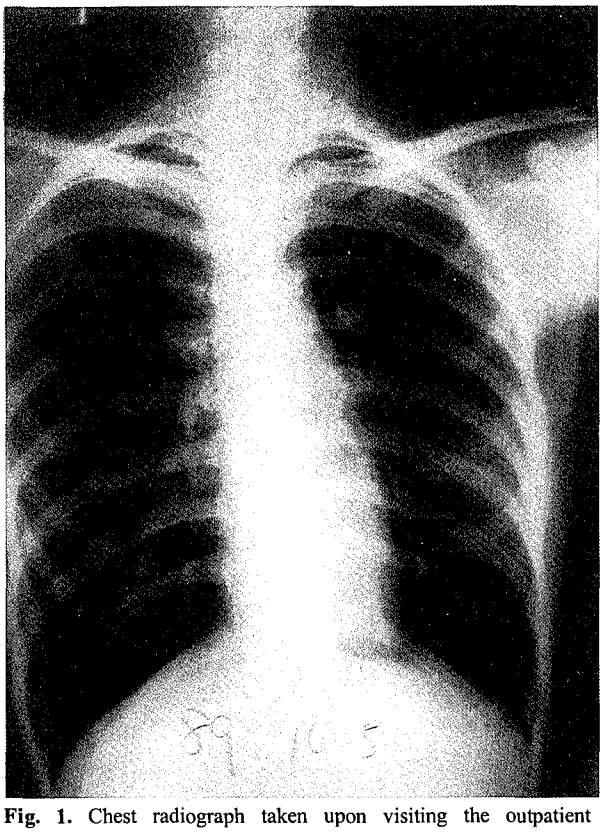

Fig. 1. Chest radiograph taken upon visiting the outpatient department.

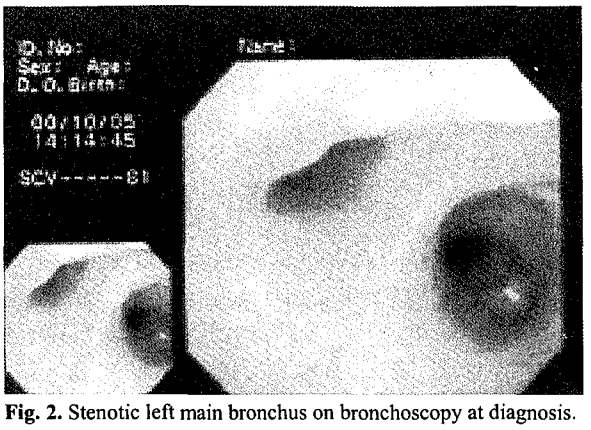

Fig. 2. Stenotic left main bronchus on bronchoscopy at diagnosis.

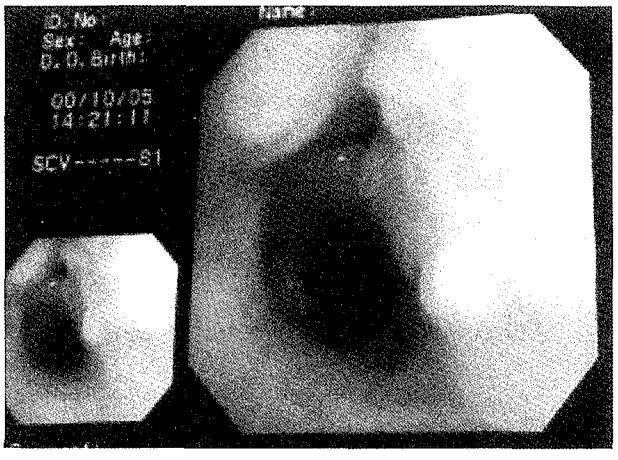

Fig. 3. Actively caseating material packing the upper left bronchus on bronchoscopy at diagnosis.

demonstrated neither atelectasis nor a reticulonodular pattern (Figure 1). Physical exami- nation revealed localized wheezing in the left hemithorax. Two sputum examinations did not reveal acid-fast bacilli. A fiberoptic bronchoscopic examination revealed a stenotic left main bronchus with caseous material obstructing the orifice of the upper left lobar bronchus (Figure 2). An endobronchial polypoid lesion leading to the total occlusion of the left lingular bronchus was identified (Figure 3). Sputum collected from the bronchoscopic examination demonstrated acid- fast bacilli. A bronchoscopic biopsy confirmed the diagnosis of endobronchial tuberculosis (EBTB). This patient was treated with isoniazid, rifampicin, ethambutol, and pyrazinamide (HERZ), but the pyrazinamide was later discontinued due to drug resistance, as determined by a sensitivity test. Negative conversion of the sputum was noted two months after antituberculosis chemotherapy. A follow-up bronchoscopy six months after the antituberculosis chemotherapy demonstrated a resolution of the caseous material at the orifice of the upper left lobar bronchus (Figure 4). In addition, only a slightly stenotic change was observed at the orifice of the left main bronchus (Figure 5), in comparison with the picture observed before the antituberculosis chemotherapy. A complete course of nine months of antituberculosis chemotherapy was administered. The patient was then found to be free of localized wheezes upon physical examination.

Discussion

The primary endobronchial localization of tuberculosis without change on the chest X-ray is a rare clinical entity, and a bronchoscopic examination is most appropriate to reveal such an

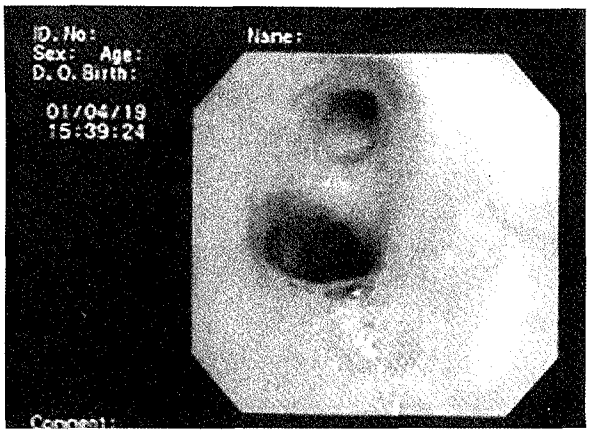

Fig. 4. Resolution of the obstruction of the upper left bronchu orifice 6 months after antituberculosis chemotherapy.

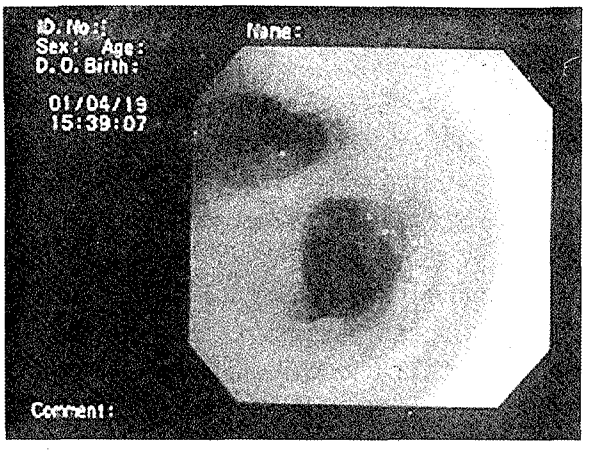

Fig. 5. Slightly stenotic left main bronchus 6 months after antituberculosis chemotherapy.

occurrence [2]. The peak incidence of endobronchial tuberculosis (EBTB) occurs in the second decade, with a 3.8-times higher incidence noted in females than in males [3]. A barking cough with sputum has been the most common symptom (61.1%) [3], and parenchymal infiltration and/or consolidation the most common radiographic finding of the chest (58.6%) [3]. The chest radiograph upon visiting the physician demonstrated no abnormal finding in approximately 13% of cases in one study [4]. The diagnosis of EBTB is frequently delayed until the onset of serious bronchial stenosis with resultant atelectasis and bronchiectasis [6]. The duration of symptoms before the initiation of antituberculosis chemotheray has been long (six months, on the average), and the condition is often treated as bronchial asthma or bronchitis [1]. Sputum smears for acid-fast bacilli have been positive in two thirds of cases, while the remaining one third of cases remains a diagnostic challenge [4].

Patients with pulmonary tuberculosis and radiographic evidence of volume loss or localized wheezes upon physical examination are recommended to undergo bronchoscopy to rule out EBTB. Bronchoscopy is essential for early diagnosis. Hypertrophy with luminal narrowing has been the most common bronchoscopic finding (43%) [3]. Bronchoscopically, the upper right and right main bronchus were most frequently involved (30.5%) [3]. Multiplanar and 3D images appear to be useful for the precise diagnosis and evaluation of the extent of the disease involving the airways, particularly for an evaluation of the focal stenosis of the airways, thus providing valuable information for preparing a road map for bronchoscopy, and for the follow-up to treatment response [10]. The exact pathogenesis of EBTB is not yet completely understood, and the course of EBTB differs according to the type [6]. There are seven subtypes of endobronchial tuberculosis (EBTB), classified by bronchoscopic findings: actively caseating, edematous-hyperemic, fibrostenotic, tumorous, granular, ulcerative, and nonspecific bronchitic [5]. The prognosis of the actively caseating type and the edematous-hyperemic type EBTB is grave, resulting in fibrostenosis in two thirds of patients [6]. The fibrostenotic type EBTB shows no change in or worsening of the stenosis. The prognosis is good for the granular and non-specific bronchitic type EBTB; however, the prognosis of the tumerous type is poor, frequently resulting in bronchial stenosis despite adequate treatment [6]. Antituberculosis chemotherapy is effective in controlling the infection, but does not prevent residual bronchostenosis [6]. Although early corticosteroid therapy in addition to standard chemotherapy is effective in certain groups of EBTB [6-7], one study suggests that corticosteroid therapy would not influence the outcome of endobronchial tuberculosis and that

early diagnosis with prompt treatment, before the formation of fibrosis, would be necessary to prevent the complications of endobronchial tuberculosis, such as bronchostenosis [9].

In this particular patient, complete obstruction of the upper left bronchus was prevented by the antituberculosis chemotherapy, and the left main bronchus healed without clinically significant obstruction. However, a follow-up bronchoscopy is indicated, and surgical intervention should be considered, if EBTB leads to significant narrowing of the left main bronchus. Balloon dilatation and stent insertion is an alternative treatment for bronchial stenosis, if the obstruction of the stent by granulation tissue overgrowth can be prevented [6].

In conclusion, endobronchial tuberculosis must be considered in the differential diagnosis of prolonged cough, especially in those patients whose cough is barking and resistant to antitussive agents, and therefore, bronchoscopy is indicated [8]. Fiberoptic bronchoscopy allows not only a substantial, meaningful assessment of the endobronchial tuberculosis, but also relieves atelectasis, and eventually results in successful treatment with antituberculosis drugs [3]. Future research should focus on the pathogenesis of the bronchial inflammatory reaction and resulting fibrosis to prevent bronchial stenosis in the early stage [6].

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支氣管結核病—病例報告

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這位 24 歲女性慢性咳嗽和呼吸困難已有五個月之久。雖然以前並沒有氣喘病史，卻接受吸入型類固醇及擴張劑治療。間隔五個月的胸部 X 光片並沒有發現任何明顯病灶。兩次痰液檢查並沒有發現結核菌。支氣管鏡檢查顯示左主支氣管明顯狹窄且可見乳酪狀塊狀物填塞左上葉氣管的共同開口氣管內塊狀物完全阻塞了左肺舌葉的支氣管。從支氣管鏡抽出的痰液經鏡檢可見結核菌。經支氣管鏡所作氣管內切片証實了支氣管內結核。對於這種呈現出活動性乳酪狀病變的支氣管內結核，我們採用了複合型抗結核菌藥物治療，抗結核菌藥物治療後六個月,再重作支氣管鏡檢查顯示左上葉支氣管開口處的乳酪狀病變已經消失，而且和抗結核菌藥物治療前的支氣管鏡檢查比較，左主支氣管僅呈現輕微狹窄。理學檢查並沒有單側肺部之喘鳴聲。 ***(胸腔醫學 2002; 17: 149-153)***

關鍵詞：支氣管內結核，活動性乳酪狀病變的類型

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Idiopathic Thrombosed Saccular Aneurysm of the Azygos Vein—A Case Report

Chien-Hung Chin, Yung-Fa Lai, Sui-Liong Wong, Sheung-Fat Ko*, Ming-Jang Hsieh**

The idiopathic azygos vein aneurysm is a very rare abnormality, and frequently mimics a mediastinal tumor. The etiology of this rare entity is unknown, though most generally consider it to be of congenital origin. Computerized tomography is thought to be very important for diagnosing this abnormality, though to date it is not clear what an appropriate therapeutic strategy would entail.

Herein, we present a case of a large, saccular, totally thrombosed azygos vein aneurysm found in a 33-year-old man complaining of cough and chest pain. The chest radiograph revealed a large mass in the right paratracheal region. Enhanced computerized tomography showed some rim enhancement of the mass, only, and magnetic resonance imaging did not demonstrate a flow void. Surgery then confirmed a thrombosed azygos vein aneurysm. ***(Thorac Med 2002; 17: 154-158)***

Key words: azygos vein aneurysm, mediastinal mass

Introduction

An idiopathic aneurysm of the azygos vein is very rare and, to our knowledge, only 16 cases have been reported [1-8]. The aneurysm is usually asymptomatic, except for its becoming larger and exerting some pressure on the surrounding structure, and is often detected incidentally on chest radiographs, on which the aneurysm looks like a mediastinal tumor. Its natural course is unclear and there has been no mention of cases with rupture. Thrombosis occurring in an azygos vein aneurysm is much more exceptional, with only one such case having been previously described [1].

However, we recently encountered a patient with a right mediastinal mass which finally proved to be a large, idiopathic, thrombosed saccular azygos vein aneurysm.

Case Report

A non-smoking 33-year-old male patient

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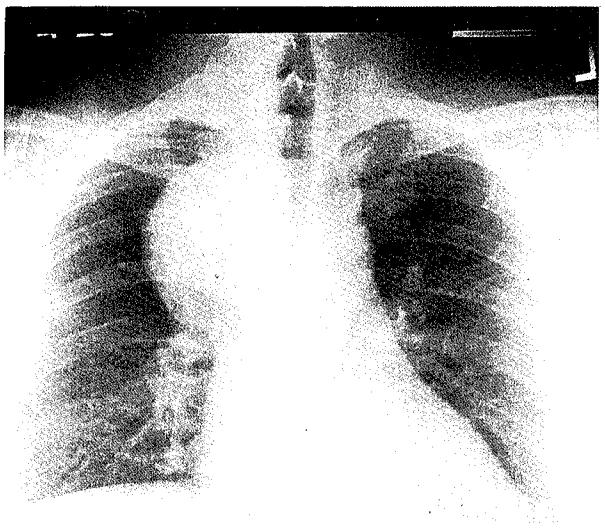

Fig. 1. Chest radiograph showing a large well-defined right paratracheal mass.

was referred to our hospital because of a cough and chest pain that had persisted for two weeks. Chest radiograph and computerized tomography, taken in a local hospital, showed a suspicious right mediastinal tumor mass.

The patient's past medical history was unremarkable, and he denied any significant prior trauma. The physical examination was normal, showing no sign of heart failure, portal hypertension, or abnormal collateral circulation induced by an obstruction of the superior vena cava. Vital signs showed a blood pressure of 130/80 mmHg, body temperature of 36.5°c, pulse rate of 82 beats per minute, and a respiratory rate of 18 breaths per minute. The routine laboratory study, arterial blood gas tension in room air, coagulation ability, and tumor markers (αFP, β-HCG, CEA) were all within normal limits. Neither the electrocardiograph nor the pulmonary function study showed any abnormality. The chest radiograph at our hospital showed an approximately right mediastinal mass with obliteration of the right paratracheal stripe and a mild downward conjunction on the right main bronchus (Figure 1). Pre-enhanced computerized

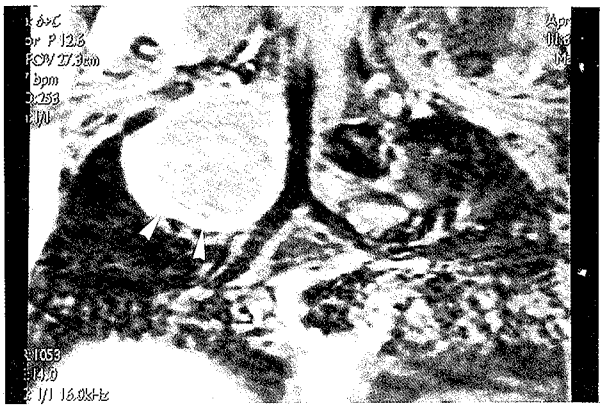

Fig. 2. Magnetic resonance imaging (enhanced T1 weighted) showing the rim enhancement (arrowheads) of the paratracheal mass.

tomography revealed a hyperdense mass with a hypodense rim, and an enhanced computerized tomography revealed some rim enhancement only, suggesting the hyperdense part with a large thrombus. Magnetic resonance imaging demonstrated a slightly hyperintense right paratracheal mass with a markedly hyperintense rim, and enhanced T1 weighted imaging showed the rim enhancement of this mass lesion (Figure 2), further confirming the presence of a large thrombus in the middle right mediastinal mass. This lesion was subsequently suspected to be a tumor with marked central hemorrhaging and thrombosis. Later, a fiberoptic bronchoscopic examination revealed only an external compression of the right wall of the lower trachea and right main bronchi. No endobronchial lesion was seen.

An exploratory right posterior lateral thoracotomy was then performed through the fifth intercostal space. Intraoperatively, we found a paratracheal, retrocaval, large saccular mass measuring about 7x6x5.5 cm and bulging from the azygos arch. The mass was resected along with the azygos arch after the ligation of the distal and proximal azygos vein. There was no evidence of traumatic aetiology such as bleeding, adhesion, or fibrosis around the mass lesion.

The pathology report indicated an aneurysmal-dilated vein containing organizing blood clots (Figure 3). The final diagnosis was a

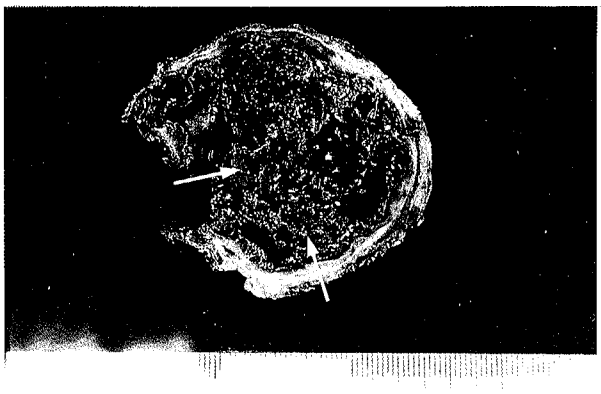

Fig. 3. Cross section of the aneurysm showing total thrombosis (white arrows).

thrombosed saccular aneurysm of the azygos vein.

Discussion

The azygos venous system of the thorax collects drainage from the intercostals and vertebral venous plexus, and terminates in the superior vena cava; it also communicates with the inferior vena cava in the abdomen by means of ascending lumbar veins, thus possibly providing collateral venous drainage for the lower body when the inferior vena cava is obstructed.

The normal diameter of the azygos vein, as measured on a radiograph, is less than 7 mm [2]. Azygos vein enlargement is uncommon and may be due to various causes, including occlusion of the superior vena cava, right heart failure, pregnancy, portal hypertension, azygos continuation of the inferior vena cava, tumor- or thrombosis-induced obstruction of the inferior vena cava, and even traumatic A-V fistulas [3-5]. In these situations, the high blood flow status and increased pressure of the azygos venous system may lead to abnormal vein dilatation. However, in our case, no signs of the above causes of azygos vein enlargement could be found, despite extensive clinical and radiographic investigations; in addition, the patient did not have a past history of chest trauma, or central vein or cardiac catheterization. For these reasons, we postulate that this patient's azygos vein aneurysm was congenital rather than acquired.

Embryologically, the azygos vein is formed by the union of the right supracardinal vein with the proximal portion of the posterior cardinal vein. The right supracardinal vein forms the azygos vein and the proximal portion of the posterior cardinal vein forms the transverse portion of the azygos vein. At this stage, aneurysms may occur, due to abnormal development, at the anastomotic site or along the course of either embryologic vein. [2]. Another possible origin of an aneurysm may be a remnant of the embryologic vein, such as the right posterior cardinal vein, the subcardinal vein, or the primitive subclavian vein, which empties into the transverse portion of the azygos vein [6].

Azygos vein aneurysms are usually asymptomatic and are often discovered incidentally on chest radiographs. Their size may vary in diameter from several centimeters to more than 10 cm [7]. As the aneurysms become larger, they may compress surrounding structures such as the superior vena cava, trachea, right main bronchus, and upper right lobe, leading to associated pressure effects [4,7]. Furthermore, especially in our case, an aneurysm with total thrombosis theoretically carries the risk of pulmonary embolism, although this patient showed no clinical evidence of it.

Kurihara et al. [6] have reported dynamic computerized tomography to be a useful diagnostic tool for the azygos vein aneurysm, by demonstrating the delayed but marked enhancement of the paratracheal mass; however, the typical "flow void" of the vascular structure on magnetic resonance imaging may be absent, leading to the initial impression of a non-vascular structure, such as a solid mediastinal tumor. In fact, this diagnosis may be missed due to a very slow turbulent flow through the narrow entrance of the aneurysm. In our patient, and because there was total thrombosis in the aneurysm, computerized tomography revealed only the rim enhancement of the mass lesion, and magnetic resonance imaging found no flow void. We did not find that

this lesion was a venous aneurysm until we later performed an exploratory thoracotomy.

An appropriate strategy for the treatment of this rare azygos vein aneurysm has not been clearly outlined. The opinion of Atsushi and associates [4] is that it is not necessary to remove the aneurysm if it can be diagnosed preoperatively and if the size of the aneurysm is not very large. However, we think that because of the potential risk of aneurysm rupture and thrombosis with a pulmonary embolism, the resection of the aneurysm is probably necessary. This point of view is also shared by Icard et al [1].

In conclusion, and in spite of its rarity, the azygos vein aneurysm should be one of the differential considerations of a right paratracheal or mediastinal mass.

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自發性栓塞性奇靜脈囊狀瘤—病例報告

秦建弘 賴永發 王瑞隆 高常發* 謝敏暲**

自發性奇靜脈囊狀瘤是一種非常罕見的血管變異，且它常常看起來極似縱膈腔腫瘤。它眞正的病因並不清楚，但一般較傾向先天性來源。電腦斷層被認為是診斷此種血管變異的一項重要檢查。至於此病適當的治療對策則至今仍不清楚。

我們在此報告一個完全栓塞的奇靜脈囊狀瘤的病例。它發生在一位 33 歲男性有咳嗽胸痛的主訴。胸部 X 光顯現出右側氣管旁有一個大的腫塊狀的病灶；胸部電腦斷層顯示出這個病灶僅有周邊對顯影劑顯影而磁振攝影檢查也顯示不出此病灶有明顯血流信號。手術後來証實這是一個栓塞的奇靜脈囊狀瘤。***(胸腔醫學 2002; 17: 154-158)***

關鍵詞：奇靜脈囊狀瘤，縱膈腔腫塊

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Multiple Intrapulmonary Metastases of Atypical Bronchial Carcinoid Tumor—A Case Report and Literature Review

Jong-Rung Tsai, Chau-Chyun Sheu, Jen-Yu Hung, Te-Hung Hsu, Kun-Bow Tsai, Ming-Shyan Huang

The bronchial carcinoid tumor is a low-grade malignant neoplasm which is believed to be derived from neuroendocrine cells, and is subdivided into typical and atypical categories. Owing to the significant difference in prognosis, it is important to differentiate typical from atypical. Atypical bronchial carcinoid tumors have a carcinoid morphology with 2-10 mitoses/2mm^2(10HPF) or necrosis (often punctate). They usually appear as solitary lesions and are more often endobronchial than peripheral. Atypical carcinoid tumors are more prone to metastasis than typical carcinoid tumors. Multiple intrapulmonary metastases are rarely reported, although other sites of metastasis, such as the brain, heart, skeleton, kidney, lymph nodes, etc, have been reported. In this report, we present a 46-year-old female with hemoptysis and progressive malaise. Multiple nodules of varying size on both lungs were found on the chest radiograph. The thoracoscopic biopsy revealed a neuroendocrine neoplasm with amyloid deposition, so a carcinoid tumor of the lung or metastatic thyroid medullary carcinoma was also taken into the differential diagnosis. However, there was a negative thyroid study. We concluded that this was a rare case of atypical carcinoid tumor of the lung with bilateral intrapulmonary metastases. ***(Thorac Med 2002; 17: 159-164)***

Key words: typical, atypical bronchial carcinoid tumor, multiple intrapulmonary metastases

Introduction

The bronchial carcinoid tumor is a low-grade malignant neoplasm comprised of neuroendocrine cells. This tumor accounts for 1%-5% of all lung cancers, and is subdivided into typical & atypical categories. Typical carcinoid tumors compose 80%-90% of bronchial carcinoid tumors, and have a good prognosis. The atypical carcinoid tumor tends to have a higher rate of metastases and a more aggressive course. These tumors are usually located centrally in the major or segmental bronchi, and evidence of bronchial obstruction is the most common radiographic finding. Peripheral carcinoid tumors usually appear as solitary nodules and are asymptomatic. To our knowledge, only rare carcinoid tumors present with intrapulmonary metastasis. [1-4]. We report herein a case of atypical bronchial carcinoid tumor with multiple intrapulmonary metastases.

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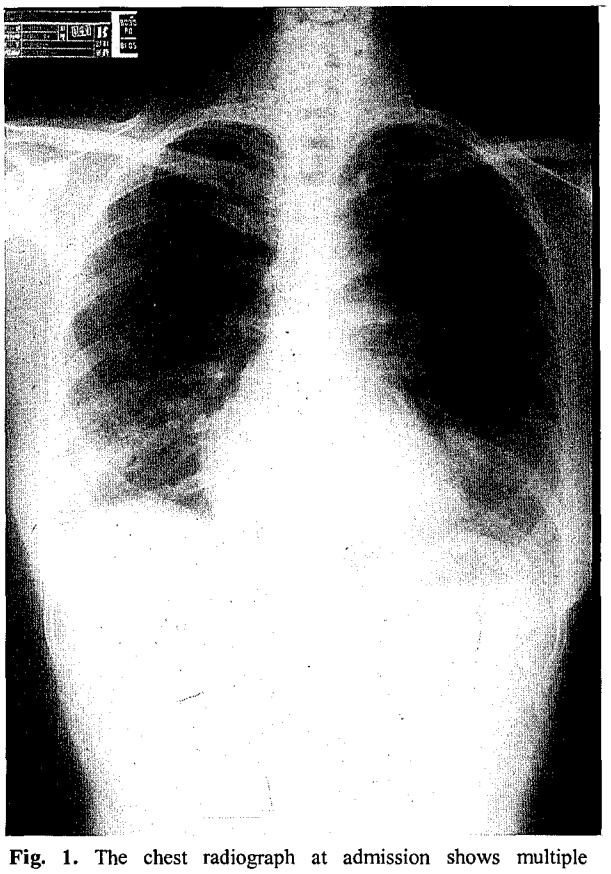


Fig. 1. The chest radiograph at admission shows multiple pulmonary nodules of varying sizes in both lung fields.

Case Report

A 44-year-old female was admitted to our hospital with a history of hemoptysis and progressive malaise. She also felt short of breath, but no obvious fever, chills, and body-weight loss were found. Chest radiography upon admission revealed multiple nodules of variable sizes in both lung fields. (Figure 1) A CT scan of the chest confirmed the presence of pulmonary nodules of variable sizes of in both lungs, and post-inflammatory fibrosis and calcified granulomas in the left apex. (Figure 2) On physical examination, fine inspiratory crackles in both basal lung fields were noticed. Under the suspicion of multiple pulmonary metastases, we arranged an intervention which included transbronchial biopsy, abdomen sonography, bone scan, tumor marker, etc. The lab tests were unremarkable except that

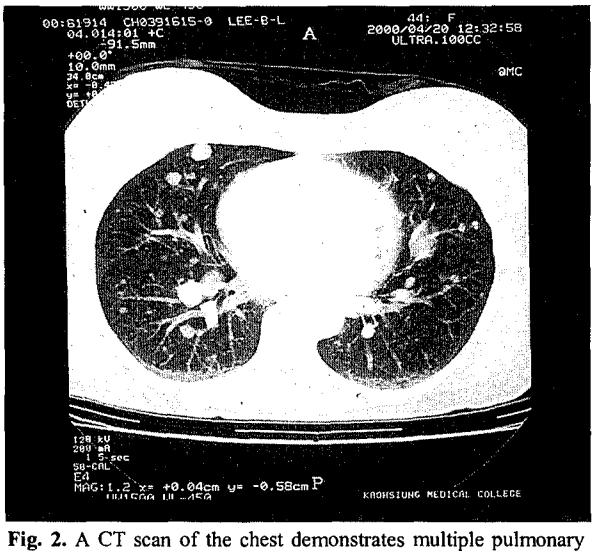
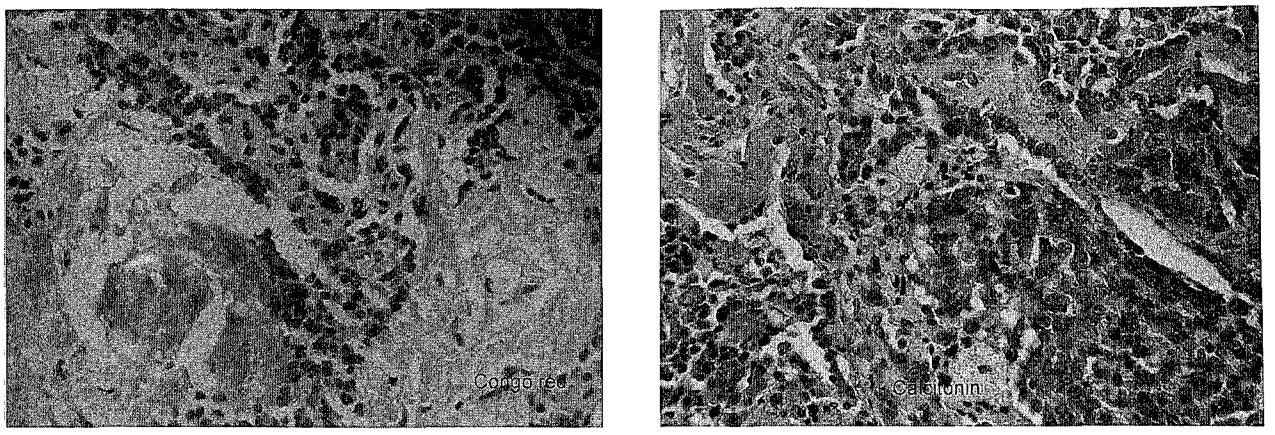


Fig. 2. A CT scan of the chest demonstrates multiple pulmonary nodules in both lungs.

the carcinoembroynic antigen (CEA) was elevated (329 ng/ml). However, no endobronchial lesion was noted by bronchoscopy, and a transbronchial biopsy was done. The result was negative, and a thoracoscopic biopsy was arranged later. The thoracoscopic biopsy results (Figure 3-a, b) showed a nest of round or oval cells, with uniformed, round to oval nuclei, and ill-defined cytoplasm focally. A marked amyloid deposition surrounded by fibrosis and a few inflammatory cells was noticed. The marked deposits of amyloid were highlighted by Congo red stain under a polarized light. Moreover, the immunohistochemical stain revealed a positive reaction with cytokeratin, vimentin, chromogranin, and calcitonin. Based on the above findings, a neuroendocrine neoplasm with amyloid deposition was most likely. Under these circumstances, the following conditions were considered; (1) a metastatic thyroid medullary carcinoma, and (2) an atypical carcinoid tumor of the lung. We performed some thyroid examinations, and the results were as follows: no enlarged thyroid; thyroid echo: single nodular goiter; aspiration cytology: sheets of follicular cells; anisonuclei and colloid lymphocytes. Based on these findings, an atypical bronchial carcinoid tumor was diagnosed.

Discussion



(A) (B)

Fig. 3. The histophathology of the thoracoscopic biopsy shows: (A) Apple-green birefringence highlighting the amyloid deposits with Congo red stain under polarized light. (Congo red stain; original magnification, 56X) (B) The neoplastic cells showing a granular stain with calcitonin immunohistochemically. (Immunohistochemical stain; original magnification, 56X)

Carcinoid tumors which are thought to arise from neuroendocrine cells were first described over 100 years ago by Lucarsch, who found multiple tumors in the distal ileum of two patients at autopsy. Viewed through an electron microscope, carcinoid tumors are typically found to contain numerous membrane-bound neurosecretory granules. These granules are composed of a variety of hormone and biogenic amines. Serotonin is the most characterized substance and is metabolized to 5-hydroxyindoleacetic acid (5-HIAA). The urine concentration of 5-HIAA is helpful in the diagnosis of carcinoid tumors. Carcinoid syndrome demonstrates the triad of flushing, diarrhea, and right-sided-valvular heart disease, which is caused by serotonin and other vasoactive substances [5]. Only a 0-3% incidence of carcinoid syndrome has been found in bronchial carcinoid tumors. Cushing's syndrome is the most common paraneoplastic manifestation of bronchial carcinoid tumors caused by ACTH production. Acromegaly is another paraeneoplastic syndrome.

Carcinoid tumors are classified according to their presumed derivation from the different embryonic divisions of the gut [5]. Pulmonary carcinoids are thought to arise from neuroendocrine Kulchitsky's cells, which belong to the amino precursor of the uptake decarboxylation (APUD) system located in the bronchial mucosa [6]. According to the 1999 WHO criteria for the diagnosis of pulmonary neuroendocrine tumors, there are four types of these tumors, including typical, atypical carcinoid, large cell neuroendocrine carcinoma, and small cell carcinoma. Overall, there appears to be a slight female preponderance, however, some investigators have observed that atypical tumors are more frequently found in men. The mean age at diagnosis is 40-60 years old.

The accurate classification of pulmonary neuroendocrine tumors is essential to determine the prognosis. Histologically, typical carcinoid tumors, which account for 80%-90% of all cases of bronchial carcinoid tumors, have well-defined, generally smooth margins, and may be separated from the surrounding tissue. Paladufu et al have described some differentiating criteria for typical and atypical tumors, including mitosis, necrosis, nuclear DNA, a cellular pattern, and lymph node metastases. [6] But there is still some difficulty in differentiating these two tumors. The 1999 WHO classification utilized a combination of mitotic activity and the presence of necrosis to separate typical from atypical carcinoid tumors, and suggested that atypical tumors have a carcinoid morphology with 2-10 mitoses/2mm^2(10HPF), or necrosis (often punctate). The typical carcinoid tumor has a good prognosis, with 5-year survival

rates ranging from 87%-100%; in contrast, atypical carcinoid tumors have a greater tendency to metastasize and 5-year survival rates of 25% - 69% [3,7].

The main clinical presentation of bronchial carcinoid tumors is an asymptomatic but radiologic abnormality. The other signs and symptoms include hemoptysis, dyspnea, and recurrent or obstructive pneumonitis [2]. Typical carcinoid tumors are located centrally (80-85%), and the remainder are peripheral. Atypical carcinoid tumors are more frequently peripheral, and most occur at a similar incidence in the peripheral and central locations. Therefore, centrally-located tumors and typical carcinoid tumors tend to manifest themselves earlier than the peripheral or atypical varieties. Right middle lobe involvement has the highest prevalence [1-2]. Metastasis is usually found in the atypical carcinoid tumor more often than the typical and 10% of patients present with metastasis [6]. The regional lymph nodes, liver, brain, choriodal, and lung are the reported metastastic sites. Intrapulmonary metastases has been reported only by Fink *et al* [1], McCaughan *et al* [2], Akiba *et al* [3], and Watanable *et al* [4]. Multiple lesions are frequent pathological findings; they are occasionally seen by CT, but usually are tiny and are not recognized radiologically.

The carcinoid tumor is a hypervascular structure and carries a risk for biopsy. Fortunately, significant bleeding is rarely noted; a carcinoid crisis after biopsy was once reported, although carcinoid syndrome is rare in bronchial carcinoid tumors [8,13]. Carcinoid tumors have many histologic patterns, including papillary (sometimes with sclerosis), follicular (resembling the thyroid gland), interstitial etc. The most common consist of sheets (insular pattern), trabeculae, or small nests of cells. Antibodies to synaptophysin, chromogranin A, Leu-7, and neuron-specific enolase (NSE) are among the most common markers used to detect neuroendocrine differentiation in lung carcinomas. The medullary carcinoma is a prototypic neuroendocrine neoplasm which is derived from parafollicular cells within the thyroid, and secretes a characteristic hormone, calcitonin. This type of tumor can metastasize to the lymph nodes, lung, liver, and bones. In our case reported here, varying sizes of multiple intrapulmonary nodules were found radiologically. A neuroendocrine tumor is the impression gained from the immunohistochemical stain. We must be able to differentiate the metastasis of the medullary thyroid carcinoma from bronchial carcinoid tumors. Although calcitonin is a characteristic hormone of the medullary thyroid carcinoma, it has also been found in bronchial carcinoid tumors [10,17]. So, using the serum calcitonin level to differentiate a medullary thyroid carcinoma from a bronchial carcinoid tumor is less significant. Amyloid deposition is another characteristic of medullary thyroid carcinomas, but some cases of bronchial carcinoid tumors with amyloid deposition have also been reported [11,16]. It is very hard to differentiate these two tumors. However, with no defined evidence of thyroid malignancy, a primary lung carcinoid tumor is then considered.

As previously mentioned, carcinoid tumors have a fair prognosis compared to other lung cancers. For the peripheral type of bronchial carcinoid tumors, a lobectomy or pneumonectomy is done. For centrally-located tumors, lung preservation surgery (ie, bronchial sleeve resection) is recommended when possible [2,7]. Several poor prognosis factors, including a regional lymph node, tumor size, large or small cell morphology, a mutation of the p53 gene and a DNA aneuploid, have been reported [1-3,7,12,18]. Chemotherapy, radiotherapy, and promising new altered experimental agents are still under investigation [14]. The carcinoembryonic antigen (CEA) has been used as a tumor marker for follow-up [5,9].

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非典型肺類癌合併多發性肺內轉移一病例報告與文獻回顧

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肺類癌是一種低度惡性之腫瘤，起源於神經性內分泌細胞，可分成典型與非典型兩型。因兩型之預後有相當之差別，所以如何去分類是相當的重要，其分類依據為細胞分裂數及壞死之有無。肺類癌常以單一病變表現，氣管內腫瘤比週邊常見，非典型肺類癌比典型肺類癌易有轉移現象。多發性肺部轉移則不常見，腦、心臟、骨頭、腎臟、淋巴等也偶有例子報告。我們報告一名46歲女性因咳血及全身性衰弱求診，X光發現兩側肺野有數個大小不一的結節。經胸腔鏡切片診斷為肺類癌或轉移性甲狀腺髓質瘤，因甲狀腺檢查並無明顯病變，所以診斷為非典型肺類癌。 ***(胸腔醫學 2002; 17: 159-164)***

關鍵詞：典型肺類癌、非典型肺類癌、多發性肺部轉移

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High-Grade Bronchial Mucoepidermoid Carcinoma—A Case Report

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Bronchial mucoepidermoid carcinoma is a rare lung tumor comprising only 0.1%-0.2% of all primary lung cancers. Histologically, this neoplasm is characterized by the coexistence of mucus-secreting cells, squamous cells, and cells of an intermediate type. It can be found in all age groups, usually presenting with symptoms associated with airway irritation or obstruction, such as cough, hemoptysis, dyspnea, or wheezing. The treatments and outcomes vary depending on the histological grades and the clinical stages. We herein report a case of high-grade bronchial mucoepidermoid carcinoma in a 38-year-old woman with skin, breast and spine metastases. The patient presented with four cutaneous nodules and one in the right breast. She had dry cough for 6 months, which, however, was ignored. An excisional biopsy of one of the cutaneous nodules was reported as metastatic carcinoma. Chest radiography revealed a central lung mass. Bronchoscopy found an endobronchial tumor in the anterobasal segmental bronchus of the left lower lobe. The bronchoscopic biopsy proved the diagnosis of mucoepidermoid carcinoma. Despite aggressive chemotherapy and radiotherapy, the disease progressed rapidly with spinal metastasis and bronchial obstruction. The patient died 75 days after diagnosis. ***(Thorac Med 2002; 17: 165-171)***

Key words: mucoepidermoid carcinoma, Lung cancer, endobronchial tumor

Introduction

Bronchial mucoepidermoid carcinoma (MEC) is a rare lung tumor originating in the mucous glands of the large airways, and comprises only 0.1%-0.2% of primary lung cancers [1-2]. It was first recognized by Smetana et al in 1952, who reported it as a third histological type of bronchial adenoma behind carcinoid and adenoid cystic carcinoma [3]. According to the 1999 WHO/IASLC histological classification of lung and pleural tumors, MEC along with adenoid cystic carcinoma were classified as carcinomas of the salivary gland type [4]. Histologically, this neoplasm is characterized by the coexistence of mucus-secreting cells, squamous cells, and cells of an intermediate type [5]. Patients with bronchial MEC have ranged from 3 months to 78 years of age [6]. Almost all

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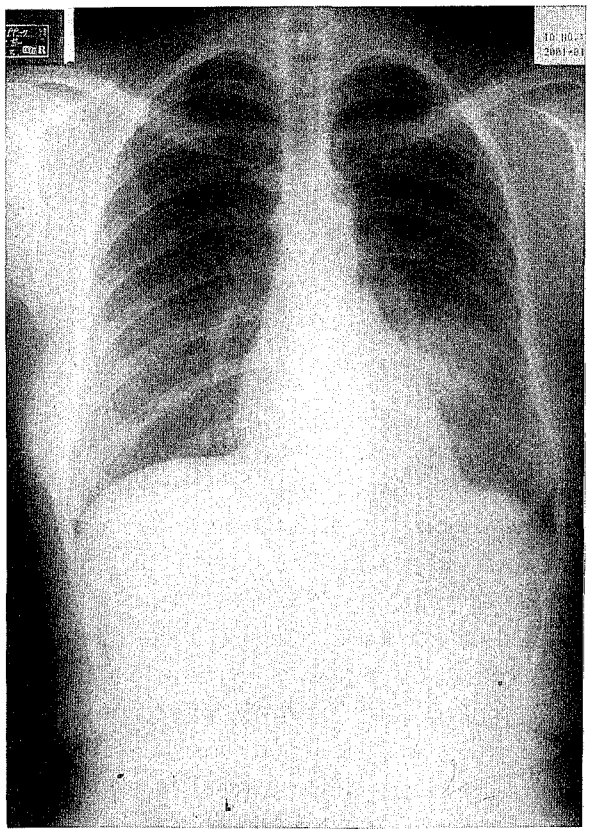


Fig. 1. The chest X-ray reveals a lung mass near the left hilum.

tumors found in young patients were of the low-grade variety [2]. High-grade tumors characterized by high-mitotic counts (>4 per 10 high power fields), cellular atypia, pleomorphism, and areas of necrosis and hemorrhage, tended to occur in older patients [7-8]. Although most of the bronchial MECs behave in a benign fashion and can be successfully treated by surgical resection, without recurrence [9], up to 20-25% of this type of tumor are high-grade tumors, and thus might have a malignant course. Herein, we describe a case of high-grade bronchial MEC with a malignant clinical course.

Case Report

A 38-year-old woman presenting with multiple cutaneous nodules was referred to our hospital in December 2000, because an excisional biopsy of one of these nodules was reported as metastatic carcinoma. This patient

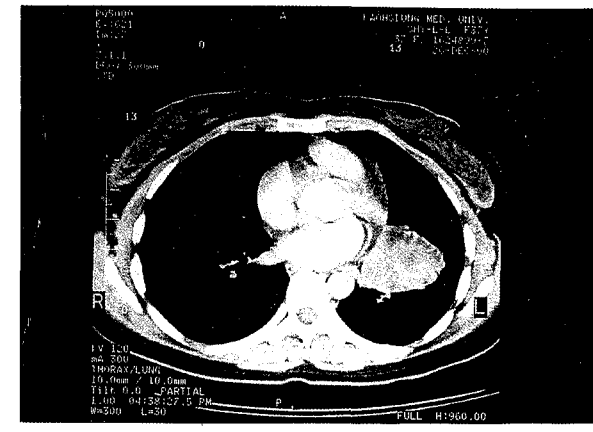
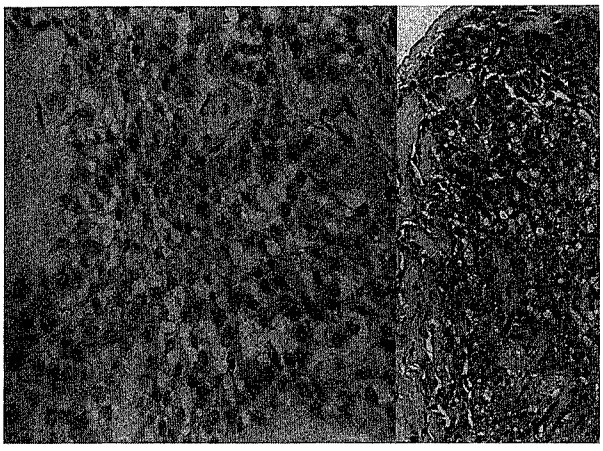


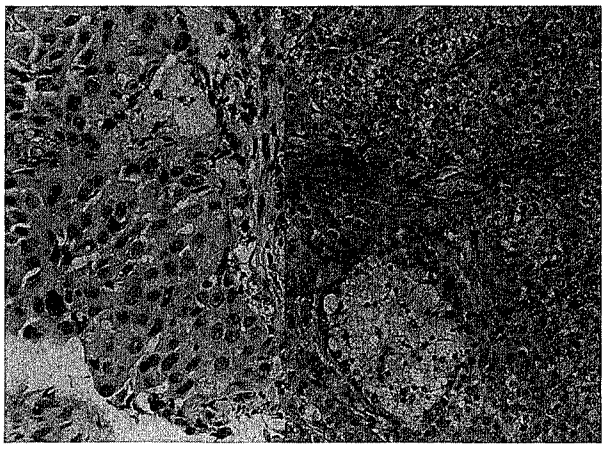
Fig. 2. Chest CT demonstrats a well-defined lobulated tumor with heterogeneous enhancement occupying the left hilum and central zone of the left lower lobe.

was a nonsmoker, and the medical history was unremarkable except for an episode of left lower lobe pneumonia 2 years before admission. The family history was also unremarkable. She had had dry cough for 6 months, however, the symptom was so mild, and there were no other associated respiratory symptoms such as hemoptysis, dyspnea, chest pain or fever that she did not see a doctor until multiple cutaneous nodules had appeared. The physical examination on presentation revealed four cutaneous nodules located in the right shoulder, right abdomen, left upper arm, and left thigh, and one nodule in the right breast. These nodules were all firm, movable, and non-tender in character, ranging in size from 1 to 2 cm. The breathing sound was clear, and all other physical findings were within normal limits. Chest radiography revealed a roughly 6-cm centrally-located lung mass (Figure 1). Chest computerized tomography (CT) demonstrated a well-defined lobulated tumor with heterogeneous enhancement, occupying the left hilum and central zone of the left lower lobe (Figure 2). Fiberoptic bronchoscopy found an endobronchial tumor obstructing the orifice of the anterobasal segmental bronchus of the left lower lobe. The tumor was covered with some necrotic tissue.



(A) (B)

Fig. 3. (A). Sheets or organoid structure of the mucous cancer cells with brisk mitotic activity in the bronchial tumor. (H&E stain; original magnification, 56X) (B). The intracytoplasmic mucoid droplets of mucous cancer cells demonstrated by PASD stain. (PASD stain; original magnification, 28X)



(A) (B)

Fig. 4. (A). Foci of pleomorphic squamoid cancer cells with a tendency to form an intercellular bridge in the bronchial tumor. (H&E stain; original magnification, 56X) (B). Intermediate or squamoid cells admixed with mucous cancer cells in the breast tumor. (H&E stain; original magnification, 28X)

The pathologic findings of the bronchoscopic biopsy demonstrated a coexistence of the mucus-secreting cells, squamous cells, and cells of an intermediate type, confirming the diagnosis of mucoepidermoid carcinoma. The brisk mitotic activity, pleomorphism, and presence of a necrotic area helped us to classify it as a high-grade tumor (Figure 3). The nodule in the right breast was subsequently excised and proved histologically identical to the bronchial tumor (Figure 4).

Because of the advanced stage, surgical intervention and radiotherapy were abandoned. The patient underwent chemotherapy with a regimen of gemcitabine 1000 mg/m^2 on days 1, 8, and 15, and cisplatin 100 mg/m^2 on day 1. During the first cycle of chemotherapy, the patient complained of progressive back pain. A bone scan and spinal CT revealed multiple spinal metastases. Palliative radiotherapy was then started concomitantly. The regimen of the second cycle of chemotherapy was changed: docetaxel 25 mg/m^2/wk, 5-fluorouracil 1600 mg/m^2/wk, leucovorin 200 mg/m^2/wk, and cisplatin 20 mg/m^2/wk. However, the tumor still grew and finally obstructed the left main bronchus. The patient died of respiratory failure and sepsis 75 days after diagnosis.

Discussion

Mucoepidermoid carcinoma is a rare lung cancer that usually involves the proximal bronchi or trachea. The symptoms, such as cough, hemoptysis, fever, dyspnea, wheezing and stridor, are usually related to bronchial irritation and obstruction. Rare cases have presented as airway hyperresponsiveness [10], unilateral hyperlucent lung [11], cardiac tamponade [12], intracranial metastasis [13], and cutaneous metastasis [14]. Up to 28% of the patients may be asymptomatic [2].

Suzuki KH *et al* have reviewed 104 reported cases in Japan [15]: 29 of these 104 cases were tumors located in the lobar bronchus, 22 in the segmental bronchus, 20 in the periphery, 16 in the main bronchus, 11 in the trachea, and 6 in the truncus intermedius. Among those known as low-grade MEC (n=60) and high-grade MEC (n=24), the latter seemed to have a more prominent peripheral location (14/24) than the former (5/60). Mass and atelectasis (35 and 31 of the 104 cases, respectively) were the most common findings on chest roentgenograms.

According to Kim TS *et al* [16], MEC appears on CT as a smoothly oval or lobulated airway mass. Several clues have helped us to determine the endobronchial location of the tumors: the non-spherical shape of the tumor with its long axis parallel to that of the nearest major bronchovascular bundle; and associated findings of distal bronchial dilatation with mucus impaction, postobstructive pneumonia, atelectasis, or air trapping. Because of their airway origin and frequent central location, most of the MECs can be visualized and diagnosed by fiberoptic bronchoscopy. Grossly, these tumors may vary in size from less than 1 cm to greater than 6 cm in dimension. They are polypoid and are usually covered with respiratory mucosa. However, high-grade tumors appear more infiltrative. Both lymphangitic and hematogenous routes of dissemination have been demonstrated. The usual metastatic sites are the regional lymph nodes (48%), other portions of the lung (25%), bone marrow (25%), distant lymph nodes (18%), the adrenal glands (14%), brain (14%) and, skin (14%) [12].

Mucoepidermoid carcinomas are initially perceived to be slow-growing neoplasms with benign biologic behavior. However, many authors have reported malignant-type tumors with widespread metastases [17-21]. Therefore, several authors have attempted to predict the malignant clinical course from the histological appearance, dividing them into low-grade and high-grade categories [17,22]. However, discordance between the tumor's histological grade and biological behavior, ie, low-grade tumors with a malignant course, have been reported [13,22]. It can be said that the histological malignancy level of this tumor does not always agree with its clinical malignancy level. In our case, the histological features showed high-grade malignancy, and the clinical course was as malignant as our histological prediction.

Mucoepidermoid carcinoma is a common malignant salivary gland tumor that can arise less commonly in the esophagus, lacrimal passages, bronchus, pancreas, prostate, thymus, and thyroid [23-24]. Primary mucoepidermoid carcinomas of the skin and breast have been reported, but are rare [25-26]. In our case, the tumors were found not only in the bronchus, but also in the skin and breast. It was difficult to identify the origin histologically because they shared the same histological features. However, a main mass in the lung, and the first clinical presentation of respiratory symptoms followed by the skin and breast nodules, helped us to classify this tumor as a primary lung tumor with metastasis.

Patients with low-grade MEC generally have an excellent prognosis. Local recurrence or metastases is rare. Several authors have reported the successful treatment of low-grade MEC with surgical resection alone [15,27]. Pneumonectomy or lobectomy were the standard procedures in the past, but more cases are receiving conservative sleeve resection or bronchoplasty now. The prognosis of high-grade MEC has been reported to be variable. Hartman reported survival to be less than 2 years [28], and others have reported the median survival to be less than 6 months. It has been debated whether or not these results were based on the inclusion of adenosquamous carcinoma, which is the most important differential diagnostic consideration with high-grade MEC. Although some authors have suggested that these two tumors are indistinguishable histologically, adenosquamous carcinomas have more intercellular bridges and lack the transitional areas from low- to high-grade tumors. Squamous cell carcinoma in situ is not usually seen in adenosquamous carcinomas, and these tumors are usually much larger (and often more peripheral) than MECs. The optimal treatment for high-grade MEC is still controversial, lacking large data support. Combined use of surgical resection and radiation therapy is recommended [7]. The role of chemotherapy is palliative and should be restricted to patients with metastatic disease [29-30]. Because the unexplained chronic cough was ignored, our patient presented in an advanced

clinical stage. Chemotherapy was among the most appropriate treatment options for this patient. However, it failed.

Bronchial MEC carries a more favorable prognosis in children than adults, because almost all bronchial MECs in children are low-grade tumors, and can be cured [28]. Clinical studies have found an overall mortality of less than 30% in an adult population with bronchial MEC, much better than that of the common bronchogenic carcinomas [8].

In conclusion, we again emphasize the importance of an evaluation of the cause of any unexplained cough lasting for more than 3 weeks. Chest radiography, a lung function test, or even bronchoscopy for detecting any possible airway diseases, should be considered based on the clinical conditions. Bronchial mucoepidermoid carcinoma, a rare primary lung cancer originating from the mucous glands of the central airways, usually presents as airway irritation or obstruction, and should not be viewed uniformly as a low-grade malignant tumor. It can sometimes be highly malignant, with an aggressive clinical course. Low-grade MEC can be easily cured by surgical resection, without recurrence. However, the optimal treatment for high-grade MEC requires further study.

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高度惡性支氣管黏液類上皮癌一病例報告

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劉景勳* 蔡坤寶* 黃明賢

支氣管黏液類上皮癌為一種罕見之肺腫瘤，約佔原發性肺癌的0.1%至0.2%。組織學上，可見黏液細胞、鱗狀細胞及中間型細胞同時存在，依其表現可區分為低度惡性(low-grade)和高度惡性(high-grade)腫瘤。它可在任何年齡發生。患者之臨床症狀通常與氣道之刺激及阻塞有關，如咳嗽、咳血、喘鳴或呼吸困難。治療及預後則視組織學上之分級和臨床之分期而有所不同。雖然此腫瘤大多具有良性的臨床病程，但其中20%-25%屬高度惡性腫瘤，其臨床表現亦較為惡性。

一位44歲的女性病患，於左下肺葉支氣管發生黏液類上皮癌，併有皮膚、乳房及脊椎等多處轉移。患者在因皮膚及乳房結節求診前已經咳嗽近半年，而皮膚結節之病理切片報告為轉移癌。胸部X光檢查發現在近左肺門處有一肺腫塊。支氣管鏡檢查則發現在左下肺葉前支有一氣道內腫瘤，切片病理報告証實為黏液類上皮癌。雖經積極之化學治療及放射治療，病情仍急速惡化，患者於診斷後75天死亡。此種罕見的原發性肺癌，臨床症狀並無特異性；但經由影像學及支氣管鏡檢查，很容易發現腫瘤的存在，加上組織學表現有其特色，診斷並不困難。低度惡性腫瘤可以外科手術切除治癒，高度惡性腫瘤之癒後不一。本例即為一具高度侵犯性，併多處轉移之病例，其治療方式仍需多方探討。 ***(胸腔醫學2002; 17: 165-171)***

關鍵詞：黏液類上皮癌，肺癌，支氣管內腫瘤

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Ultrasound-Guided Transthoracic Core Biopsy for the Diagnosis of Mucosa-Associated Lymphoid Tissue Lymphoma (MALToma) of the Lung—A Case Report

Chih-Yen Tu, Te-Chun Hsia, Chih-I Lin*

Mucosa-associated lymphoid tissue lymphoma (MALToma) of the lung is a rare low-grade B cell lymphoma. Pulmonary MALToma is difficult to diagnose because most patients with MALToma of the lung are asymptomatic or just present with a long and indolent course. The definite diagnosis of pulmonary MALToma is based on histological studies. In the past, specimens were obtained by thoracotomy, thoracoscopy, or anterior mediastinotomy, because the image modality and cytopathology were not as advanced as today. However, recent advances in the technique of ultrasonographic image guidance have greatly improved safety and diagnostic accuracy. We report a 40-year-old man with pulmonary MALToma who presented with dry cough and right-side chest pain, and was finally diagnosed using echo-guided transthoracic core biopsy, without any complications. ***(Thorac Med 2002; 17: 172-177)***

Key words: Mucosa-associated lymphoid tissue lymphoma (MALToma), ultrasound, core-biopsy

Introduction

MALToma of the lung is a rare low-grade B cell lymphoma, which was initially termed a "pseudolymphoma" by Salzstein in 1963 [1]. This term describes a group of tumors composed of small polyclonal lymphocytes with mixed cellular infiltrates, and germinal centers without local nodal involvement. Pulmonary MALT lymphomas arise in sites normally lacking of lymphoid tissue, but are preceded by chronic antigen stimulation, usually autoimmune, which results in the accumulation of lymphoid tissue. The diagnosis of the disease requires an adequate specimen. Transbronchial biopsy, video-assisted thoracoscopic biopsy, and open lung biopsy have been used to diagnose MALToma of the lung [2-4]. Recent publications have supported the role of radiologically guided core-needle biopsy in the diagnosis of malignant lymphoma under certain clinical conditions [5-6]. We present a case of pulmonary MALToma that was diagnosed using an ultrasound-guided transthoracic core biopsy.

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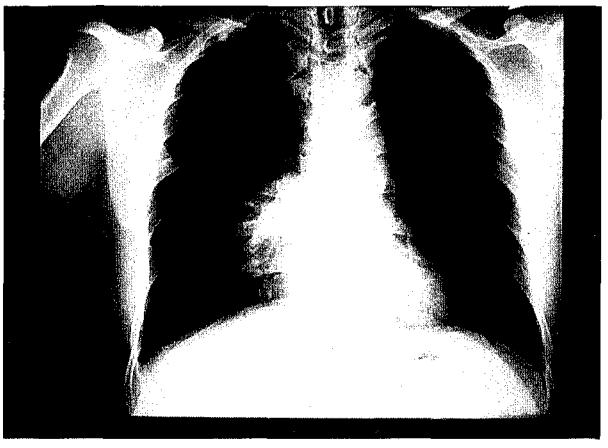

Fig. 1. Chest X-ray reveals a middle right lung mass

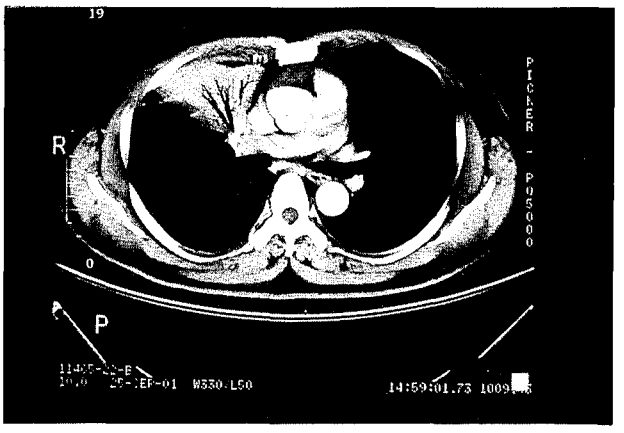

Fig. 2. CT scan of the lung reveals a solitary mass with air-bronchograms of the middle right lung

Case Report

A 40-year-old male office manager was a lifelong non-smoker and had no relevant medical history. Two years before this admission, he was found to have a middle right lung alveolar consolidation by chest radiography on routine health exam. He had no discomforting symptoms, and there was no definite diagnosis even by transbronchial biopsy. After that, he was lost to follow-up until this admission. He began having episodes of dry cough and right-side persistent chest pain and was admitted to China Medical College Hospital for a further survey of his right-side pulmonary alveolar consolidation.

On physical examination, he was well-nourished and not ill-looking. No obvious abnormal findings were noted throughout the rest of the physical examination. The laboratory data, including complete blood cell count, differential count, biochemistry, blood gas, and coagulation parameters, were all within normal range.

The chest radiography revealed a right-side pulmonary alveolar consolidation lesion (Figure 1). Chest computerized tomography (CT) showed a focal mass (6x5.5x5 cm), with internal air-bronchograms, in the middle right lung (Figure 2). He received a bronchoscopic exam, and no endobronchial lesion was found. A transbronchial lung biopsy of the middle right lung was done, but these specimens provided no definite diagnosis. A real-time ultrasound (US) was performed with a 3.5 MHz convex transducer through the anterior intercostal space, and a homogeneous, hypoechoic mass (6x5 cm) was noted beneath the chest wall (Figure 3). Doppler ultrasound revealed no blood vessels or blood flow around or within the tumor.

The patient was scanned in a supine position. We assessed the tumor margin and measured the depth from the skin to the plane of the tumor by US. He was instructed to breathe deeply and hold his breathe about 10 to 15 seconds. For the tumor core biopsy, we inserted an 18-gauge needle (Temno, Allegiance, USA) by a vertical route through the anterior 4th intercostal space, using a freehand approach. We reserved a safety margin of about 2.5cm to avoid inserting the puncture needle into the aerated lung region. Four specimens were obtained smoothly, and there was no pneumothorax or hemoptysis after the procedure.

The histological findings of these core biopsy specimens showed a low-grade B cell lymphoma of the MALT type, involving the lung parenchyma with diffuse atypical lymphoid infiltrates and multi-foci of lymphepithelial lesions, a feature characteristic of the mucosa-associated lymphoid tumor (Figure 4). Immuno-histochemical studies revealed that the lymphoid cells were diffuse and strongly CD20 positive,

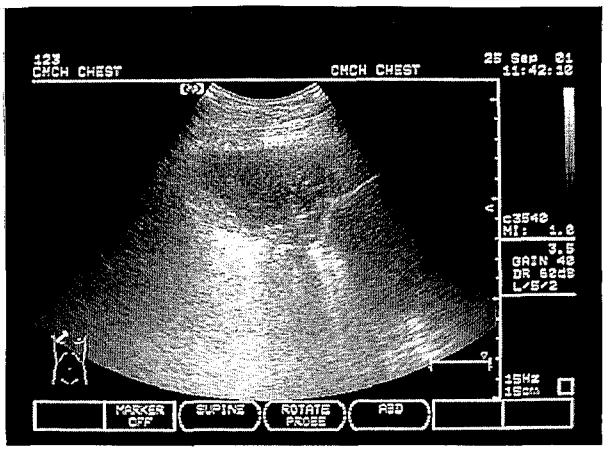

Fig. 3. Chest US shows a homogeneous, hypoechoic mass (6x5cm) under the chest wall

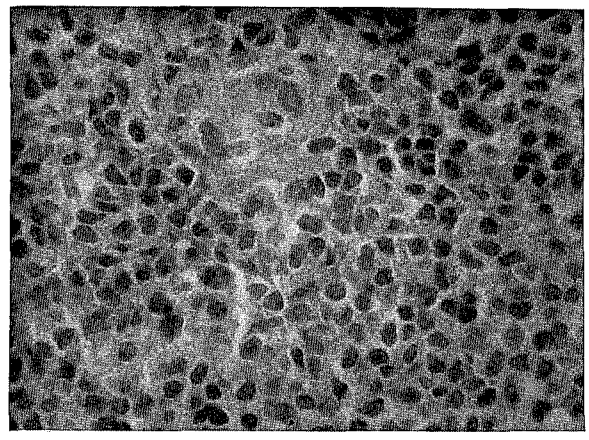

Fig. 4. Core-biopsy specimen shows diffuse atypical lymphoid infiltrates and multi-foci of lymphepithelial lesions (H&E x400)

but negative CD3, which was consistent with an immunophenotype of the MALToma [4,7]. Chemotherapy with cisplatin and vincristin, and radiotherapy for his pulmonary MALToma were instituted. He regularly follows up at our hospital, and was well at this writing.

Discussion

In the early 1980s, Isaacson and Wright [8] first put forth that MALTomas were unlike comparable low-grade nodal lymphomas. They later extended these observations to include a number of other extranodal low-grade B-cell lymphomas [9]. Unlike nodal low-grade B-cell lymphomas, MALT lymphomas tend to remain localized for prolonged periods and seldom involve the bone marrow at the time of presentation. The stomach is the most common site of MALT lymphomas; other sites of MALToma include the bronchus, salivary gland, thyroid gland, thymus, orbital organs, bladder, and female genital tract [10]. Pulmonary MALToma is very rare and often difficult to diagnose.

Its presentation is seen most frequently in the sixth decade, with a slight male predominance. Most of the patients are asymptomatic or just present with a long indolent course of cough, dyspnea, fatigue, body weight loss, or pleuritic pain. Cell characteristics can explain the long indolent course in that the lymphoma proliferates slowly and the lymphocytes infiltrating the interstitium do not compress the airway in the early stage of pulmonary MALToma. As the disease progresses, the expanding interstitium compresses the airway, causing the patients to suffer from the above symptoms. The chest radiography is nonspecific and variable: ranging from simply a solitary nodule to multiple nodules, or diffuse alveolar consolidation [11]. Kinsely *et al* [12] reviewed the computerized tomographic (CT) findings of 11 patients with pulmonary MALToma. The most common CT appearance was consolidation with air bronchograms, correlating histologically with the cellular lymphocyte infiltrates expanding the interstitium and compressing the adjacent alveoli, producing air bronchograms.

None of the above clinical symptoms, laboratory data, chest radiography, or CT findings are specific enough to diagnose pulmonary MALToma. The definite diagnosis is based on an adequate biopsy specimen. Transbronchial biopsy, bronchoalveolar lavage, and sputum cytology have been used to diagnose primary pulmonary lymphoma. However, the yield of sputum for the cytological diagnosis of peripheral lung cancer is only 10% to 25% [13], and the low diagnostic accuracy of transbronchial biopsy, if there are no

endobronchial lesions, also restricts the technique in the diagnosis of pulmonary lymphoma. Many patients with pulmonary lymphoma finally underwent an open lung biopsy or video-assisted thoracoscopic surgery to obtain the specimen. But these diagnostic procedures induce suffering, and carry the risks of general anesthesia. Image-guided transthoracic needle biopsy (TNB) has been developed to diagnose pulmonary masses. Fluoroscopic or computerized tomographic (CT) guidance are well-established techniques capable of providing sufficient material for the cytological, microbiologic, and histological diagnosis of lung lesions, and these techniques can also provide extremely high diagnostic yields (sensitivity 80% to 90%). But there are some limitations to these two techniques because of the ionizing radiation and time consumption.

The first report of the use of US to guide the TNB of pulmonary masses was by Chandrasekhar et al in 1976 [14]. However, the poor visualization quality with the not well-developed biopsy needle modality gave rise to many complications, and so was not widely adopted. Recent advances in US technology, including the quality of real-time US imaging and the precise puncture device, has made US-guided biopsy an increasingly valuable and convenient diagnostic tool for thoracic lesions.

US-guided transthoracic fine-needle aspiration has been proved to be a useful diagnostic technique for peripheral pulmonary masses [15-16]. The procedures are carried out with a fine needle (21 gauge or smaller). Its accuracy for peripheral pulmonary nodules, chest wall lesions, and mediastinal tumors is 88% to 100%. However, the tiny specimens are not adequate for detailed histological studies, including the accurate identification of tumor cell type, the degree of cell differentiation, and the immunocytochemical studies. These are important clues for the diagnosis of pulmonary lymphoma. The greatest concern of using fine-needle aspiration, rather than core-biopsy, under US guidance, is the complications, such as the possibility of bleeding or pneumothorax. But the Doppler US can easily differentiate vascular lesions from solid masses, and help to avoid puncturing great vessels around or within the mass when doing a core biopsy. Yang *et al* [17] have compared the safety and diagnostic accuracy of the US-guided transthoracic large-core cutting biopsy with that of fine-needle aspiration, in 149 patients who had a thoracic tumor. Fine-needle aspiration achieved 88% positive cytological results, but provided only 70% accuracy of histological cell type. However, a large-core cutting biopsy could provide up to 97% accuracy in a confirmative histological diagnosis, and could be as safe as find-needle aspiration.

We used the freehand approach to insert an 18-gauge needle (Temno, Allegiance, USA) through the skin directly into the plane of the view of the transducer, without a guide. With the specimen we obtained, we were able to successfully diagnose the patient, without any complications, as having pulmonary MALToma. Because the MALToma arises from the bronchus-associated lymphoid tissue and proliferates slowly, there is usually no endobronchial lesion at the time of presentation that limits the diagnostic accuracy of the bronchoscopic brush or biopsy.

Pulmonary MALToma is also a kind of lymphoma, so the histological diagnosis should include the tumor cell type, the degree of cell differentiation, the immunocytochemical studies, and the character of the normal tissue around the lymphoma. US-guided core biopsy can localize the lesions precisely and obtain enough tissue to help us diagnose more accurately and know the grading of the lymphoma. This technique is relatively fast, inexpensive, and produces no ionizing radiation. However, we have to mention that the freehand approach is only suitable for superficial or large thoracic masses, because there is no guidance during the cutting of the lung mass.

In conclusion, ultrasound-guided transthoracic core biopsy is a safe and sensitive diagnostic approach for pulmonary MALToma because,

with this method, an accurate histological diagnosis can be obtained in most patients.

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藉超音波導引切片來診斷肺部 MALToma 之病例報告

涂智彥　夏德椿　林智一*

MALToma 是一種 B 細胞淋巴癌，它可生長在胃、肺、唾液腺或甲狀腺。肺部的 MALToma 是個很少見之疾病，其診斷需根據病理切片。以前在影像診斷工具尚未成熟時，病人常藉由支氣管鏡、胸腔鏡或開胸手術來取得病理組織；然而，這些檢查除了病患不舒服外，亦有麻醉的危險性。在此，我們報告一例 40 歲男性，無抽煙史，主要臨床症狀為乾咳、右側胸痛，胸部 X 光片顯示右中肺有約 6 公分的腫塊，在接受支氣管鏡檢查及經氣管切片後，仍無法獲得正確診斷。我們藉超音波導引，使用 18 號大小的針頭做了 core-biopsy，病人做完切片後無任何併發症，病理報告為 MALToma。病人現接受放射治療及化學治療，並在門診持續追蹤觀察。對於肺部 MALToma 的診斷，藉由超音波導引做 core-biopsy 可能扮演重要的角色。 ***(胸腔醫學 2002; 17: 172-177)***

關鍵詞：肺部 MALToma，超音波，core-biopsy

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Mediastinal Parathyroid Cyst—A Case Report and Literature Review

Huan-Jang Ko, Wen-Hu Hsu

Parathyroid cysts in the neck or mediastinum are uncommon. Mediastinal parathyroid cysts occur much less frequently than those in the neck. A mediastinal parathyroid cyst may be asymptomatic, but may also be symptomatic due to a mass or functional effect. We herein report a rare case of mediastinal parathyroid cyst. ***(Thorac Med 2002; 17: 178-181)***

Key words: parathyroid cyst, medistinum

Introduction

The superior parathyroid glands arise from the fourth branchial pouch. The inferior parathyroid glands and the thymus arise from the third branchial pouch. The thymic tissue migrates caudally, and pulls the parathyroid glands with it [1]. So, the parathyroid gland may locate in the mediastinum.

Parathyroid cysts can be classified as functioning if they are accompanied by hyperparathyroidism. Most cysts, however, have been non-functioning. We herein report a rare case of mediastinal parathyroid cyst.

Case Report

A 59-year-old male patient had been generally well in the past. He complained of a cough and voice change which began one month ago. Initially, he did not pay much attention to it. The above symptoms did not improve after medication. So, a chest X-ray film was taken which showed a mediastinal mass with tracheal deviation to the right side (Figure 1). Under the impression of mediastinal tumor, he was admitted to our hospital for further evaluation. The levels of Ca^{+2}, TSH, T3, T4, CEA, AFP, and B-HCG, were all within normal limits. Computerized tomography (CT) of the chest showed a well-defined low density cystic lesion at the anterosuperior portion of the visceral mediastinum, continuous with the lower portion of the left thyroid gland (Figure 2). The bronchoscopic examination showed a tracheal narrowing with deviation to the right side.

Suspecting either lymphangioma, thymic cyst, or thyroid cyst, surgical exploration was carried out through a cervical incision. A transcervical approach without sternal splitting was used and a 10x4x3 cm cyst with clear fluid was removed. The postoperative course was uneventful, and the patient was discharged on the sixth postoperative day. After the operation, the symptoms of cough and voice change disappeared.

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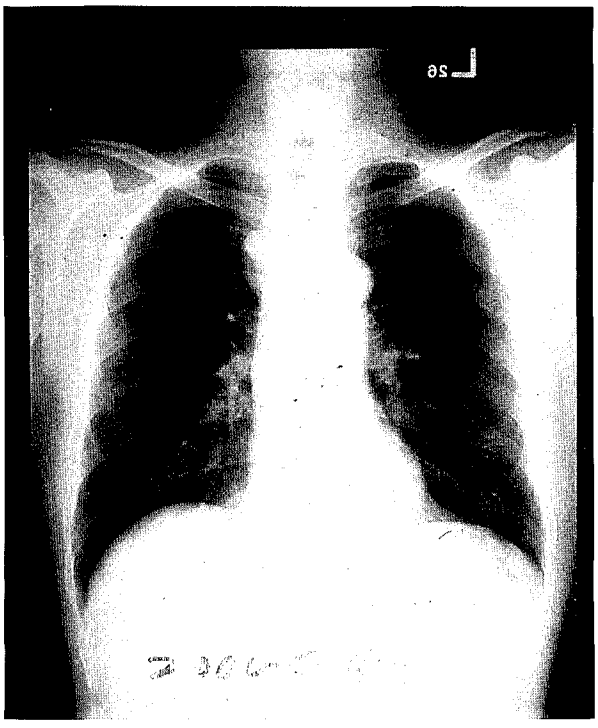

Fig. 1. A mass lesion in the superior mediastinum with tracheal deviation to the right side.

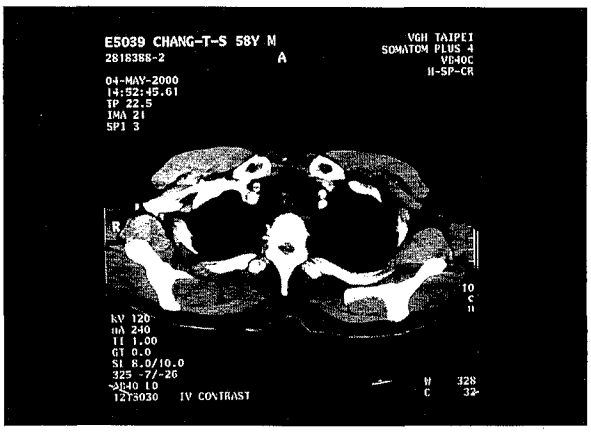

Fig. 2. A well-defined low density cystic lesion in the anterosuperior mediastinum with external compression to the trachea.

Fig. 3. A portion of the parathyroid cyst wall. The cystic wall is lined with a single layer of flattened cuboidal epithelium. The arrow depicts the cystic wall.

The pathologic examination revealed a parathyroid cyst (Figure 3).

Discussion

Tumors and cysts occur in the mediastinum. A tentative diagnosis is often made by considering the location of the lesion, because each of the lesions has a predilection for either the anterior, visceral, or posterior compartment of mediastinum [2]. Cystic tumors arising in the anterior compartment are mainly substernal thyroid goiters, and those in the visceral compartment are foregut cysts (bronchogenic, esophageal, and gastric) [3]. The parathyroid cyst is a rare case of space-occupying lesions in the mediastinum.

The first report of the removal of a parathyroid cyst from the meidastinum was published by De Quervain in 1925. Parathyroid cysts may be found in three areas of the mediastinum: 1) the anterosuperior (pretracheal) portion of the visceral compartment, which is the most common site (58.3%), as in our case report; 2) the retrotracheal area of the visceral compartment (28,1%); and 3) the true anterior or prevascular compartment (13.5%) [2]. Mediastinal parathyroid cysts can vary in size from 0.5 cm in diameter to a giant cyst of 12 cm or larger in its

greatest dimension.

Most cysts are grossly thin-walled, translucent, and unilocular. The fluid contained therein is colorless, but at times can be opalescent, gray, or serosanguinous in appearance. The fluid, when analyzed, has a significant level of parathyroid hormone (PTH); increased levels are diagnostic of a parathyroid cyst [4].

The usual presenting symptom is an asymptomatic mediastinal mass on the routine chest X-ray film. At times, the mass will become apparent on swallowing when the patient is in the supine position and the neck is extended; this type of cyst is similar to the so-called goitre plongeau. The cyst might cause dyspnea as a result of marked tracheal deviation or narrowing. Hoarseness caused by the transient paralysis of the recurrent laryngeal nerve has been reported. Thus, our patient presented a cough and voice change preoperatively. Left innominate vein compression or thrombosis also has been recorded [2].

Parathyroid cysts are classified as functional or nonfunctional. Functional cysts result from the degeneration of a hyperfunctioning gland, such as the adenoma [5]. Functional cysts are encountered in 41.4% of mediastinal parathyroid cysts [2]. Their clinical pictures vary from asymptomatic to that of a hypercalcemic crisis. Our case should be classified as a nonfunctional parathyroid cyst.

The diagnosis of a mediastinal parathyroid cyst was rarely made preoperatively in the first 75 years of the 20th century. The development of ultrasonography, CT scans, and magnetic resonance imaging to establish the cystic nature of the lesion, and the subsequent needle aspiration of clear, colorless fluid, strongly suggest the diagnosis.

All functioning mediastinal parathyroid cysts should be treated surgically, and a complete neck exploration should be done when possible to exclude other parathyroid gland involvement [6]. Nonfunctioning cysts are likewise best removed. The surgical access is dictated by the location of the cyst. Most cysts in the anterosuperior mediastinum can be removed successfully by cervical incision alone [2].

In summary, a parathyroid cyst should be considered in the differential diagnosis of space-occupying cystic lesions in the visceral mediastinum. Surgical removal is the treatment of choice and can be done through a cervical incision, with minimal morbidity.

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縱膈腔副甲狀腺囊腫—病例報告及文獻回顧

柯煥章　許文虎

臨床上，頸部或是縱膈腔的副甲狀腺囊腫都不是常見的疾病，尤其是縱膈腔的副甲狀腺囊腫更是少見。縱膈腔的副甲狀腺囊腫大部份是無症狀，偶爾會因為腫瘤壓迫附近器官或是高血鈣危象而被發現。在此我們報告一例縱膈腔副甲狀腺囊腫及回顧過去的文獻。 ***(胸腔醫學 2002; 17: 178-181)***

關鍵詞：副甲狀腺囊腫，縱膈腔

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Good's Syndrome Presenting with Bronchiectasis and Recurrent Pulmonary Infection—A Case Report

Kuen-Daw Tsai, Liang-Wen Hang, Wei-Erh Cheng, Te-Chun Hsia

Good's syndrome (immunodeficiency associated with thymoma) is a rare condition which occurs in only about 10% of patients with adult onset hypogammaglobulinemia. Patients reported in the literature develop defects in both the immune and hematopoietic systems with the clinical features of anemia, diarrhea, and recurrent pulmonary and opportunistic infections such as esophageal candidiasis, and others. We herein report a 48-year-old male with a history of bronchiectasis and recurrent pulmonary infection, beginning in 1997, which required mechanical ventilation at one time due to respiratory failure from infectious complications. In Nov. 2000, he was found to have an enlarged anterior mediastinal mass with a needle aspiration-proven thymoma. Immunological testing showed pan-hypogammaglobulinemia, a depletion of CD 19 cells, and decreased CD4 & CD8 cells with a low CD4/ CD8 ratio, indicating the presence of combined immune deficiency. Good's syndrome (GS) should be suspected when a patient with thymoma has a history of bronchiectasis combined with recurrent pulmonary or opportunistic infection. ***(Thorac Med 2002; 17: 182-186)***

Key words: thymoma, hypogammaglobulinemia, immunodificiency, recurrent infection.

Introduction

Good's syndrome (immunodeficiency associated with thymoma) was first described by Robert Good, MD, in 1954 [1]. It is a rare condition which occurs in only about 10% of patients with adult onset hypogammaglobulinemia [2]. Patients develop defects in both the immune and hematopoietic systems. The clinical features may be any one or a combination of anemia, thrombocytosis, diarrhea, and recurrent pulmonary and opportunistic infections such as esophageal candidiasis, and others. [1-5]. We herein report a 48-year-old male with history of bronchiectasis and recurrent pulmonary infection, beginning in 1997, which was finally diagnosed as Good's syndrome via a series studies in Nov. 2000. We found it of interest that Good's syndrome may be occulted in aggravated bronchiectasis which is associated with recurrent pulmonary and opportunistic infection.

Case Report

This 48-year-old male who reported a 20-year

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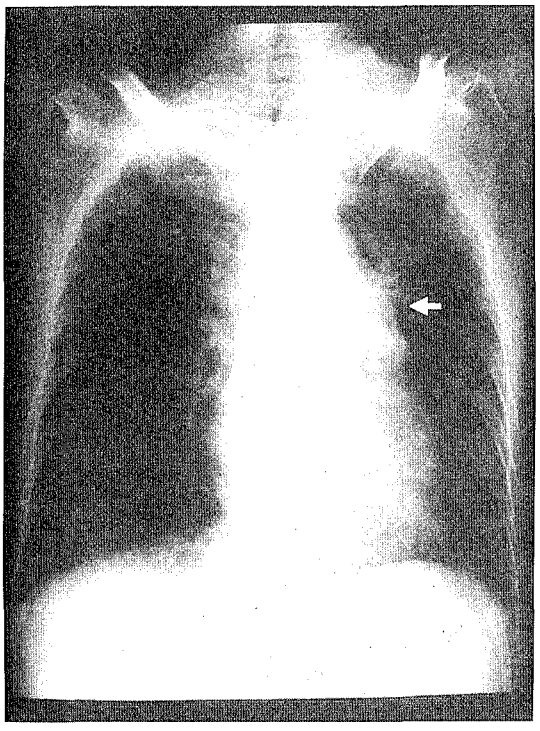

Fig. 1. The chest X-ray reveals reticular nodular lesions in the bilateral lower lung fields and an enlarged left hilum .

productive cough with whitish sputum had been diagnosed with brochiectasis based on radiologic findings in 1997. He developed exaggerated dyspnea and recurrent pulmonary infection during the most recent three years. He even required mechanical ventilation due to respiratory failure from infectious complications in Feb. 2000. Later, he was put on the regular use of a bronchodilator, oxygen, and daily chest physiotherapy as maintenance therapy. Antimicrobial agents were prescribed based on the various infectious pathogens found during exacerbation. The pulmonary function test revealed mild obstructive and restrictive ventilatory impairment. In Oct. 2000, he was readmitted due to a recurrent pulmonary infection presenting with fever, copious foul purulent sputum, and wheezing dyspnea. There were multiple white spots over oral mucosa. Diffuse wheezing crackles was auscultated in the bilateral lung fields. No morning malaise, weakness, cyanosis, nasal dripping, hemaptysis, orthopnea, chest distress, skin lesions, arthralgia, or lymphadenopathy were

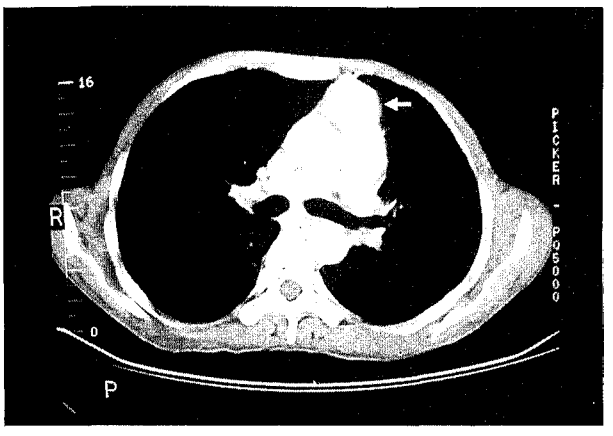

Fig. 2. The computerized tomography of the chest confirms an anterior mediastinal mass (heterogenous content).

found. He denied any past special occupational exposure, sexual experience, drug abuse, or significant comorbidity. The laboratory data were as below: Hb 11.9gm/dl (MCV 86fl/ MCH27pg), platelet 327000/ul, WBC 10800/ul (neutrophil 65%, lymphocyte 13 %, monocyte 20%), AST 28 IU/L, ALT 11 IU/L, BUN 8 mg/dl, creatinine 0.5 mg/dl, sodium 131 meq/L, potassium 2.8 meq/L, cloride 91 meq/L, calcium 9.1mg/dl, and alpha antitrypsin 341 mg/dl. Sputum cultures yielded *Pseudomonas aeruginosa* and *Enterobacter cloacae*.

The chest radiograph showed reticular nodular lesions in the bilateral lung fields and an enlarged left hilum (Figure 1). Computerized tomography of the chest confirmed an anterior mediastinal mass and bronchiectatic changes (Figures 2, 3). Fine needle aspiration proved the presence of thymoma (Figure 4). Because of thymoma, bronchiectasis, recurrent pulmonary infection, and mucocutaneous candidiasis (an unusual clinical course), a series of immunological tests were done. The results showed pan-hypogammaglobulinemia with IgG 222 mg/dl, IgM <25 mg/dl, IgA <40 mg/dl, IgE 4.8Iu/dl, the depletion of CD 19 cells, and decreased CD4 and CD8 cells with a low CD4/ CD8 ratio indicating the presence of combined immune deficiency. He refused a thymectomy, and was treated with antibiotics and monthly intravenous immunoglobulin.

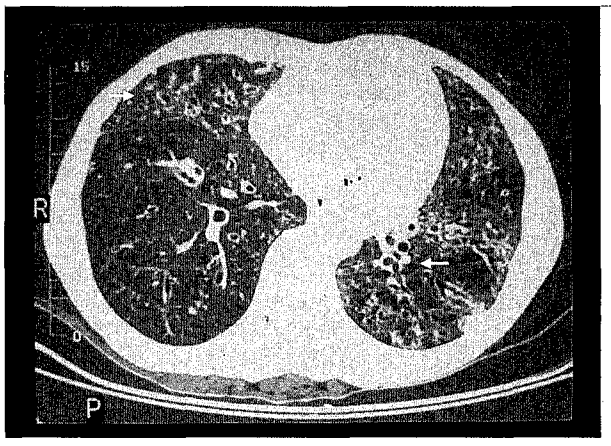

Fig. 3. The high resolution computerized tomography of the chest characterizes the bronchiectatic changes in the bilateral lower lung field.

Fig. 4. The fine needle aspiration cytology shows an epithelial nest with spindle cells. (10x40X Diff Quick stain)

Discussion

Thymomas originating from the epithelial cells of the thymus are the most common neoplasms, accounting for 45% of anterior mediastinal tumors [6-7]. Thymomas are often associated with paraneoplastic syndromes including myasthenia gravis (up to 50%), hematologic alterations (pure red cells aplasia, polycythemia, pancytopenia, leukemia), autoimmune disorders (lupus erythematous, rheumatoid arthritis, Graves' disease, Sjogren's syndrome, dermatomyositis, Whipple's disease, limbic encephalitis, stiff-person's syndrome), hypogammaglobulinemia, granulomatous myocarditis, Cushing's disease, etc. [6-9] Thymomas are malignant in 7% to 33% of all cased, and are highly associated with autoimmune diseases [8].

However, thymomas accompanied with hypogammaglobulinemia (Good's syndrome) occurs in about 10% of cases of thymoma or adult onset hypogammaglobulinemia [2-3]. The histological findings are predominantly spindle cell-type with only 10% malignancy [1]. The clinical characteristics of Good's syndrome (GS) are diverse and related to the involved system. Pure red cell aplasia, macrocytic anemia and thrombocytosis, neutrophil agranulocytosis, diffuse panbronchiolitis, lung abscess, recurrent and opportunistic infection, and chronic diarrhea have been reported [1-13]. This case report demonstrates that GS can only present with brochiectasis and recurrent pulmonary and opportunistic infections which predispose and exaggerate the bronchiectasis. The infectious pathogens are Gram-negative bacilli predominantly. A review of 51 cases in the literature reveals that nearly 38% of cases are with recurrent pulmonary infection (generally encapsulated bacteria); 10% with CMV disease; 14% with bacteremia; 10% persistent mucocutaneous candidiasis; 10% chronic diarrhea; 8% urinary tract infection; 6% P. carinii pneumonia; and 4% with tuberculosis and other infections like varicella, mycoplasma, Clostridium perfringen and Kaposi's sarcoma [10].

In immunity, a deficiency of immunoglobulin may be monoclonal or with multiple defects. A depletion of B lymphocytes, decreased CD4 helper T cells and a low CD4/CD8 ratio develops in almost all patients, although the level of CD8 is variable [1, 3-5, 14-16]. This patient had negligible B cells, decreased CD4 & CD8 T lymphocytes, and a low CD4/CD8 ratio, which should procede to a recurrently worsening pulmonary infection and opportunistic infection. The whole clinical process is similar to that of patients with HIV or common variable immunodeficiency, and may have a worse

prognosis [10].

In spite of the poor prognosis and no known cure, intravenous immunoglobulin is recommended, even combined with early antibiotics intervention, as infections are suspected. Thymectomy may provide only a transient improvement of the clinical features and is not beneficial in hypogammaglobulinemia and recurrent infection. Steroid and immunosuppressive agents are largely not effective, except if autoantibodies are produced (especially in patients with autoimmune manifestations) [1-10].

Conclusion

We emphasize that Good's syndrome should be keep in mind when patients with thymoma have a history of bronchiectasis combined with recurrent pulmonary or opportunistic infection. Early recognition and treatment may yield a decreased frequency of infection and lead to the avoidance of unnecessary cost.

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以支氣管擴張症和反覆肺部感染表現的 Good's 症候群—病例報告

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Good's 症候群(免疫缺乏合併胸腺瘤)是一種少見的疾病，僅發生在約百分之十的成人型低免疫球蛋白病人。臨床上病人都發現有免疫及血液系統的缺陷，其表徵有貧血、下痢、反覆性肺部及機會性感染，如念珠菌食道炎等。本報告為一位 48 歲男性病患，從 1997 年就有支氣管擴張症和反覆肺部感染，甚至因此呼吸衰竭而需機械性通氣。在 2000 年 10 月，病人被發現有前縱隔腔腫塊，經細針抽取的細胞學抹片証實為胸腺瘤。免疫檢查發現全免疫球蛋白低下，CD19 細胞缺乏，CD4、CD8 細胞減少和低比例的 CD4/CD8 細胞。當病人有胸腺瘤，且合併支氣管擴張症和反覆性肺部及機會性感染病史時，Good's 症候群應被懷疑。***(胸腔醫學2002; 17: 182-186)***

關鍵詞：胸腺瘤，低免疫球蛋白症，免疫不全，反覆感染

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