迎接分子生物基因學的新世紀

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分子生物基因學爲廣泛的研究目標及運用的技術。1857 年基因學之父 Mendel 發表了 Mendel law，說明成對的遺傳物質會分離且隨機的分配於配子(gamete)中；1950 年基因的化學結構被發現，而建立現代分子生物學的基礎；1982 年基因工程的 insulin 爲美國 FDA 認可用於治療糖尿病病患；1990 年 finger-printing 被運用於犯罪偵防；1990 年人類首次嘗試基因治療(gene therapy)；1994 年美國 FDA 認可基因工程食物—蕃茄上架出售；1997 年英國桃麗羊(Dolly)誕生。

最近基因食物的安全性受到了廣泛的討論，基因食物的產生是運用現代分生技術及透過對各種基因的了解，而給予農作物某些基因，以增加農產品的風味、營養、抗蟲性、抗除草劑或耐受惡劣天候。例如玉米自細菌轉殖得到產生殺蟲劑基因，能自然的產生殺蟲劑使農作物不須再噴灑農藥；基因食物預期能解決第三世界糧食不足及營養不良等問題，減少殺蟲劑的使用及農藥問題，減少人工操作時間，例如農作物有抗除草劑基因，則農人能快速的使用大量除草劑以去除雜草，且不會危害到農作物。但是安全性受到質疑；例如這些轉殖的基因有可能會轉移到自然界的他種植物中造成基因污染，或是具有抗蟲植物的花粉飄到他處造成他種昆蟲幼蟲死亡。人類吃下含殺蟲劑的農產品，可能對人體產生不良影響。在美國及歐洲都有報導基因植物含新的過敏原，造成人體嚴重的過敏現象。基因食物的褒與貶仍有待證實，在新的世紀人類可能會扮演著上帝的角色—改變物種及插手演化過程。

在今年春天 Human Geneme Project (人類基因計劃)的草稿已完成，草稿只是個架構，仍有許多錯誤有待修正及缺口等待補整。預估再過 2~3 年人類基因約有 30 億個鹼機將被定序，約有 10 萬多個功能性基因將被找出。此外在下五年的計劃中多國科學家將找尋更好的定序方法(sequencing)，尋求更好的方法以找出 singnal nucleotide polymorphisms (SNP), SNP 的發生率爲千分之一，目前相信 SNP 與各種及慢性病如腫瘤、糖尿病、心臟血管疾病有密切相關。同時人類基因將與其他物種的基因作比較以推論人類未知基因的功能，這些資訊將公佈在網路上以供全球科學家研究之用，有了這些資訊將可促進基因診斷與基因治療，同時人類基因計劃的技術也將轉移民間團體，以供研究之用。

桃麗羊(Dolly)的產生是基因世界的一大震撼。在此之前人類一直以爲體細胞基因無法長成一個完整的個體，因爲體細胞的基因無法完全表現，某些基因已失去功能，但由於桃麗羊的產生，動物的無性生殖體(clone)包括人類無性生殖體成爲熱門話題及研究的課題，人類無性生殖體可爲人類創造另一個自己或下一代，或改變不良的基因而創造一個優生學的自己，甚至爲自己保留備用的器官，如肢體或內臟器官以備不時之需。美國在桃麗羊誕生後立即召開爲期三個月的會議，會後宣佈美國至少在這五年內不允許任何人類無性生殖體的誕生，英國則允許人類無性生殖體的誕生，其餘國家包括台灣在內則無法律可循。

分子生物基因學的運用多樣化，不及備述，唯一的限制是自己的想像力。正所謂登高必自卑，胸腔醫學自本期起，將力邀國內外專家逐一討論各種被廣爲應用的分生基因研究技術，如 PCR, northern analysis, western analysis, *in situ* hybridization……等，並儘可能加上實例，以增加內容的可看性。

The Technique of *In Situ* Hybridization and its Application in Respiratory Diseases

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Introduction

Nucleic acid hybridization and gene mapping have permitted the direct analysis of genes in DNA or messenger RNA (mRNA) in the nuclei or in the cytoplasm of cells. *In situ* hybridization (ISH) (also called "hybridization histochemistry" or "hybridization cytology") was originally described in 1969 by Gall and Pardue and was first applied in order to localize ribosomal DNA in Xenopus oocytes [1]. Since then, ISH has been gradually used for chromosomal gene mapping, for the location of viral DNA and for the detection of mRNA transcripts. ISH contrasts with hybridization performed on solid support systems; such as Southern blot or Northern blot. Southern Blot is used for DNA study in which DNA fragments are extracted, electrophoretically separated and transferred onto nitrocellulose or nylon membranes, and then hybridized with a labelled DNA fragment (i.e. probe). Northern blot is a technique for RNA study in which total RNA isolated from cells or tissue are hybridized with a labelled DNA or RNA probe after electrophoresis transferring samples onto a membrane. The advantage and attraction of ISH is that it enables localization by microscopy of specific DNA or RNA target sequences to single cells in tissue sections or cells of cytospins or even on chromosomes which solid support hybridization cannot provide. ISH is also a more sensitive technique than other hybridization technique. For instance, a highly expressed gene in a few cells might be missed by Northern blot due to the dilution effects of large numbers of irrelevant cells not expressing the gene. Thus, ISH allows people to analyze the relationship between gene expression and individual cells in tissues. Additionally, combination of two techniques, ISH and immunohistochemistry, provides a powerful tool to identify the phenotype of cells expressing the gene of interest and to explore mechanisms of cell-cell interaction.

Quick Guides for ISH

1. Principle of ISH

The principle of ISH is based on the fact that the bases, adenine (A) or cytidine (C), from DNA/or RNA sequences can pair specifically to the complementary bases, thymine (T), guanine (G) or uridine (U), of other sequences of DNA/or RNA, by hydrogen bonds, respectively. Using a labelled nucleotide (i.e. probe), the DNA or RNA molecules in cells or sections of tissue are complementarily hybridized to the known sequence nucleotide (probe). Autoradiography or immunohistochemistry or fluorescence, depending on the methods of labelling the probe, then visualizes the labelled hybrid (Fig. 1). ISH obeys the same rules of nucleic acid hybridization as on solid supports (i.e. Southern or Northern analyses). The procedure of ISH, however, is more complicated

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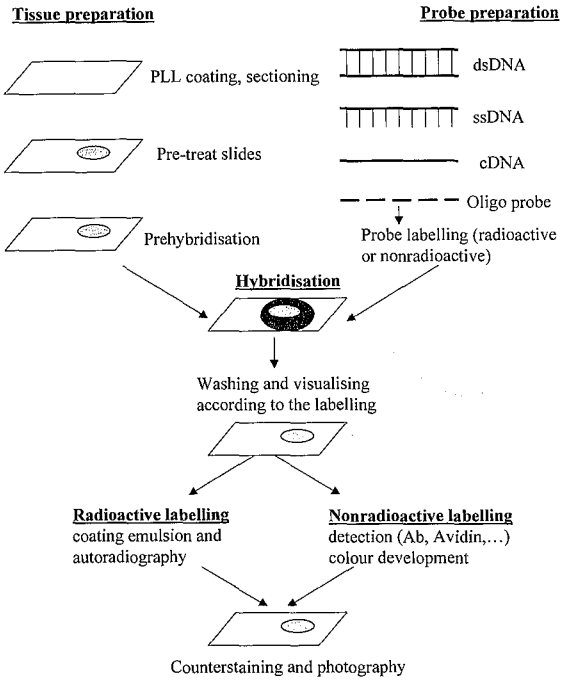

Fig. 1. The diagram of *in situ* hybridization

than with solid supports, because the probe for ISH must gain access to the target sequences in the cytoplasm or nucleoplasm of cells. Cellular constituents such as cytoskeleton proteins, lipids and the macromolecules of cells may bind the probe nonspecifically, impair diffusion, and impede access of the probe to intracellular target sequences. Fixatives may impede further diffusion and cross-link nucleic acids to each other and also to associated proteins. The molecular pathologist balances the conditions of hybridization, in situ, such that the probe gains access to the interior of the cells and its target without undue damage and loss of tissue structure.

2. Choice of Probes

Labelled DNA or RNA can be used as probes for the localization of either DNA or mRNA by ISH. There are a number of distinct forms of probes: a) double-stranded DNA (ds DNA) probes. Usually, this probe can be prepared by methods of "random primer-labelling" [2], or "nick translation" [3]. However, since the amount of probes labelled by random primer is less than that of nick translation, the latter is often used for labelling of double-strand DNA for ISH. b) single-stranded DNA (ssDNA) probes. Single stranded DNA probes can be obtained from target sequences inserted into the filamentous bacteriophage M13 or phagemids and labelled by 3' or 5' end labelling. Due to difficulties in subcloning it has been gradually replaced by asymmetrical polymerase chain reaction (PCR) to produce high specific single stranded DNA probes [4, 5]. c) oligonucleotide probes. This probe is easily and commercially obtained by artificial DNA synthesis [6, 7]. The 5' end extension (using T4 polynucleotide kinase) or 3' end extension (using terminal deoxyribonucleotidyl transferase) can be performed for labelling oligo probes. A major disadvantage of oligo probes is their relative insensitivity and non-specific binding due to their small sizes (in general 20-50 nucleotides of unique sequence). d) single-stranded RNA probes. This probe, also termed "riboprobe", was first described in 1984. Using this method, Cox and colleagues had reported a sensitivity of 20 mRNA copies per cell [8]. Riboprobes are obtained by cloning or subcloning a specific complementary DNA (cDNA) fragment into a transcription vector in which there is a RNA polymerase promoter, either for T3, T7 or SP6 RNA polymerase, immediately "up-" or "downstream" of the cloned cDNA fragment (Fig. 2) [9, 10]. When the RNA polymerase and nucleotides (UTP, GTP, ATP, and CTP, one of them is "labelled") are added, *in vitro* transcription is initiated. The "labelled" nucleotide is incorporated into the newly formed antisense probe (or cRNA, with complementary sequence to target mRNA) or sense probe (with identical sequence to target mRNA). The labelled antisense probes (cRNA probes) hybridize with target mRNA in the individual cells. In contrast, sense probes can not hybridize to the target mRNA and can be used as a control (Fig. 2). The resultant sequence of the sense or antisense probe depends upon the direction of the inserted cDNA fragment and which polymerase is added, and the specific

Table 1. Methods for labeling probes

Probe	template	Method	Enzyme	Vector
DNA	dsDNA	Nick Translation	DNase I DNA polymerase I	Plasmid
DNA	dsDNA	Random Primer	Klenow polymerase I	Plasmid
DNA	ssDNA	3' end labeling	TdT	M13 phage
Oligo	—	5' end labeling	T4 polynucleotide kinase	no need
RNA	dsDNA	in vitro transcription	Sp6/T7/T3	RNA expression Vector

ds=double strand; ss=single strand; TdT=terminal deoxynucleotidyl transferase

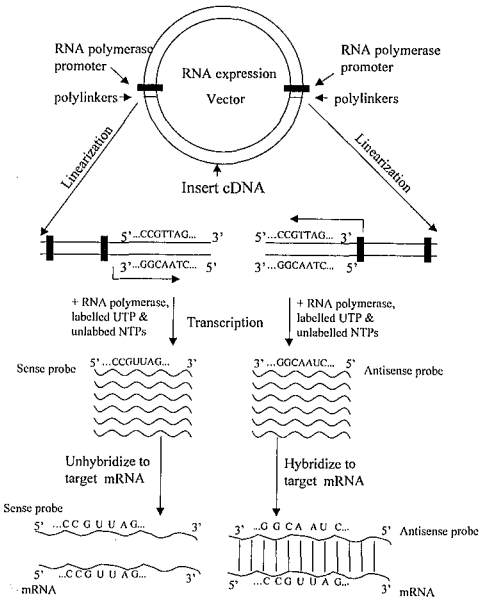

Fig. 2. The preparation and principle of riboprobe for ISH.

vector chosen (Fig. 2). So far, several RNA expression vectors are commercially available, such as the pSP72 (Promega), pGEM (Promega), pT7/T3 (GIBCO BRL) and pBluscript (Northumbria Biologicals Ltd) systems. These vectors have two reverse orientation promoters of RNA polymerase (SP6/T7 or T7/T3) and polylinkers between two promoters. Before initiating transcription, the circular plasmid must be linearized by restriction endonuclease so that the vector sequences are not transcribed to form part of the probe. The unwanted vector sequences not only increases the size of the transcripts but may also cause high background. Due to the inconvenience of subcloning of desired cDNA fragments into RNA expression vectors, some investigators have attempted to use PCR to generate cRNA probes [11].

Using RNA probes have several advantages: 1) they are single-stranded and form RNA-RNA hybrids which are stable; 2) unlike double-stranded DNA probes, they do not re-anneal in solution and thereby provide a relatively high probe concentration which drives the hybridization reaction favouring retention of the hybrids and yielding strong signals; 3) following hybridization, RNase digestion can be used to remove any remaining unhybridized single stranded probe, reducing the background considerably and giving a high signal to ratio [8]. The main disadvantage is that both the RNA target and the single stranded unhybridized probe are highly susceptible to destruction by RNases which are ubiquitous. Hence, tissue must be fixed quickly and freshly and kept cool until snap-frozen or processed as paraffin section. All glassware must be baked to destroy RNase. Gloves must be worn to avoid contamination by skin RNase. All reagents must be of the highest purity and maintained so.

The types of probes and methods for labelling are summarized in Table 1.

3. Probe Labelling

Labelling of probes for ISH may be radioactive or non-radioactive. Radioactive isotopes used to label the probe sequences includes tritium (^{3}H), sulphur (^{35}S), phosphorus (^{32}P, or ^{33}P) and iodine (^{125}I). ^{3}H has the lowest energy emission and gives the finest resolution, and is therefore suitable for both cellular and subcellular localization of targets (i.e. chromosome mapping). However, the low energy emission needs longer exposure time, ranging usually from 6 weeks to several months. ^{35}S is a popular label because of its short exposure time (7-14 days), although the background is somewhat higher than with ^{3}H, and the resolution is not as high. ^{32}P label can be used for rapid analysis because of its high sensitivity and very short exposure time (3-5 days) but with the risk of high background and poor resolution. ^{125}I provides a good resolution coupled with relatively short exposure time, allowing the demonstration of sequences of low density, but with higher background [12]. Conventional methods can be used to radiolabel the nucleotides which become incorporated during synthesis of the DNA or RNA probe. The localized probe can then be detected by autoradiography employing either liquid emulsions, stripping film or by X-ray films which are both stable and sensitive.

The considerations of safety, waste disposal, low stability, poor single-cell resolution and speed of visualization of radioactive probes have stimulated the development of non-radioactive probes. A number of non-isotopic labels have been used for ISH, such as biotin-, digoxigenin-, fluorescence- or chemiluminescence-labelled probes [13-15]. The most effective and sensitive methods involve use of a nucleotide derivative with a hapten incorporated for which an antibody or other hapten-specific binding protein is available [13]. Biotin and digoxigenin-linked nucleotides are widely used [13, 14]. Following hybridization and several washes, the labelled probe-target hybrid can be detected by its complex to avidin or anti-digoxigenin antibody respectively. The report enzymes, such as alkaline phosphatase or peroxidase, conjugated second layer can be visualized by the use of an appropriate substrate for the enzyme to produce an insoluble, coloured precipitate in the cell or tissue. The major limitation of non-radioactive probes is the relatively reduced sensitivity compared with isotopic methods. Additionally, combining radio- and non-radio-labelled probes in which distinct labels are employed, multi-mRNAs can be detected in the same slide.

Other non-isotopic labelling molecules can be employed such as fluororescein, dinitrophenyl, bromodeoxyuridine, colloidal gold and sulphonated and mercurated probes [13, 16-20]. The characteristics, and utilization of labels are summarized in Table 2.

Table 2. Characteristics of common radio- and non-radio- labels used in ISH

Label	emission	maximum energy (Mev)	half life	exposure time	resolution
^{32}P	β	1.71	14.3d	3-5d	poor
^{35}S	β	0.167	87.4d	7-14d	moderate
^{3}H	β	0.018	12.35y	month(s)	excellent
Digoxiginin	-	-	N/A	-	excellent
Biotin	-	-	N/A	-	excellent

Note: The sensitivity of different labels: $^{32}P \geqq ^{35}S > ^{3}H >$ or = non-radiolabels. The resolution of the labels: ^{3}H = non-radiolables (biotin or digoxigenin) $> ^{35}S > ^{32}P$.

4. Probe Accessibility

The length of probe used in ISH strongly influences the result. Probes >1,000 bases give weak signals probably due to their poor penetration of tissue and cell membrane. The optimal length of a probe ranges from 50-500 bases, depending upon its type. Such a size range facilitates its entry into the cell yet provides sufficient complementary sequences to encourage strong hybridization. For double stranded DNA probes the length can be determined by the DNase I during nick-translation or by the concentration of primers present in random-priming labelling mixture [21]. For PCR-generated probe, the length can be determined by designing appropriate primers flanking the amplified fragment [4, 5]. The length of riboprobes depends on the length of cDNA fragment. If the RNA probes are too long, they can be cleaved by limited hydrolysis with alkali following transcription [22]. It is vital that the probe size is checked before hybridization since too small a probe will not only lead to high background but will also result in a low level signal after the high 'stringency' washing required for specificity.

5. Tissue Preparation and Pre-hybridization Treatmemt

The specimen preparation for ISH is dependent on the nature of the sample and the specific requirement of the experiment [5]. The time between obtaining a sample and fixation must be minimised because target sequences, especially mRNAs in tissue specimens are degraded rapidly by RNase. However, ISH in post-mortem material has been successfully carried out even though the tissue had been collected up to 10 hours after death [23]. Cells obtained by bronchoalveolar lavage (BAL) or bronchial lavage (BL), sputum, cell culture, bone marrow and samples of blood can be spun onto slides prior to fixation. Biopsies, obtained during bronchoscopy, open lung biopsy or fine needle aspiration, can be a) fixed by immersion, snap-frozen and sectioned or b) snap-frozen, sectioned and subsequently fixed or c) fixed, embedded in paraffin and cut at suitable time. To avoid losing cells or sections during ISH procedure, poly-lysine (PLL)-coated microscopic slides are recommended for making cytospins and cutting sections.

Successful ISH depends upon the retention of target nucleotide sequences (e.g. mRNA) and the preservation of tissue/cell morphology [24]. Optimal fixatives should have the following advantages: the preservation of the tissue integrity, retention of mRNA within the tissue and provision for efficient access of the probe to the target RNA. Generally, there are two types of fixatives, namely precipitating- and cross-linking-. The former (e.g. combinations of methanol and acetone) provides the highest probe penetration and reasonable preservation of the tissue morphology, but relatively poor retention of RNA. The latter (e.g. glutaraldehyde) provides the best RNA retention but with poor probe penetration because of wide cross-linking of tissue, which may block recognition of epitopes by antibodies used for immunohistochemistry. Another cross-linking fixative, buffered 4% paraformaldehyde appears to meet all three requirements [25]. Comparison of various fixatives is summarized in Table 3.

Pre-treatment of sections or cytospins with proteases (such as proteinase K or pepsin) can increase probe penetration into cells. The concentration of protease and time of digestion must be ascertained in pilot experiments since the sensitivity of the tissue to protease digestion differs between tissues, fixatives and is affected by the fixation time. The optimal objective of protease digestion is to increase access for the probes to the target yet retain tissue morphology. After protease digestion, post-fixation is often used to avoid subsequent disintegration of the tissue. In order to prevent non-specific binding of probe to positively charged amino groups, acetylation of slides by immersion in acetic anhydride can be useful also.

Table 3. Comparison of Fixatives for ISH

Fixative	Fixation time (minutes)			
	Cell	Tissue	RNA Retention	Morphology
4% Paraformaldehyde	30	2-4 hr	+++	+++
2% Glutarmaldehyde	30	2-4 hr	+++	++++
Ethanol/acetic acid (95/5)	15	30	++	++
Methanol/acetone (50/50)	4	20	+	++

6. Hybridization and Post-hybridization

The optimal conditions of hybridization vary with different tissue, and type of probes used. Hybrid formation is a dynamic process involving association and disassociation of probe and target. The aim of successful hybridization is to drive the reaction towards the formation of stable hybrids, where there is a high degree of complementary and maintain them for detection during the subsequent high stringency washing procedures. The specificity of hybridization is based on the types of probes, temperature, pH, and the concentration of formamide and salt in the hybridization solutions. The extent to which mismatching base pairs are allowed is termed "stringency". Under high stringent conditions, the stable hybrids can be formed only when high homology sequences between probe and target RNA exist. In contrast, under low stringent conditions, the target sequences with 70-90% homology will also hybridize with the probe, causing non-specific binding.

Post-hybridization is performed by washing the hybridized slides to remove any of the probe which is weakly hybridized to sequences of low homology or that which has bound non-specifically. Usually the washing is carried out using solutions in which the probe-target hybrids will maintain their stability. Varying concentrations of standard saline citrate (SSC) are commonly used. Generally, raising the temperature of the reaction and reducing the concentration of salt solution can increase the "stringency" [22]. Occasionally, formamide is also added to the washing solution in order to decrease the washing temperature and preserve tissue section integrity. The ideal conditions must be determined empirically by pilot experiments. For RNA probe, a ribonuclease step is also carried out in order to remove any single-stranded (i.e. unhybridized probe remaining), and leave only hybrids (double-stranded) for detection. Thorough decontamination of RNase from all equipment should also be carried out afterwards prior to any further hybridization experiments as RNase will destroy target mRNA transcripts in subsequent experiments.

7. Detection and Visualization of Signals

The final step in the ISH technique is detection and visualization of the stable, labelled hybrids seen against a background of retained tissue morphology. The methods of detection really depend upon the labels of the probes. Autoradiography is used for detection of radioactive probes, in which the tissue sections are coated by photographic emulsion, dried, exposed to the radio-emitter in light-tight containers and subsequently developed [22]. The exposure time depends upon section thickness, the type of radioisotope, the concentrations of probes used, and the numbers of specific mRNA transcripts (i.e. "copy number"). After developing and fixation, the slides are counterstained, either with haematoxylin or Giemsa, or any other staining methods which can permeate the photographic emulsion to reach the tissue. The

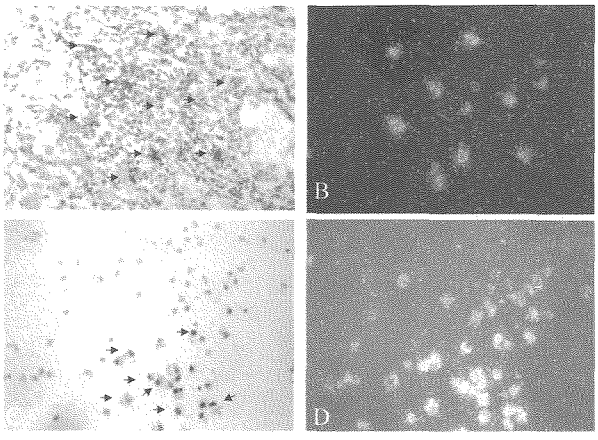

Fig. 3.(A-D) Typical examples of ISH with ^{35}S-UTP-labelled riboprobes. A depicts ISH for IL-4 antisense riboprobe in bronchial mucosa. B is the same section of A shown in darkfiled illumination. C shows ISH for IL-5 riboprobe in a cytospin of BAL. D is the same cytospin of C shown in darkfiled. Some IL-4 and IL-5 mRNA$^+$ cells are indicated (arrows)

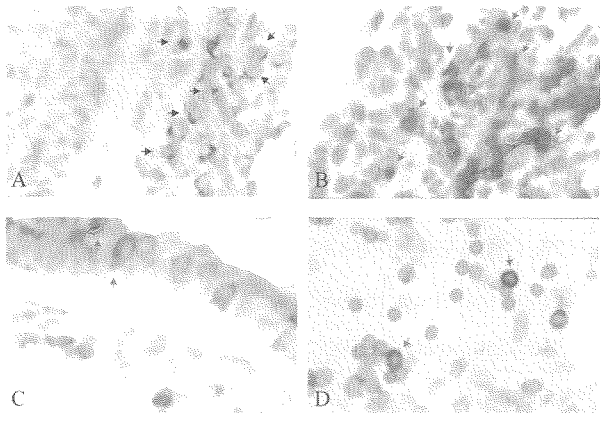

Fig. 4. The examples of ISH with digoxigenin-labelled riboprobes. A shows IL-5 mRNA$^+$ cells in bronchial mucosa. The positive cells are dark/blue black (arrows). B is a serial section of A showing double immunohistochemistry (IHC)/ISH. CD3$^+$ cells are red. The cells bearing CD3 and expressing IL-5 mRNA are red/dark blue (blue arrows). C shows double IHC/ISH for eotaxin mRNA$^+$ in bronchial mucosa. Some cytokeratin$^+$ epithelial cells (red) expressing eotaxin mRNA$^+$ are indicated (blue arrows). Some eotaxin mRNA$^+$ cells (dark blue) are not cytokeratin$^+$ in epithelium and submucosa. D shows that some CD3$^+$ T cells express eotaxin mRNA. The double positive cells are red/dark blue (blue arrows).

developed autoradiographic silver grains can be visualized under bright-field or dark-field illumination using epipolarization to visualize both autoradiographic grains and tissue simultaneously (Fig. 3).

For non-radioactive labelled probes, the detection and visualization are the same as those of immunohistochemistry or immunofluorore-scence, depending on the labels of probe [22]. As mentioned earlier, digoxigenin and biotin are currently the most popular haptens for probe labelling. Antibody or hapten-binding protein conjugated to fluorescent, or conjugated to an enzyme such as alkaline phosphatase which can consume substrate to yield an insoluble coloured end-product may all be used (Fig. 4), [13]. The advantage of non-isotopic enzymatic detection is that the visualization process can be in conjunction with radioisotopic labelling to detect several distinct target sequences [26] or to identify the cell phenotype expressing the gene of interest by double labelling techniques [27-31].

8. Controls of ISH

As we have seen above, many factors can influence the outcome of ISH and the generation of a 'signal'. In order to interpret the results, appropriate controls must be included. For positive controls, tissue or cells (such as cell lines) known to contain the target nucleotide sequences of interest should be included. Southern blot, Northern blot or RT-PCR can confirm this. Alternatively, using labelled probes specific for a housekeeping gene (e.g. β-actin) can be used as a method control. Following methods can be used for negative controls: a) omit probe in hybridization buffer; b) pre-treat sections or cytospins with nuclease (i.e. DNase or RNase) to remove the total DNA or RNA from the samples; c) hybridize the slides with an irrelevant probe (i.e. labelled vector sequences); d) hybridize the slides with unlabelled probes; e) use the sense probes (having identical sequence to the target mRNA, therefore no hybridization occurs) and f) omit primary antibody as a negative control for the non-radioactive ISH (i.e. omit anti-Dig

antibody during Dig-ISH procedure).

9. Quantification of ISH Signals

Theoretically, the number of sliver grains (in radio-ISH) is proportional to the number of hybrids formed which, at saturation, is equivalent to the number of mRNA sequences detected. In another words, counting the number of silver grains may reflect the number of mRNA copies. This provides the basis for quantitating the hybridization signals using computer assisted image analysis system [32]. However, it is a far from routine application because the results may be influenced by many factors, including the thickness of emulsion, the thickness of the sections, the amount of radioactivity of probes, exposure time, etc. Thus, other two semi-quantitative methods are often used. One method counts the number of ISH positive cells compared with background. The results are expressed as number of positive cells per unit of tissue section (i.e. per mm^2 of section) or per unit of total cells (i.e. per 500 or 1000 total cells) in cytospin preparations. This method has been used in our department for quantification of ISH with either radio- or non-radio-labelled probes [26-31]. Another method counts the number of silver grains presumably to represent the number of target mRNA copies [33]. Using ^3H-labelled probes, this semi-quantitative method may be more reliable due to the high resolution of ^3H. However, long exposure time is the greatest disadvantage for this labelled probe.

Application of ISH for detection of Cytokines and Chemokines in Asthma and Rhinitis

There is now considerable evidence that atopic asthma is a chronic inflammatory disease, driven by Th2-type $CD4^+$ T cells. However, it was not clear until direct evidence was obtained from lung of atopic subjects. In 1986, Mosmann and colleagues suggested that murine $CD4^+$ T helper cell clones could be divided into two distinct subsets, termed Th1 and Th2, based on their different pattern of cytokine secretion [34]. Th1 cells are characteristically induced during immune responses to intracellular pathogens such as mycobacteria and viruses and produce IFN-gamma, lymphotoxin and IL-2. These cytokines activate macrophages, NK cells and $CD8^+$ cytotoxic T cells, promote Ig class switching to IgG2a, and induce further Th1 cell differentiation. Th2 cells are characteristically induced during host responses to helminthic parasites and produce IL-4, IL-5, IL-10, and IL-13. These cytokines promote mast cell and eosinophil growth, differentiation as well as Ig class switching to IgG1 and IgE, and favour further Th2 development, which are the feature of allergic inflammation, including asthma. Although many data from animal models supported this, the existence of Th1- and Th2-like cells had been the subject of considerable debate in man. Since 1991, using ISH we had first demonstrated that *in vivo* expression for Th2-type cytokine mRNAs (IL-4, IL-5, IL-3, and GM-CSF) was significantly increased in allergen-induced cutaneous late-phase reactions (LPR) in atopic subjects [36]. In contrast, there was little expression for Th1-type cytokine mRNAs (i.e. IL-2 and IFN-γ). This Th2-type cytokine profile was not only the feature in skin but also in other types of organs, such as lung and nose. For instance, similar cytokine patterns were also observed in bronchial mucosa and BAL from atopic asthmatics and nasal mucosa from atopic rhinitis at baseline and after allergen provocation (Fig 5) [37-41]. Compared with normal, increased numbers of cells expressing Th2-type cytokine pattern were observed in BAL fluid cells and bronchial biopsies from atopic asthmatics at baseline [29, 38, 42]. The numbers of IL-4 and IL-5 $mRNA^+$ cells were correlated with measures of disease severity such as bronchial responsiveness or FEV_1 [42, 43]. A reduced number of cells expressing

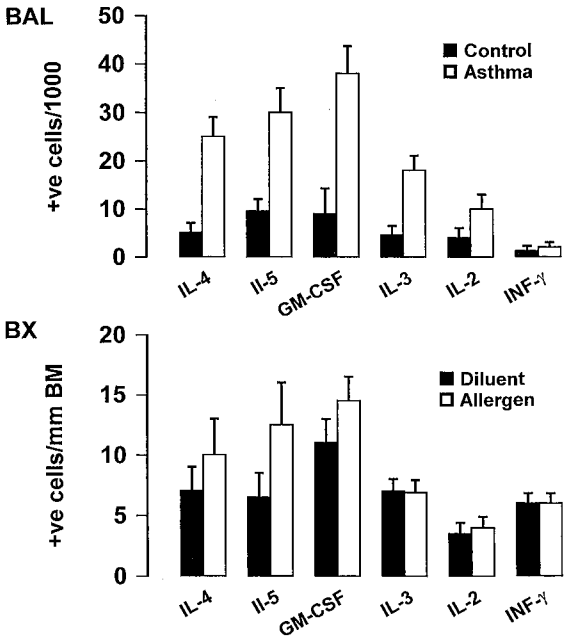

Fig. 5. *In situ* hybridization for detection of Th1- and Th2-type cytokine mRNA$^+$ cells in bronchoalveolar lavage (BAL) at baseline and bronchial biopsies (Bx) 24 h after diluent or allergen inhalation. The results are expressed mRNA$^+$ cells per 1,000 total BAL cells, or mRNA$^+$ cells per mm length of basement membrane (mm BM) of biopsies.

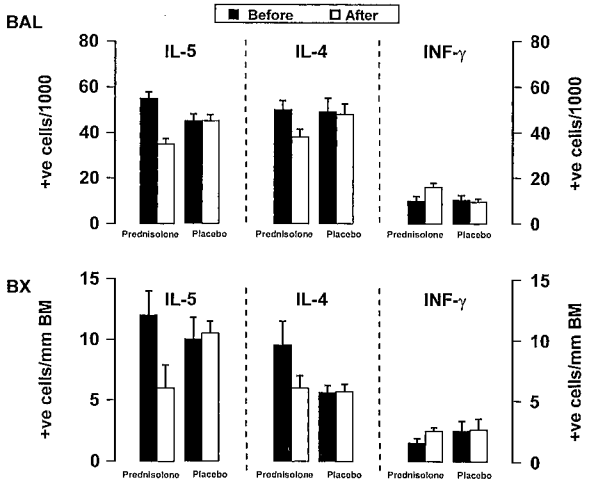

Fig. 6. *In situ* hybridization for detection of Th1- and Th2-type cytokine mRNA$^+$ cells in BAL and in bronchial mucosa before and after treatment with prednisolone or placebo. The results are expressed mRNA$^+$ cells per 1,000 total BAL cells, or mRNA$^+$ cells per mm length of basement membrane of biopsies.

mRNA for IL-4 or IL-5, and a small increase in IFN-gamma mRNA$^+$ cells, were observed after corticosteroid treatment of asthma associated with clinical improvement (Fig. 6) [44, 45]. In contrast, significant increase in the numbers of cells expressing IFN-r mRNA was observed in BAL cells from patients with tuberculosis, while there were no differences in the numbers of IL-4 or IL-5 positive cells between patients and normal controls [46]. These *in vivo* data suggest that Th1- and Th2-like functional subsets exist in man, and also indicate that Th2-, but not Th1-like cells, contribute to allergic inflammation through synthesising favourite cytokines.

Interestingly, Th2-tye cytokine profile was also observed in non-atopic asthma. Non-atopic asthmatics or intrinsic asthmatics show negative skin tests and are lack of clinical or family history of allergy. Bronchial biopsies from such asthmatics show eosinophil infiltration and activated T cells in the bronchial mucosa, as in atopic asthma. Although one study did not detect IL-4 in concentrated BAL fluid from non-atopic subjects, more recent biopsy studies have reported a Th2 cytokine profile at both mRNA and protein level [43, 47]. In addition, increased number of cells bearing FcεRI were detected in bronchial biopsies from non-atopic asthmatics when compared to control subjects. Increased expression of IgE germline transcripts (Iε) and heavy chain (Cε) was also observed in bronchial mucosa from both atopic and non-atopic asthmatics, but without differences in the numbers of CD20$^+$ B cells between asthmatics and controls [48]. This suggests that there may be local IgE production. What the role of IgE in this non-atopic variant of asthma is, and whether it is directed against specific antigens remains to be established.

Using combination of immunohistochemistry and ISH, we have demonstrated that IL-4

and IL-5 mRNA were predominantly localised to $CD4^+$ cells in the nasal mucosa from atopic rhinitis, in bronchial mucosa from asthmatic subjects, and in BAL, with lesser contributions from $CD8^+$ cells, mast cells, and eosinophils [28, 29, 48].

Eosinophilia is another feature of asthma and of other allergic inflammation. However, the mechanisms of eosinophil infiltration into local tissue were largely unknown. Th2-type cytokines have no direct effects on eosinophil chemotaxis. In contrast, some small peptides, named as chemokines, particularly CC chemokines induce eosinophil chemotaxis *in vitro and in vivo* in animal models [49]. Using ISH, increased CC chemokine $mRNA^+$ cells, including eotaxin, eotaxin-2, RANTES (regulated upon activation in normal T cells expressed and secreted), MCP-3 (monocyte chemotactic protein-3) and MCP-4, have been observed in bronchial mucosa from atopic and non-atopic asthmatics [50]. Among these chemokines, there are significant correlations between the eotaxin expression and histamine PC_{20}, and the numbers of eosinophils infiltrated in the bronchial mucosa [50]. Double immunohistochemistry/ISH showed that $cytokeratin^+$ epithelial cells and $CD31^+$ endothelial cells are major cell sources of these chemokine mRNAs [50]. Using allergen-induced skin LPR as a model, we have investigated the kinetics of expression these CC chemokine and relationships to the infiltration of inflammatory cells in the local tissue [51]. Our results showed that eotaxin expression contributes to eosinophil infiltration at the earlier time point (i.e. 6h after allergen challenge), while eotaxin-2 and MCP-4 expression is involved in later eosinophil recruitment (i.e. 24h after allergen challenge). Taken together, these studies indicated that several chemokines, also possibly Th2-type cytokines may participate in infiltration of inflammatory cells in local tissue.

In summary, the technique of ISH has become a powerful tool in molecular virology, molecular immunology, molecular pathology and molecular oncology and is being gradually extended to a number of new fields such as molecular pharmacology and molecular physiology. The resulting data combined with tissue morphology provides a perfect complement to those obtained by other molecular techniques in these fields.

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Resection for Pulmonary Metastasis of Colorectal Cancer

Pei-Jan Chen, Tzu-Chi Hsu*, Chang-Jer Huang**

Surgical resection remains an important procedure for treatment of pulmonary metastases from colorectal cancer. To evaluate the efficacy of pulmonary metastasectomy, we retrospectively studied 12 patients who underwent pulmonary resection for lung metastases from colorectal cancer from 1990 through 1999. Ten patients had solitary nodule, and 2 patients had multiple nodules. Eleven patients underwent a single thora- cotomy. Wedge resection was the main surgical procedure.

The average survival following thoracotomy was 40.8 months. The cumulative 3 year and 5 year survival rates were 66%, and 25%. Seven of these patients were still alive up to date without evidence of recurrence after pulmonary metastasectomy.

There is a tendency for longer survival with a normal preoperative CEA level, longer disease free interval and solitary pulmonary metastatic nodule in this small retrospective study.

The resection of pulmonary metastases from colorectal cancer may translate into survival benefits. ***(Thorac Med 2000; 15: 70-76)***

Key words: metastasectomy, pulmonary metastases, colorectal cancer

Introduction

Colorectal cancer is the second most common malignancy in the United States. In Taiwan, it is the third most common cause of cancer mortality [1]. In an autopsy study, 20% of patients with colorectal cancer were found to have lung, liver and other distant metastases, and 2% had isolated lung metastases [2]. To date, the results of treatment for metastatic colorectal cancer are disappointing, and there is no effective chemotherapy available. Several retrospective studies have shown that after resection of isolated pulmonary metastases, approximately one third of patients will survive 5 years, and about one fourth will survive 10 years [3,4]. These results strongly support the view that pulmonary metastasectomy is an efficient treatment in selected patients with lung metastases [3,5].

We herein retrospectively reviewed the surgical treatment of lung metastases in 12 patients with colorectal cancer and also investigated the factors affecting their survival.

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Materials and Methods

At Mackay Memorial Hospital, a retrospective review was undertaken of patients who underwent resection of pulmonary metastases from primary colorectal cancers from January 1990 to December 1999. Patients were asymptomatic, and lung metastases were discovered unexpectedly in chest x-rays performed routinely for follow up of patients who had prior resections for colorectal cancer. Patients whose pulmonary nodule(s) proved to be unrelated to the colon or rectal cancer were excluded from the study. Before pulmonary resection, the extent of disease was evaluated to be certain there was no disease elsewhere in the body. The preoperative evaluation included biochemical study, serum carcinoembryonic antigen (CEA) level, pulmonary function test, chest x-rays, chest CT scan, bone radionuclide scanning, abdominal ultrasonography and fiberoptic colonoscopy.

The selection criteria for resection includes controlled primary tumor, no extrathoracic spread, unavailability of a better treatment, and no cardiac or respiratory insufficiency.

The records of all patients were reviewed for age, sex, stage of primary colorectal cancer, number of pulmonary metastases, largest diameter of resected pulmonary metastasis, type of pulmonary resection, preoperative CEA level and postoperative survival. The disease-free interval (DFI) between the date of diagnosis of the primary tumor to the date of diagnosis of pulmonary metastases was also noted.

No postoperative adjuvant chemotherapy was administered unless additional metastatic disease develop. All postoperative patients were regularly followed. Physical examination, chest x-rays, abdominal ultrasonography and serum CEA level were performed every 3 or 4 months. Follow-up information included the site of recurrence after pulmonary resection and the cause of death.

Results

The study population consisted of 12 patients, 5 males and 7 females, with an average age of 61 years, range from 42 to 72 years. In 9 patients, the primary site was the colon, in 3 it was the rectum. The surgical stage of the primary tumor was Duke's B in 5 patients, and Duke's C in 7. The histologic grading of the original tumor was well differentiated adenocarcinoma in 1 patient, moderately differentiated in 10 and poorly differentiated in 1. Table 1summarizes the characteristics of the 12 patients.

The average DFI was 29.8 months and range from 14 to 50 months. One patient had a previous resection of liver metastases, another patient developed hepatic metastasis following lung resection, which was removed by segmental hepatectomy.

Intraoperatively, 10 patients had single, unilateral nodule, right lung in 8 and left lung in 2. Two had multiple and bilateral nodules, 1 had 3 nodules, and another had 12 nodules. A single wedge resection was done in 7 patients, and lobectomy in another 3 patients with solitary metastasis. Multiple wedge resection was performed in 2 patients with multiple nodules. One patient received repeat thoracotomy for multiple nodular recurrence 1 year after the first lung resection. Only one patient, who had a lobectomy, was detected to have positive hilar lymphadenopathy. He died 36 months after pulmonary metastasectomy. There were no postoperative deaths, nor any postoperative complications observed.

The characteristics of the patients with pulmonary metastases, as well as the extent of pulmonary resections are listed in Table 1.

All 12 patients were available for follow up after initial pulmonary resection from 10 to 74 months, average, 40.8 months. The cumulative survival rate was 66% at 3 years and 25% at 5 years (Figure 1). Five patients including one who survived more than 5 years, died during

Table 1. Characteristics of Patients with Resection of Pulmonary Metastases from Colorectal Cancer

	No. of Patients
Sex	
Male	5
Female	7
Primary site of tumor	
Ascending colon	1
Descending colon	8
Rectum	3
Surgical stage of primary tumor	
Duke's B	5
Duke's C	7
Histologic grading of primary tumor	
Well differentiated	1
Moderately differentiated	10
Poorly differentiated	1
Number of pulmonary metastases	
One	10
Three or more	2
Location of pulmonary metastases	
Right lung	8
Left lung	2
Both	2
Surgical procedure	
Lobectomy	3
Wedge resection	9

follow-up. Recurrent lung metastases with or without bone and liver metastases was the cause of death. Seven patients were alive and disease free at 22, 36, 37, 42, 56, 62, and 74 months.

Of the 10 patients with solitary metastases, 3 died at 24, 36 and 61 months, the 2 patients with multiple metastases died at 10 and 30 months. Of the patients who had resection for liver metastasis, one was still alive and free of tumor 42 months after lung resection, while the other died at 24 months.

The 5 year survival rate and average survival duration for 6 patients with a DFI of more than 24 months were 50% and 49.5 months, compared with 0% and 32 months, for 6 patients with a DFI less than 24 months. Seven of 10 patients with a normal preoperative CEA level were still alive up to date, and the average survival duration was 43 months. None of the patients with an elevated CEA level survived 5 years.

Potential prognostic factors after lung resection, such as, sex, age, location and stage of primary tumor, size and number of pulmonary metastases, surgical procedure, DFI and preoperative CEA level, are summarized in Table 2.

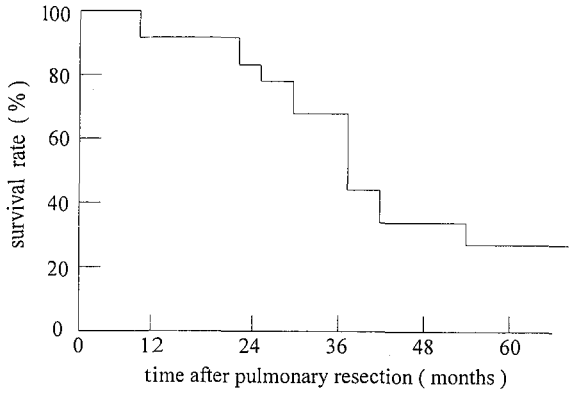

Fig. 1. Overall Survival Curve after Resection of Pulmonary Metastases

Discussion

The overall median survival of patients with metastatic colorectal cancer was approximately 10 months, with a 5 year probability of survival of less than 5% [6]. Only 2% of these metastatic colorectal cancers are limited to the lung without evidence of disease elsewhere [2]. Since Blalock, in 1944, reported the first thoracotomy for pulmonary metastases from colorectal cancer [7], pulmonary metastasectomy has been considered an appropriate therapy. A reported 5 year survival rate of around 30% to 43% after resection [2,3,4,8,9] further supports a surgical approach in this setting.

Our study bears all the disadvantages of a retrospective analysis in a small population, however, these data represent the complete experience on pulmonary resection for lung metastases from colorectal cancer in our hospital. The survival rate at 3 years and 5 years in this study was 66% and 25%, and the average survival duration was 40.9 months. Seven patients were still alive without evidence of recurrence or distant metastases after pulmonary resection.

Pulmonary metastasectomy is a safe procedure with low morbidity and low mortality. This was also confirmed by other studies in which no postoperative deaths were noted [8,9]. The type of pulmonary resection does not seem to affect the prognosis [10], however, Grunenwald et al does not recommend pneumonectomy because of a high risk of postoperative complications and mortality, as well as poor prognosis [11]. Van Halteren et al suggested staged bilateral thoracotomy or synchronous bilateral multiple wedge resection for patients with bilateral lung metastases [9], but resection of four or more metastatic nodules cannot be recommended for surgery by Girard et al because of early tumor recurrence and relatively short survival time [6].

In this study, we had one patient with a previous resection of liver metastases before the lung metastases. This patient remains alive and disease free 42 months after pulmonary resection. Indications for resection of pulmonary metastases in pulmonary and hepatic metastases developing synchronously or metachronously is controversial. For selected cases with completely resectable hepatic metastases, an operation is still worthwhile to improve survival [2,10,12].

Because the dissection of hilar and mediastinal lymph nodes cannot control disease, hilar or mediastinal lymph node involvement may be associated with poor prognosis [8,12]. Hilar lymph nodes metastases were found in only one of our cases, who died of multiple bone and lung recurrences within 3 years after pulmonary metastasectomy.

The identification of various prognostic factors with improved survival after pulmonary resection in different studies had shown inconsistent results [1,13,14]. Factors which do not seem to have a significant influence on survival are patient's age and sex, site and original stage of the primary tumor, the size of the largest metastatic lesion and extent of pulmonary resection [13,14]. Girard et al and the Mayo Clinic series demonstrated that a normal prethoracotomy CEA level correlated with a longer survival [6,15], but was not confirmed by the Memorial Sloan-Kettering Cancer Center series [2].

A recent report from the International

Table 2. Potential Prognostic Factors after Pulmonary Resection

Variables	No. of Patients	Survivor		Average Survival Time
		Alive	3 Year	5 Year	
Sex					
Male	5	3	4	2	50.4 months
Female	7	4	4	1	34 months
Age					
> 60 year	8	5	6	2	43.3 months
< 60 year	4	2	2	1	36 months
Location of primary site					
Colon	9	5	6	2	42.3 months
Rectum	3	2	2	1	36.3 months
Stage of primary tumor					
Duke's B	5	4	4	2	47.2 months
Duke's C	7	3	4	1	36.3 months
Size of metastatic lesions					
> 3 cm	2	1	2	1	49 months
≤ 3 cm	10	6	6	2	39.2 months
No. of pulmonary metastases					
Solitary	10	7	8	3	45 months
Multiple	2	0	0	0	20 months
Surgical procedure					
Lobectomy	3	2	2	1	40 months
Wedge resection	9	5	6	2	41.1 months
Disease free interval					
> 24 months	6	4	5	3	49.5 months
≤ 24 months	6	3	3	0	32 months
Preoperative CEA level					
> 5 ng/ml	2	0	1	0	30 months
≤ 5 ng/ml	10	7	7	3	43 months

Registry of Lung Metastases showed three significant prognostic parameters after resection of pulmonary metastases. These were completeness of resection, DFI of over 36 months, and solitary metastases [16], although not consistently reported in the literature [10]. To resolve this dilemma, a randomized prospective trial with a large number of patients is needed to obtain meaningful results.

Since the lung is the most frequent site of recurrence after pulmonary metastasectomy, multiple sequential resection can be performed with an acceptable long-term survival [3,17]. However good results were not seen in our study,

again probably due to a small study population.

In summary, pulmonary metastases of colorectal cancer could be treated with pulmonary metastasectomy in selected patients who have controlled primary tumor, exclusive lung metastases and no cardiac or respiratory insufficiency. Long-term survival is possible. Only large retrospective and prospective studies can further improve the identification and significance of potential prognostic factors.

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大腸直腸癌肺轉移的切除

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以外科手術作局部肺部切除，已成為大腸直腸癌合併肺轉移的主要治療方式，為評估此種治療的有效性，我們回顧性研究從 1990 至 1999 年間，有 12 位大腸直腸癌合併肺轉移病患，作過此種轉移癌的切除手術。其中 10 個病人為單獨轉移結節，2 位病人為多發性結節，有 11 位病人僅作一次開胸手術，1 位病人因局部復發作過 2 次手術，主要的手術方式是作肺部楔狀切除。

手術後這些病人平均存活期為 40.8 個月，3 年與 5 年的存活率分別為 66%與 25%。其中有 7 位病人術後目前仍存活，且沒有任何轉移或復發的現象，由此研究發現病人如果為單獨肺轉移結節，手術前的癌胚抗原值正常，或原發癌至發現肺轉移的期間越長，病人會有較長存活期的趨勢。所以大腸直腸癌合併肺轉移的病人經篩選後作局部肺切除手術有助於提高病人的存活率。*(胸腔醫學 2000; 15: 70-76)*

關鍵詞：轉移癌切除手術、肺轉移、大腸直腸癌

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台南地區居家呼吸器依賴個案照顧者之返家決策及其遷移照護經驗探討

葉莉莉　薄景華

本研究旨在探討台南地區居家呼吸器依賴個案照顧者之返家決策思考與其遷移照護經驗感受。對十二位已返家照顧至少一個月以上之照顧者進行深度訪談，將訪談過程錄音並轉換成文字後進行資料分析。結果顯示照顧者決策返家思考之六項因素為：環境變數——院醫囑之遵從、後續照護資源取得困難、對後續照護資源提供之照護品質存疑、家庭經濟困窘。個人變數——體認醫療照護的有限性、為維持家庭系統的平衡因素。對遷移照護之正向感受源於持續性照護經驗，負向感受源於中斷性照護經驗。遷移照護過程中，照護技能的學習大都經歷破碎的指導。沒有照顧者後悔所做的返家決策，亦無照顧者需求長期安置機構。以上現象加深對居家呼吸器依賴個案返家決策與遷移照護經驗之認識，相關結果得以強化健康專業人員對此類個案及其照顧者之服務。*(胸腔醫學 2000; 15: 77-84)*

關鍵字：居家呼吸器依賴個案、返家決策、遷移照護。

前　言

使用呼吸器的個案中約 9%~37%無法脫離呼吸器[1]，這些個案於病情穩定後如何遷移至成本較低，又具安全的環境，是近十年來健康照顧體系所努力的方向。

美國於 1950 年代始，將使用呼吸器病患送返家庭安置得到良好的成果後，此類服務需求便逐年增加[2-4]。為何家庭成為最被看好的安置場所，主因居家照護成本較低、院內感染率低且病患居家的活動力及對環境的控制感增加後，有更好的生活品質[5-7]。1980 年代迄今許多研究放在照護成本分析，結果一致發現此類個案採居家照護是最經濟且最具人性化照顧[3,6,8]。

臺灣地區全民健保對長期照護之給付並未將安養中心納入範圍，雖給付居家護理費用，但從公保試辦迄今，有關呼吸器租借及購買費用皆需民眾自付；相對於此類病患若住院，不僅可省下呼吸器租借或購置費且有專業人員 24 小時照顧，因此其返家意願不高。惟雖如此，仍有少數個案被接回家照護，即所謂的居家呼吸器依賴（Home Ventilator Dependent 以下簡稱 HVD）個案。若能針對 HVD 個案之返家決策深入瞭解，或有助於對此類個案之遷移照護服務；而台灣目前未有研究探討此議題。

有關呼吸器個案出院決策，由國內外文獻搜尋，並未找到類似文獻。僅有少數探討決策[9-11]與出院決策[12,13]；有關決策部分，Baumanm[9]指出，有效的決策是在充分被告知相關訊息，且其抉擇與個人的價值、行為相一致；Jones 等人[10]指出影響決策的因素包括決策產生不良後果的嚴重性如何？找到更好選擇的可能性如何？以及有多少時間可以尋找不同的選擇？而個人過去的經驗將影響其所做決策。而 Balneaves 等[11]在回顧 Janis 與 Mann 於 1997 年所發展的決策衝突理論，指出做決策的過程，因為充滿模糊、不確定感、或資源不足，因而是深具壓力的經驗；其強調決策過程中決策者所處的情境極為重要，因為只有在具選擇的情境下，才會發生決策衝突；其並進一步將壓力與因應的概念與決策衝突理論相連結，將屬情境之前置因素（環境變數、個人變數、一般信念與決策衝突），列入決策架構中，本研究於分析照顧者返家決策思考，即引用其前置因素中之變數進行結果之呈現。

出院決策方面，兩篇質性研究 Abramson[12]探討出院決策的不一致性，Wells[13]探討老人出院的決策過程；文獻中發現在醫院的父權式情境及組織架構下，病人角色沒有權利，因而在出院決策過程中，多為單向溝通。由於醫護人員被視為專家，因此對病人/家屬而言具有合法的

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權力，而具權力者所設定的目標，可能反應的是組織所期望的目標（儘速讓病人出院），這些目標不能被質疑或加以討論；因此，看似由醫師協調出院過程，實際上是專業人員在控制此過程，少與病人/家屬討論。上述文獻證實出院決策大部分受機構（體制）的力量所影響，少有病人/家屬之參與。

當病人由醫院移轉到家庭或另一機構的過程，即所謂遷移照護（transitional care），本研究所指之遷移照護，主要引用 Brooten[14]之定義：當病人由醫院遷移到家庭或其他照護機構所需的服務，此服務內容包括出院準備服務(discharge planning)及後續照護服務的協調。其並指出高危險的老人以及依賴機器爲生者特別需要此種介於兩安置點間的照護；依其定義 HVD 者極需給予此服務，以保障返家照護之安全。

本質性研究目的擬對台南地區 HVD 個案之主要照顧者(以下簡稱照顧者)進行下列瞭解：

1.爲何決策返家？思考之因素爲何？

2.由醫院遷移至家庭的過程中，對醫院準備其返家之經驗感受。

本研究結果將加深對 HVD 個案返家決策與其遷移照護經驗之認識，相關結果得以使健康專業人員強化對此類個案及其照顧者之服務。

材料與方法

本研究採半結構式會談法，藉以補捉 HVD 個案照顧者的觀點，探索 HVD 個案照顧者決策返家的思考因素與自醫院準備返家之經驗感受。

一、研究對象

研究對象爲居住於台南地區（含縣市）返家至少一個月以上，且仍居住在家之 HVD 個案及其照顧者。研究者由服務台南地區兩家呼吸器公司取得符合條件之十個案，並由服務台南地區五居家護理機構取得另兩個案連繫電話，在徵得照顧者同意後進行居家訪談。

二、資料收集與分析

每位照顧者平均訪談約三小時，將訪談過程錄音並將其轉換成文字，細讀多遍以得整體概念後進行釋義，分析語言及非語言資料，並進一步探索資料隱含意義，以詮釋研究者所瞭解的照顧者之主觀經驗。本研究會談指引如下：

1.當初決定返家的考量爲何？（是否後悔返家？是否從未想過送機構照護？未來有無可能送機構照護？）

2.請描述您在遷移過程中，自醫院準備返家的經驗感受。

研究者另收集個案及其照顧者下列資料：

1.個案方面：性別、年齡、診斷、每日呼吸器使用時數、外表意識、巴氏量表得分、留置導管種類及數目與出院前住院月數。

2.照顧者方面：與個案關係、年齡、每日照顧時數、居家照顧期間。

質性研究資料收集與分析的嚴謹度，主要由觀察或會談者直接收集，因此需考慮觀察者或會談者的能力與偏差[15]。本研究參與會談與觀察者即本文兩位作者；第一作者從事護理相關工作二十年，教學工作需在臨床帶實習，投入居家護理領域七年，參與中華民國長期照護協會居家護理師培訓，指導多位居家護理師執行實務工作。第二作者訪談時爲居家護理師，從事護理工作十一年，投入居家護理實務四年，照護過上百位居家護理病人及七位 HVD 個案。由於經驗累積，對資料的意義有較高敏感度，能深入瞭解照顧者的真實感受。資料分析的可信度，主要由兩位作者檢視內容，在彼此皆同意其歸納下進行分析與討論。

結 果

一、個案與照顧者資料

資料收集期間，十二個案之照顧者皆願意接受訪談，有關個案及其照顧者資料如表一。個案中以男性居多，計 66.7%；年齡分佈廣泛，範圍 3 至 81 歲。58.3%之個案診斷爲神經肌肉疾患（包括脊髓空洞症、脊髓損傷、脊髓神經瘤及運動神經元障礙），41.7%爲呼吸衰竭。每日呼吸器使用時數顯示 91.7%需 24 小時使用，一案僅在夜眠時使用陽壓輔助呼吸（計 7 小時）；此案爲唯一在身上未有任何導管者。外表意識以清醒警覺多，計 75.0%，因此在表達需要與理解他人談話多無困難。83.3%之個案巴氏量表得分爲零分，顯示其身體功能狀態需完全依賴他人。身體留置導管之比率由多至少依序爲氣切管 91.7%、胃管 50.0%、尿管 25.0%，導管留置總數三種者爲 8.3%、二種者爲 58.3%、一種者爲 25.0%。

照顧者與個案關係中，六位是母親；妻子、先生及女兒各兩位。照顧者年齡範圍 26 歲至 76 歲；每日照顧時數幾乎皆爲 24 小時，僅一位聘有固定菲傭。兩位照顧者因家中自營生意，偶而可兼顧，餘皆爲全職照護。個案返家照護期間平均 19.1 個月（範圍 1-52 月），其中三位照顧者已照護超過兩年（有關此 12 案之居家照護花費、使用照護資源種類及其所需之社會資源可參見作者 1999 年之文章[16]）。

表一 台南市居家呼吸器依賴病患及其照顧者之基本資料

個案編號	性別	年齡	診斷	每日呼吸器使用時數	外表意識	巴氏量表得分	留置導管數目	出院前住院月數	照顧者與個案關係	照顧者年齡	每日照顧時數	照顧期間(月
C1	女	59	呼吸衰竭	7	清醒警覺	95	0	1.5	女兒	26	24	5
C2	男	81	呼吸衰竭	24	昏迷	0	2	1	女兒	48	16	24
C3	男	42	運動神經	24	清醒警覺	0	2	2	妻	35	24	9
C4	男	54	元障礙呼吸衰竭	24	昏迷	0	2	3	妻	48	24	20
C5	女	60	脊髓	24	清醒警覺	0	2	7	夫	64	24	1
C6	女	76	神經瘤呼吸衰竭	24	昏迷	0	3	1	夫	76	16	12
C7	女	34	脊髓	24	清醒警覺	0	1	14	母	59	24	22
C8	男	18	空洞症SCI C4-5	24	清醒警覺	0	2	3	母	51	24	1
C9	男	22	肌肉萎縮	24	清醒警覺	15	1	4	母	44	24	52
C10	男	11	呼吸衰竭	24	清醒警覺	0	1	1	母	40	24	7
C11	男	7	脊髓	24	清醒警覺	0	2	31	母	30	24	47
C12	男	3	空洞症脊髓神經肌肉萎縮	24	清醒警覺	0	2	2	母	33	24	29

二、出院返家決策因素

HVD 個案照顧者所以決定返家，其思考的因素，依 Balneaves[11]決策模式中之前置因素加以分析，呈現如表二所示，包括(一)環境變數——需求：出院醫囑之遵從；資源：後續照護資源取得困難、對後續照護資源提供之照護品質存疑；限制：家庭經濟困窘。(二) 個人變數——價值信念：體認醫療照護的有限性；為維持家庭系統的平衡等六項因素。以下分述：

(一) 環境變數

需求：出院醫囑之遵從

HVD 個案返家照護的複雜性與困難度，照顧者多在住院期間有深刻體會，因此十二案中，僅一案因家庭經濟已無力負擔，主動表達出院的想法外，餘皆未主動要求返家。其所以決定返家主因醫師權威式告知需出院，不可再住。如照顧者們表示「醫師告訴我們可以出院了，說不能住那麼久……」(C2、C4、C6)，或告知「去別家醫院住10天再回來……」(C6)。當家屬擔心病人狀況，表達「是否可以讓我們更穩定些再回去？醫師卻說這樣已經很穩定了……每次探視都一直趕我們出院，說可以回去了……」(C1)。由以上可知，HVD 照顧者多在無奈的情況下思考何去何從的問題。

資源：後續照護資源取得困難

在思考何去何從的問題時，照顧者為何不考慮送往慢性醫院或護理之家等機構照護，有其對後續照護資源的考量。高[17]指出，照護呼吸器依賴個案之困難度高、成本高且收益低，多數機構未有人員與設備，故未將其列入收案對象。因此，照顧者在後續照護資源的取得上經驗較大之困難。如兩位案夫(C5、C6)因住在偏遠地區，醫療資源不豐富，因此出院時無法選擇就近送往機構接受照護。想將案妻轉送其他醫院的案夫表示「當初到××醫院，告訴他們我們的情形，醫師都不想聽……頭都不抬……告訴我們也不需要治療了……」(C6)。對於使用呼吸器的兒童，尋求後續照護更顯困難，如七歲及三歲個案之母親分別表示「那時候有去問過別的醫院，可是沒有可以接受這種使用呼吸器的小孩……」(C11)；「根本沒有地方可以去，其他醫院不收，曾跑去問××醫院，她們說你們原來住哪家醫院，就在哪家醫院……聽起來不想收，在那邊推，我想就算了！……」(C12)。

資源：對後續照護資源提供之照護品質存疑

訪談中，多位照顧者亦質疑後續照護機構所能提供的照護品質，因此未考慮送往照護。如某案妻在先生已呈植物人狀態下表示「我曾經去某中心看過，一看就不喜歡，……就是覺得那種地方不可能有好的照顧……我想那時候，如果住進去，大概也活不到現在」(C4)。三歲大

表二 台南地區呼吸器依賴個案照顧者決策返家因素

變數	項目
環境方面	需求：出院醫囑之遵從
	資源：後續照資源對提供之照護品質存疑
	後續照護資源取得困難
	限制：家庭經濟困窘
個人方面	價值信念：體認醫療照護的有限性
	爲維持家庭系統的完整

患孩之案母表示「剛開始回來很嚴重，有肺炎，常常黑掉，要送急診，如果那時候送療養院，大概現在也沒了（表死亡）」（C12）。

限制：家庭經濟困窘

訪談中，不少照顧者揭露出院的另一個主因爲已無力負擔住院花費才決定返家。如唯一要求主動出院的案母表示「雖然醫師叫我們再住，但是已經花了一百多萬了，沒錢可以再住……」（C9）。住院兩年半的案母表示「醫藥費繳不出來，人家會笑啊！欠了那麼多錢……也不是辦法，經濟壓力好大」（C11）。其他如「住院時，看護一天天的花費，相當可觀……」（C5）。「在那邊一天要一千多元，……我們又沒錢，父親一天也賺不到一千元……」（C12）。皆表達出雖然全民健保業已實施，但是加護病房及其他病房的補貼費，健保所不給付之藥費，以及看護雇用費，對一個需要提供長期照護的家庭而言，仍極爲吃重。

有關呼吸器依賴個案之轉介，高[17]指出，轉介之後續照護資源若未設胸腔專科醫師，則無法申請健保給付；因此若住機構，仍需自付呼吸器租金，每月花費至少五萬元以上。如前述，照顧者於住院中已感受經濟困窘的壓力，因此在安置場所的決定中，很少考量送往機構照護。如某案母表示在經濟無法負擔的情況下「一個月聽說要五萬多元……已經沒那麼多錢了……」（C9）。

（二）個人變數

價值信念：體認醫療照護的有限性

所謂醫療照護的有限性，指的是照顧者於住院過程中，觀察醫護人員的照護行爲並評估個案之照護成果，體認長期住院並無法得到有品質的照護或改善個案的健康狀態。

多數照顧者，期望於住院期間，個案病情得以改善，或可嚐試脫離呼吸器，並獲得有品質的照護。然而醫療照護亦有極限，照顧者於住院期間，觀察醫護人員的照護行爲並評估個案之照護成果，因而體認此限制而加強返家動機。如對中醫略有涉獵的某案夫在太太住院的七個月中觀察到「在ICU，醫師也沒辦法有什麼治療……只看到護士在打抗生素……西醫對腦幹也沒辦法...住院沒效果……；在那邊都沒有大便，她們只有灌腸，也沒有挖清，塞在那邊當然解不出來……」（C6）。住院超過兩年半的7歲小孩之案母表示「覺得住越久，小孩得到的照顧並不好，因爲她們覺得這是死病人了，會比較疏忽……看一個人照顧那麼多床……想想小孩子自己在那邊（ICU）真的很可憐」（C11）。某住院兩個月的案母說「醫師後來也不看小孩了……，我們在醫院就是希望有醫師護士看，結果只有我一個人照顧，一天還要付一千多元……怎麼不回家？！」（C12）。

價值信念：爲維持家庭系統的平衡

一人生病，全家動員往返醫院的現象，普遍存於臺灣醫療體系中，爲減少家屬往來醫院的奔波，也是HVD照顧者決策返家的重要因素。此處所指維持家庭系統的平衡指的是減少家屬往返醫院之奔波與維持家庭生活正常。

某案女表示「媽媽住院，我24小時無法離開，除了回家換衣服...吃飯都要姊姊送，需要有另外一個人照顧我的吃……」（C1），對太太住××醫院，兒子需來回奔波的老先生表示「兒子每天天母與××醫院兩邊跑，十分辛苦……雖然兒子們都很孝順，但是……每個人都有自己的家庭啊……」（C5）。某案母表示「我在醫院，我娘家的兄弟姊妹大家都每天這樣往醫院跑……」（C8）。在醫院照顧兒子的母親則說「在那邊洗澡不方便，妹妹要每天來幫忙，跑過來跑過去，我女兒（案姐）在家也是要有人照顧啊！我們大人也很累，……當初我照顧他，不是只有我照顧而已啊，媽媽還要一天跑好幾趟，幫我買吃的，送東西……」（C12）以上顯示個案住院影響家人之生活作息極大，許多照顧者深以爲苦。

返家照護後立即改善此現象；如自營文具生意的案妻表示「回家後，覺得比較像一個完整的家，……我也比較方便，可以照顧到家裡的生意，子女間的向心力比較好，……現在放假，兒女們都會回家幫忙，比住院時好很多」（C4）。往返醫院兩年半的案母更表示返家後.「不用每天跑醫院了，……」（C11）。以上分享得知爲維持家庭系統之平衡亦是照顧者決策返家的重要因素。

三、遷移照護之經驗感受

對一位HVD照顧者言，出院返家需面對的兩大問題爲後續照護資源的提供——呼吸器與相關設備的安排、居家護理服務的提供，與返家後各項照護技能的學習。以下分述照顧者於遷移照護過程中，自醫院返家的經驗感受。

（一）後續照護資源的提供

照顧者在此部份，有經驗不同的正負向感受。正向感

受源於後續照護資源與訊息的提供充分，使照顧者在遷移至家庭的過程中經歷持續性照護經驗。

持續性照護經驗

照顧者表示「出院時呼吸器公司的人陪我們一起回家，……幫我們安排……我們比較放心」（C1,C9），某案女表示「醫院在回家的安排上不錯，因爲呼吸器若有問題，只要打電話，即使晚上她們都會來處理……」（C2），一位剛出院的案母則說「××醫院在出院準備上蠻細膩的，像我們轉到××醫院去，他還請那邊的小姐幫我們看...出院時有幫我們聯絡居家型呼吸器……，居家護理師也告訴我們出院後要準備什麼……」（C8），某案妻則說「回家前告訴我們可以定期來換管子，我便比較放心……，醫院也說萬一急診可以再回去……我就更放心……」（C4）

中斷性照護經驗

照顧者的負向感受源於後續照護資源與訊息提供不足，使照顧者感受中斷的照護。

某案女表達「之前機器沒有弄好，便一直叫我們出院，我告訴他們，你們要叫那一家(呼吸器)公司，我們也不知道……，碰到××醫師，問他幫我們問得怎麼樣了……，他便說，那不是我該問的，是你們要自己去問的，我說我們不知道要去哪裡問，他才叫我去呼吸治療室，……他們給我名片，叫我自己去聯絡……去問價錢多少……，我也沒辦法比較其他家……」（C1）。某案因居住偏遠，已返家一個月，卻無法找到願意服務的居家護理機構，案夫無奈的表達「找居家護理機構怎會如此困難？……真不方便……當初醫院有幫我們聯繫，誰知道回家後卻沒有人願意來……」（C6）。另某案夫（C5）返家照護超過一年、某案母（C9）已返家超過四年，皆因未被轉介居家護理而需定期回院更換導管，照顧者多表達不便但也無可奈何。

（二）照護技能的學習

遷移照護的過程中，多數照顧者經歷破碎的照護技能指導。所謂破碎的指導指的是醫療體系未提供有計劃、具結構性的指導、提供不完整的照護訊息或給予照顧者學習的時間匆促不足。

詢問某未接受居家護理服務之案夫，其對醫院的指導，仍氣憤的表達「現在回家能照顧就好了，不要去回想醫院如何準備……。消毒、灌食都是××（呼吸器公司的呼吸治療師）教的，醫院只有聯絡機器啦……沒有提醒回來的照顧，……醫師當你是……看都不看……」（C6）。某案母表達「沒有教，住院時自己看護士如何抽，……我們也記不了這麼多……，有告訴我們回家後要如何照顧，但是沒有示範技術或叫我們做給他們看……」（C9）。

多位照顧者抱怨學習時間匆促不足，如某案女表達「原來的醫院住不到一個星期就出院了，一星期中大約學會如何抽痰……，但是呼吸器也只用了一天就回家了……，也是回家後才慢慢的學……」（C2）。某案夫則說「加護病房出來後，到普通病房 2-3 個月、復健病房 2-3 個月，卻到最後一星期才告訴我們需練習抽痰，並給機會做……覺得準備時間不夠……」（C5）。七歲個案之母表示「快出院時，才讓我們去實習一個星期，時間很緊……」（C11）。三歲個案之母生氣的表示「做氣切裝上呼吸器的隔天，便催我們出院，說 ICU 不能住那麼久……，我說都不會照顧，他說很簡單，……」（C12）。由以上分享得知 HVD 照顧者在照護技能的學習，多經歷破碎的指導。

討 論

一、照顧者返家決策思考因素

Coulton 等人[18]之研究顯示出院準備服務中，安置場所的決定受病人與家庭特質、健康專業人員的行爲與決策時周邊資源影響。其結果可由本研究加以印證；本研究發現照顧者返家之初始動機受健康專業人員行爲所影響；如出院醫囑之遵從、由醫護人員的照護行爲與照護成果體認醫療照護之有限性。照顧者之所以遵從醫囑，符合多位學者[12,13,19]指出，醫療情境中不平衡之權利關係，可由醫師對訊息之控制與對醫囑遵從之要求窺見。而鑑於出院決策由專業人員壟斷之不宜，Wells[13]建議採用 Habermas 的溝通-行動（communicative-action）做爲介入策略，在醫病的雙向溝通中，了解彼此的社會需求、所重視的價值等，藉由協商、妥協而達成雙方都能接受的決定。

本研究中，照顧者經驗後續照護資源取得困難且擔憂其照護品質，因而強化返家動機，印證環境中的資源狀況影響出院安置場所之決策，此結果符合高[17]之經驗：其指出呼吸器依賴個案在轉介機構上，常面臨療養機構不受理或照顧者無法接受機構之照護品質、以及經濟花費太高之困難。

於病人與家庭特質上，本研究中 75%的個案意識清楚、具溝通表達能力，與照顧者多爲血親關係，致使照顧者不忍將其送至療養機構。經濟部分，由作者對此群體之研究[16]，發現近半年內個案之月平均花費中數爲 11265 元（範圍 2750-50040 元不等），經濟負荷使三分之一案家借貸過日、半數以上(58.3%)需求經濟補助，顯示其經濟饋乏之壓力。此外，HVD 個案照顧者，經歷家人生病、殘障、失能、以及財務改變……等；依 Holmes 等[20]之生活改變單位顯示以上皆是重大壓力事件，使 HVD 個案家庭系統飽受失衡之苦。依系統理論觀點，當其失衡時，系統會運用內外資源及回饋管路，盡力回復平衡[21,22]。

返家照護除使個案回歸家庭系統，家人的生活作息亦趨正常，此平衡對個案與照顧者皆十分重要。

後續照顧期間越長，越需考慮照護資源所能提供的照護內涵以決定照護資源的適切性[3]。本研究中，75%的HVD 個案居家期間超過半年，最久者已超過四年，以上個案仍多穩定，預期居家期間可以更長。Pierson[3]指出呼吸器依賴個案接受機構照護不僅花費高、且多數機構僅提供保護性照護，未考慮復健需求(活動力之強化與人際社會化活動之增加)，因而機構照護的適切性值得懷疑。此外，學者們多認爲機構照護不適合呼吸器依賴孩童(本研究中有三位 12 歲以下者)之身、心、社會發展需要[8,23]。有關 HVD 孩童的照顧，Miller 等[8]建議以居家照護合併個案管理方式進行，藉以整合出院準備服務，設定出院標準並積極結合家庭、社區、學校與醫院各項資源，以滿足孩童身心社會發展之需要。

本研究另發現照顧者之返家決策具高度持續性；所有照顧者皆不後悔返家且不需求長期安置機構；此結果符合Cosbey [24]以質性研究探討 42 位照顧者之安置決策，其指出照顧者決策安置場所的意念很早即形成，且持續穩定。

二、遷移照護之經驗感受

高[17]指出 HVD 個案返家，需面對的問題包括居家照護設備不足與照護知識技能不足等；與本研究中照顧者集中於後續照護資源及照護技能學習感受之分享相符合。

本研究之個案多需求 24 小時呼吸器使用且身上至少留置一種導管，日常生活需完全依賴他人協助。這些照護需求符合學者們對 HVD 個案之調查，發現除呼吸照護外，尚需求神經、活動、呼吸、營養、排泄、溝通、出院服務及社區整合等照護；因而家屬需學習呼吸照顧(包括評估呼吸功能、查核呼吸器、抽痰、使用人工甦醒球及電力無效時的緊急處置，知道如何監測及轉介)、協助移位、灌食、處理尿管及大小便照護等[8,25,26]。這些照護技能的學習，如何在短暫住院期間(本研究中八案於三個月內，三案在一個月即出院)，藉有計劃的結構式指導，教會照顧者極具挑戰性；然而本研究中，由照顧者之分享，顯示多經歷破碎的指導且時間匆促。建議對此類個案之出院準備，應強化結構式之示教與回復示教、預留充分的學習時間，使照顧者確實學得各項照護技能，保障返家之安全。

國內現有可提供 HVD 個案之後續照護資源中，以居家護理服務較爲便利可得，且多數個案確需定期更換各種導管。然本研究有三分之一個案未能有效連結此資源，致照顧者經歷中斷的服務，產生負向感受。此結果符合Bull[27]探討病人對出院準備服務之品質感受，其發現病人在意的是能否有效連結後續照護資源。此外，Anderson等[28]亦指出不中斷的服務應做爲評價出院準備服務品質的重要指標。

HVD 個案照護模式之發展，是我國長期照護與出院準備服務政策明訂之重點工作項目之一[29]；然而至今國內未有此類個案整體性居家照護模式之規劃。國外文獻顯示，要保障 HVD 個案之照護品質需靠醫療團隊（胸腔科醫師、居家護理師、呼吸治療師、物理治療師、營養師、心理治療師等）之協同合作[3,4,22]。以現況言，國內某些 HVD 個案已有居家護理師、呼吸器公司之呼吸治療師與機器維修人員介入，如何在此基礎下建構合作模式，以助於未來多重醫療團隊合作模式之建立迄待努力。

結 論

科技進步使呼吸器之研發比以往更輕便、便宜、功能更佳。然而返家安置並不適合所有個案，文獻指出返家後結果，受病人特質、因應能力、照顧者照護意願、原有家庭功能等影響；因此建議出院之安置決策應對個案與照顧者進行心理及精神評價[3,4,6]並給予相當的教育訓練[2,8,26]。本研究中照顧者雖肯定返家照護之益處，然而亦傳達許多照護之壓力感受，對這些返家後需求高科技設備才能維生之個案與負荷甚重之照顧者，Arras 等[30]呼籲決策返家是否符合醫學期望與倫理考量值得重視。作者以爲以台灣現況(多重專業照護團隊尚未形成、社會福利資源不足且未整合、出院準備服務方起步仍未臻完善) 對其呼籲特別值得深思。

本研究限制爲侷限於台南地區、案數不多、個案年齡分佈廣(3-81 歲)、照顧者照顧期間不等(1-52 月)、且爲回溯性經驗感受探討。未來有關呼吸器依賴個案安置決策之研究，應針對本研究各項限制加以改善，並增加安置點爲機構者爲研究對照組，以瞭解呼吸器依賴個案後續照護安置決策之全貌。

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Discharge Decision Making and Perception of Transitional Care of Caregiver of Home Ventilator Dependent Client in Tainan

Lily Yeh, Ching-Hua Po

Purposes of this qualitative study were to thoroughly explore the discharge decision-making and perception of transitional care of caregiver for Home Ventilator Dependent (HVD) clients. Twelve caregivers that had cared HVD for at least one month were invited to participate. Semi-structured interview was designed to collect the data. The interview was tape-recorded, transcribed as a narrative verbal process recording, and then carefully analyzed. Results showed factors considered for discharge of patients. The environmental variables included compliance to doctor's discharge order, perceived limitation of quantity and quality of the post-care institutions, and perceived restriction of family's economics. Personal variables included perceived limitation of health care and wish to maintain the balance of family system. Those who experienced continuity of care had positive perception to transitional care and vice versa. In transitional care process, most of the caregivers received insufficient and non-structured instructions regarding care, skill, and knowledge. Yet, neither did the caregivers regret going home, nor did they wish to re-institutionalize whom they cared. Results of this study could be used to refine discharge planning for HVD clients and their caregivers. ***(Thorac Med 2000; 15: 77-84)***

Key words: home ventilator dependent, discharge decision making, transitional care

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Tracheobronchopathia Osteochondroplastica— A Report of Two Cases

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Tracheobronchopathia osteochondroplastica (TO) is a rare and usually benign disorder affecting the trachea, and occasionally the bronchi. We describe two cases of TO: one, a 47 y/o man with long-term intermittent hemoptysis, and the other, a 71 y/o woman with the symptoms of cough with occasional hemoptysis. Bronchoscopy revealed multiple papilla-like nodules along the anterolateral wall of the trachea in both patients, which extended to the right main bronchus in the latter patient. Pathologic examination confirmed the diagnosis of TO. Bronchoscopic examination revealed no changes after 4 years in the latter case.

The etiology and pathogenesis of TO are unknown. The severity of TO ranges from no symptoms to severe dyspnea, hemoptysis, or pneumonitis. Treatment is seldom necessary. The differential diagnosis of nodular lesions includes amyloidosis, endobronchial sarcoidosis, calcified lesions of tuberculosis, papillomatosis, tracheobronchial calcinosis, and neoplasms. Awareness of this condition is important so as to avoid unnecessary surgery or chemotherapy. ***(Thorac Med 2000; 15: 85-89)***

Key words: tracheobronchopathia osteochondroplastica, hemoptysis

Introduction

Tracheobronchopathia osteochondroplastica (TO) is a rare disorder. It is characterized by the structure of bony and cartilaginous tissue within the submucosa of the trachea and/or bronchi. This disorder is usually benign and the clinical manifestations are variable. The majority of patients are asymptomatic during their lifetime, therefore, treatment is seldom needed. We present two cases with prolonged hemoptysis in which the diagnosis of tracheobronchopathia osteochondroplastica was confirmed by bronchoscopic and pathologic examination.

Case 1

A 47-year-old man, who had no smoking history, presented with intermittent hemoptysis for 1 month. Chest radiography and laboratory data, including CBC, PT, PTT, and routine biochemistry, provided negative findings. Bronchoscopy revealed multiple nodular lesions with a smooth surface located at the anterior wall of the middle trachea (about 5 cm in length) (Figure 1). The mucosa was hyperemic and the cartilage under the mucosa was indistinct. Pathology revealed that the submucosa lesions were composed of bone, cartilage, and calcified

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acellular protein matrix, which was compatible with the diagnosis of TO (Figure 2).

Case 2

A 71-year-old female complained of repeated coughing with blood-streaked sputum for more than 6 months. She was a non-smoker. Chest radiographs (posteroanterior and lateral views) did not show any abnormalities, and the laboratory data were all within normal limits. The pulmonary function test disclosed no restrictive or obstructive defects. The DLCO was also normal. The FEF50/FIF50 value was 1.29. Bronchoscopy was then arranged to survey upper airway lesions, and disclosed multiple hard nodules presenting from 3 cm below the vocal cord, and extending all the way down to the trachea and right main bronchus, to the truncus intermedius (Figure 3). The left main bronchus was free of lesions. Pathology confirmed the diagnosis of TO. Bronchoscopy was repeated 4 years later, and showed that the lesions had remained the same without progression.

Discussion

Tracheobronchopathia osteochondroplastica was first described by Wilks in 1857, who reported large numbers of "bony plates" protruding into the lumen of the larynx, trachea, and bronchi of a 38 year-old man. However, the term "Tracheobronchopathia osteochondroplastica" was coined by Aschoff in 1910 [14]. The incidence of TO ranges from 1/125 to 1/5000 without significant gender predominance. The age distribution of reported cases is 11 to 72 years with more than half over 50 years old. No clear link between smoking and TO has been established. Because most cases are asymptomatic and diagnosed only after necropsy, some investigators believed that this disease occurred more commonly than previously reported [15].

The etiology and pathogenesis of TO are still unknown. Hypotheses include chronic infections, congenital anomaly, chemical or mechanical irritation, degenerative or metabolic abnormalities,

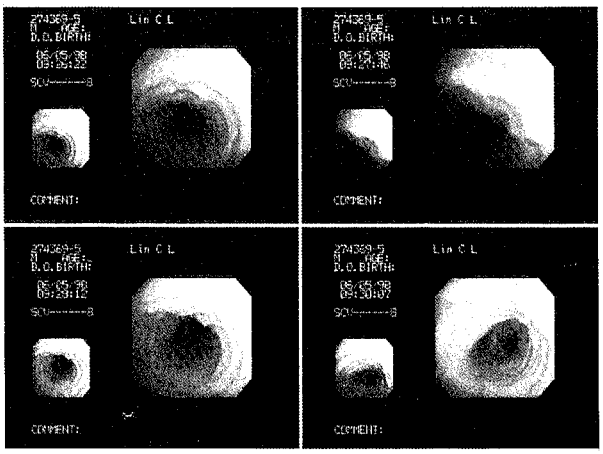

Fig 1. Multiple nodules were visible at the anterior trachea wall.

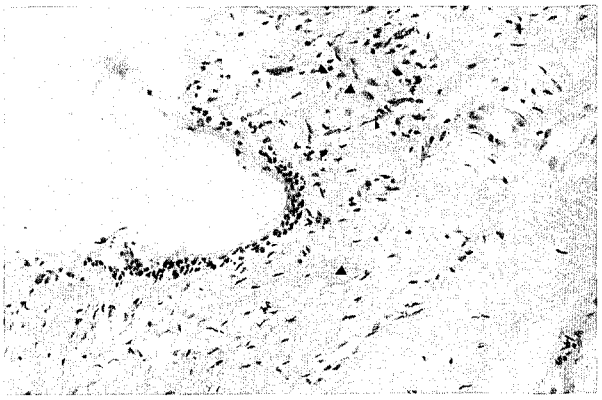

Fig 2. The submucosa lesion was composed of calcification (▲), and hyalinized fibrocollagenous tissue.

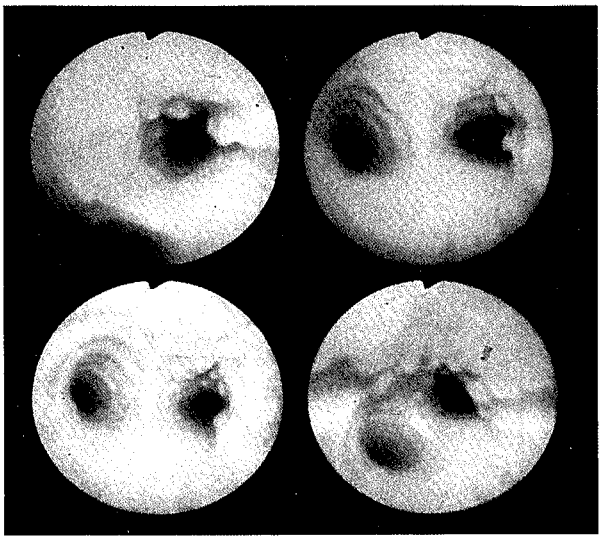

Fig 3. The bronchoscope showed multiple nodules extending along the anterolateral wall of the trachea and down to the right main bronchus. The left main bronchus was free of lesion.

and genetic predisposition. The clinical manifestations are variable. The most common presentations are cough, hoarseness, dyspnea, stridor, hemoptysis, and recurrent respiratory tract infections. Other rare manifestations include difficulty in intubation [9], middle lobe syndrome [4], an association with atypical mycobacterial disease [13], and associations with lung cancer, thyroid cancer, or thymoma. When the larynx is involved, the patient may complain of dryness of the throat, a change in voice, and a sense of foreign material in the throat. The disease usually progresses quite slowly, but the rate of development is variable. Very rapid progression with tracheal stenosis has been reported in one case [2].

The diagnosis is made on the basis of the gross appearance during bronchoscopy. Radiologic images, including CT scans, MRI, or tracheal tomograms, may be suggestive. Bronchoscopy usually shows multiple papilla-like, hard nodules on the cartilaginous part of the trachea or main bronchi [11]. The nodular lesions are usually seen in the distal 2/3 of the trachea and main bronchi, but they can also be detected in the proximal trachea, larynx, and other lobar and segmental bronchi. The intraluminal lesions usually involve the anterior and lateral walls and spare the membranous posterior wall, however, posterior involvement has been reported, too. Tracheal biopsy is often technically difficult because of the bony nature of the lesions. The final definite diagnosis depends on the histopathological examination, which often shows normal respiratory mucosa covering the nodule, although squamous metaplasia and inflammation can be present [10]. The nodules mainly consist of hyalinized fibrocollagenous tissue with an area of necrosis, fibrosis, and calcification. These nodules typically do not stain strongly with Congo red, but do stain blue or green with Masson's trichrome stain, which is consistent with collagen deposition.

The routine radiographic demonstration may be difficult [7]. Occasionally, diffuse irregular narrowing of the trachea and main bronchi may be seen. CT may be of value in detecting submucosal calcified nodules, which are the diagnostic features of TO [12]. HRCT can be used to differentiate other benign tracheobronchial lesions, such as relapsing polychondritis and tracheobronchial amyloidosis.

Pulmonary function tests usually show a normal or an obstructive pattern (extrathoracic), but a few cases have a combination of restrictive and obstructive patterns. Pulmonary function studies are valuable for diagnosis and clinical follow-up.

Clinically, the differential diagnosis of TO includes squamous papillomatosis, rhinosclerosis, polychondritis, tracheobronchial calcinosis, "saber sheath" trachea, tracheobronchial amyloidosis, tracheobronchial tuberculosis, endobronchial sarcoidosis, infiltrating carcinoma, and lymphoma.

The treatment is usually symptomatic management. Steroid therapy has been tried with good results in limited reports. Antibiotics are mandatory for recurrent respiratory tract infections. Surgical interventions are seldom needed, except in symptomatic patients. Surgical procedures include the resection of a tracheal segment, partial laryngectomy, and bronchoscopic removal of the lesions. The surgical insertion of a stent (T-Y tube) has been successfully performed in recent experiments, with good response. Laser resection of the lesions has been tried, but without a favorable response. Radiation therapy with 750 rad to relieve the symptoms has also been tried, but the benefits are doubtful.

Although TO is a rare disease, the prevalence of TO may show an increase with the development of bronchoscopy. We suggest including the disease in the differential diagnosis of endobronchial lesions to avoid unnecessary interventions.

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氣管支氣管的骨軟骨病變—兩例病例報告

陳維志　彭明仁　李聰明　林芳杰　陳碧芳*

氣管支氣管的骨軟骨病變是一種罕見而且常是良性的一種疾病。最常發生的部位是在氣管，但有時也會影響到支氣管。我們現在報告兩例病例：一位是 47 歲的男性，主訴為長時間的間段性咳血；另一位是 71 歲女性，症狀是長期的乾咳和痰中帶血絲。氣管鏡檢查發現：第一個病人沿著氣管的前外側壁，有許多顆堅硬的疣狀突起，在第二個病人身上相同的突起更延伸到右側主支氣管內。病理報告證實是氣管支氣管的骨軟骨病變。第二個病患在 4 年後的氣管鏡追蹤下顯示，並無進一部變化。

氣管支氣管的骨軟骨病變其病因和發病原理目前仍然不是很清楚。它的嚴重度可從毫無症狀到嚴重的氣喘、咳血、和肺炎。一般來說，治療的方向主要為症狀處理。而它的鑑別診斷包括：澱粉樣變性病、氣管內類肉瘤病、結核病鈣化、乳頭狀瘤病、氣管支氣管鈣化症、及腫瘤。即早明白這一種病變，可以避免不必要的外科手術和化學治療。*(胸腔醫學 2000; 15: 85-89)*

關鍵詞：氣管支氣管的骨軟骨病變，咳血

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Salmonella Lung Abscess and Empyema in a Patient with Metastatic Papillary Thyroid Carcinoma— A Case Report

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Pulmonary infections caused by Salmonella species are very uncommon. Among them, S. typhimurium and S. choleraesuis are the salmonella species most commonly responsible for respiratory infection. They usually occur in people with severe underlying diseases, preexisting abnormalities of the lung or pleura, or in patients with a suppressed immune system. The true incidence of pleuropulmonary infections due to nontyphoid Salmonella is not known. To our knowledge, empyema and lung abscess induced by nontyphoid salmonella (Salmonella enteritidis) in a patient with malignant disease has not been reported yet. We present a case of a 71-year-old female with empyema and lung abscess with underlying metastatic papillary thyroid carcinoma. Salmonella enteritidis was isolated from the lung abscess, empyema fluid, and sputum. She was first treated with antibiotics ceftazidime and then changed to cefatriazone, but she expired later due to uncontrolled secondary infection, septicemia, and multiorgan failure. ***(Thorac Med 2000; 15: 90-96)***

Key words: Salmonella lung abscess, empyema, Salmonella enteritidis, metastatic papillary thyroid carcinoma.

Introduction

Salmonella infections are found worldwide. They usually involve the gastrointestinal tract. Clinically, they present as gastroenteritis, watery or bloody diarrhea (dysentery), typhoid (enteric) fever, bacteremia, and septicemia. They can also occur as a systemic spread invading soft tissue or organs. The extraintestinal manifestation of salmonella may include osteomyelitis, arthritis, endocarditis, mycotic aneurysm, meningitis, urinary tract infection, pneumonia, and empyema. Pneumonia occurs in 11% of patients with typhoid fever, and most cases are thought to be due to superinfection[1]. Salmonella typhoid is rarely recovered from the sputum[2].Nontyphoid salmonella strains are currently recognized as an unusual cause of pleuropulmonary infection. The first case of lung abscess and empyema due to nontyphoid salmonella was reported by Besznyak et-al. in 1965[2]. We herein present another case of nontyphoid Salmonella lung abscess and empyema in a patient with papillary thyroid carcinoma with lung metastasis; the organism was proved by sputum, pleural fluid, and pus culture.

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Case report

A 71-year-old female patient was admitted to our hospital with the chief complaint of high fever and cough with sputum for one week. She also had had poor appetite and generalized weakness in recent months. She gave a history of operation for thyroid enlargement about ten years ago. The nature of the tumor was not ascertained and could not be traced back. She denied a history of radiation to the neck, blood transfusion, diarrhea, or hepatobiliary infection. On examination, the patient was ill-looking, and emaciated. Her vital signs were BP 107/71, heart rate 136/min, respiratory rate 21/min, and temperature 39.9℃. There was a mass measuring 4 x 5 cm, hard in consistency, fixed and with no tenderness, on the right side of the neck. On auscultation, the vesicular breathing sound was diminished on the right side of the lung. Laboratory tests showed the white cell count at 22100/ cumm with 94% neutrophils. Chest X-ray showed a radiopaque mass at the upper right lobe (figure 1). She was then given antibiotic cephazoline and gentamycin treatment for infection control after taking a blood culture. Despite treatment, her condition was unstable, and dopamine drip was given for hypotension. On the second day, a blood culture was taken again, and cleocin was added to the previous antibiotics.

On the third day of hospitalization, a chest CT scan was done (figure 2) and it showed a right thyroid mass compressing the trachea, a mass with areas of necrosis and liquefaction at the upper right anterior lobe area, upper right posterior lobe pneumonia, and right-sided pleural effusion. She was then referred to the chest surgeon for further management.

On the fifth hospital day, she was very dyspneic and stridor was noted. An endotracheal tube was inserted and she was given ventilatory support and ICU care. Later, a total thyroidectomy with the removal of associated supraclavicular lymph nodes was performed for the relief of dyspnea. Biopsy results showed papillary carcinoma of the thyroid with lymph node metastasis (figure 3).

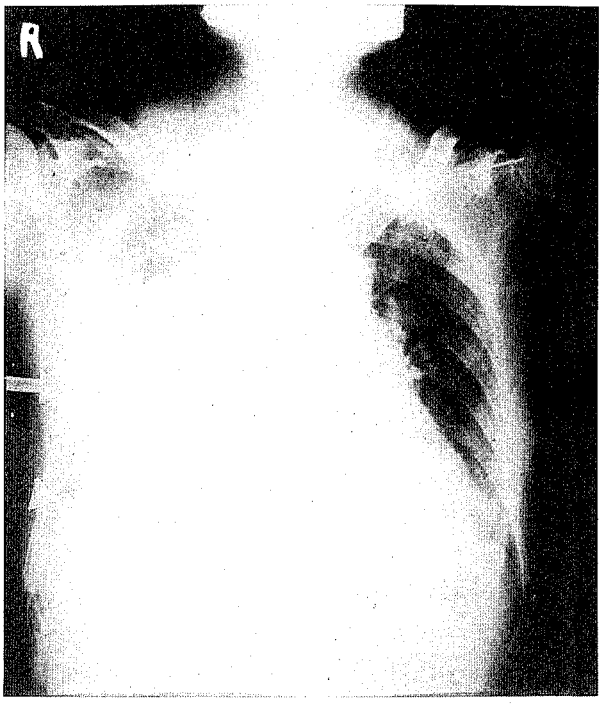

Fig. 1. CXR showing a radioopaque mass in the upper right lobe with a blunt costrophrenic angle.

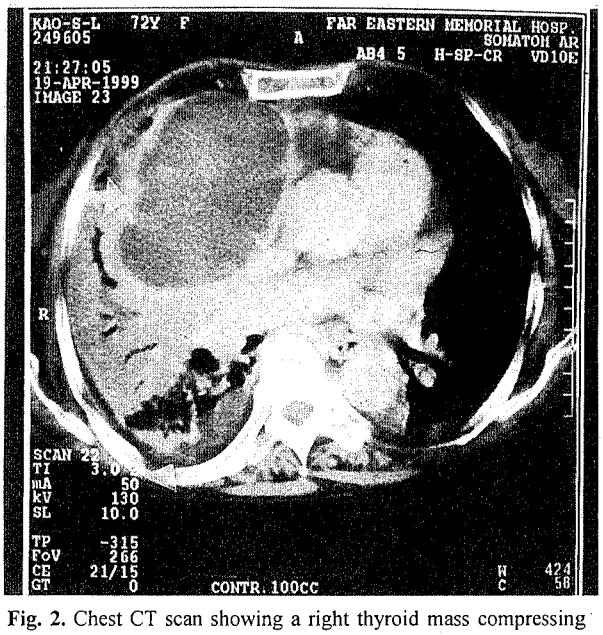

Fig. 2. Chest CT scan showing a right thyroid mass compressing the trachea with areas of necrosis.

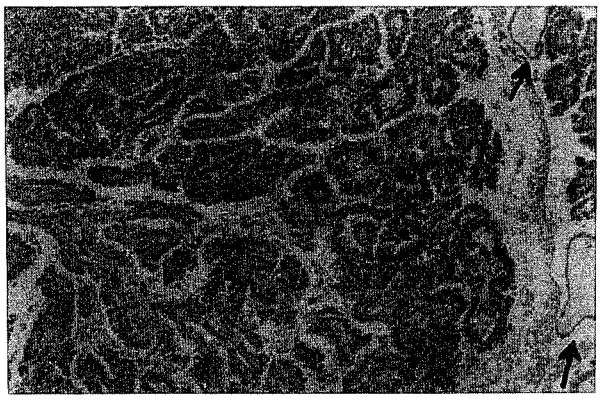

Fig. 3. Papillary carcinoma of thyroid metastasis to the cervical lymph node, the two arrows point to the neoplastic thyroid follicle (H&E stain 100*)

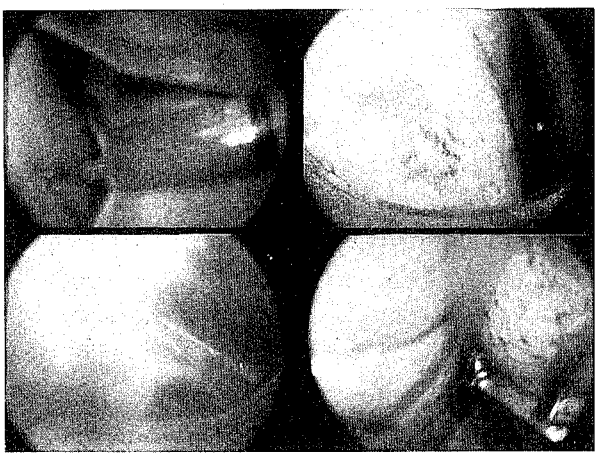

Fig. 4. Exploratory thoracotomy with abscess drainage and lobectomy.

On the sixth day of hospitalization, exploratory thoracotomy (figure 4) with abscess drainage and lobectomy was done on the upper right lobe of the lung. The right pleural cavity yielded 650 cc of yellowish fluid. Tissue necrosis and turbid pus were then removed. Chest tube insertion was done for abscess drainage. On routine examination, gram-negative bacilli were found, and Ceftazidime and gentamycin antibiotic treatment was given. Biopsy results showed metastatic papillary adenocarcinoma of the lung. (Figure 5)

On the second week of hospitalization, two out of three sputum cultures and both lung abscess cultures showed salmonella enteritidis which was sensitive to all antibiotics. The cytology examination of the abscess showed inflammatory cells. Blood and stool cultures showed no organisms. Despite the aggressive antibiotic therapy and drainage of the lung abscess and empyema, sepsis was not controlled well. Fever still persisted and WBC count remained high (WBC 22200/μl, neutrophil 91%).

On the third week of hospitalization, repeated cultures of pleural fluid drainage showed negative results, but her condition was not improved and fever, mostly between 38°C and 39°C remained. Antibiotic therapy was changed to Ceftriazone and gentamycin. Blood cultures were also showed negative results.

On the fourth week of hospitalization, the CVP tip culture showed Staphylococcus aureus (MRSA), and enterococcus. Urine culture revealed candida albican infection and antibiotics were changed to vancomycin and diflucan. Despite the above aggressive antibiotic therapy, the patient's condition deteriorated, and she expired on the 31st day of hospitalization due to multiorgan failure.

Discussion

Salmonella are gram-negative bacilli of the family Enterobacteriaceae. They are facultatively anaerobic, nonsporing, motile bacilli, and typically non-lactose fermentors. The mode of transmission is usually the ingestion of contaminated animal food products. More than 2300 salmonella organisms are present worldwide. According to current classification based on DNA relatedness, only two species have been recognized: Salmonella enterica and Salmonella bongori. The latter is nonpathogenic to humans. S.enterica has been subdivided into 6 subspecies using the serologic method: (I) enterica, (II) salmae, (III a) arizonae, (III b) diarizonae, (IV) houtenae, and (VI) indica. Based on the polysaccharide somatic "O" antigens and protein flagella "H" antigens,

serogroups are designated by the letters A, B, C, D, etc. Most human pathogenic salmonellae are members of groups A through D.

The clinical manifestations of Salmonellosis fall into four main groups: gastroenteritis, typhoidal or septic syndrome, focal manifestations, and carrier state. Among 7,779 cases of Salmonellosis, Saphra and Winter[4] found clinical signs of gastroenteritis in 68.3%, septic syndrome in 8.8%, and a carrier stage in 15.5%. Focal manifestations occurred only in 7.5% of all cases, and those involving the respiratory system (85 cases) were about 14.7% of focal extraintestinal manifestations, or 1% of all the Salmonella infections. In Aguado's report, about 10% of all extraintestinal manifestations of salmonella infection involved the lung and pleural space[5].

Although nontyphoid salmonella infection of the pleuropulmonary organ has been reported in large series of salmonellosis[4-6], there have been few reports on this topic recently. The true incidence of pleruopulmonary infections due to nontyphoid salmonella may have been underestimated. This may be due partly to more attention being paid to other gram-negative bacilli pneumonia,[7] and that it is not currently recognized as a pathogen usually causing pneumonia in the immunocompromised host[8]. The role of samonellosis in the immunocompromised host has been recently amplified due to its high incidence in patients with acquired immunodeficiency syndrome[3,9-12]. Patients with preexisting pulmonary or pleural disease are also prone to salmonella infection[5]. Malignant neoplasms involving the pulmonary parenchyma or pleura are the most frequent predisposing conditions[3,14-15]. Impaired cell-mediated immunity in the compromised host, underlying diseases causing hemolysis, and prior use of antibiotics have been implicated as important pathogenic mechanisms in salmonella infection[8-9,15]. Three other pathogenic mechanisms have also been implicated[16]. Infection may occur by extension from a nearby

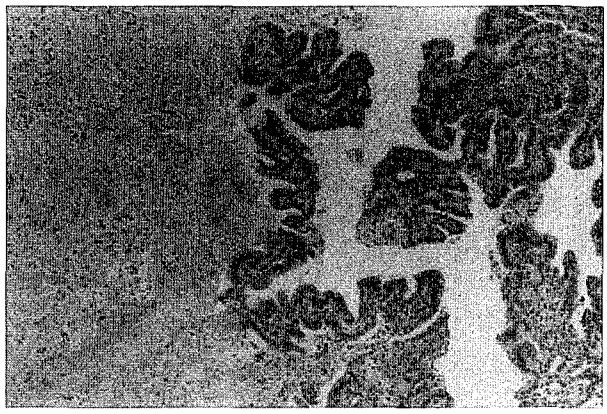

Fig. 5. Papillary carcinoma of thyroid (left half) metastasis to the necrotic lung (right half). H&E stain 100*

site[17], by the aspiration of infected gastric secretions in patients with gastrointestinal tract infection or colonization (reticuloendothelial system), and, finally, by hematogenous dissemination to the lungs[18]. Our patient had no G-I disturbance and negative blood culture. The preexistent malignant neoplasm and the patients emaciated condition induced an impair- ment of cell-mediated immunity and made our patient susceptible to nontyphoid salmonella infection.

According to Aguado's report[5], pulmonary infections with salmonella often have an acute onset. The majority of cases in the report had respiratory symptoms for less than 7 days before the diagnosis. Symptoms and signs were typical of bacterial pneumonia. There were no characteristic roentgenographic findings, and leukocytosis was absent in the majority of patients. In fact, a leukocyte count lower than $7.0\times 10^3/\mu l$ with a shift to the left could be a clue for the diagnosis of salmonella pneumonia[6]. In our case, the leukocyte count was $22.1\times 10^3/\mu l$, with 94% neutrophils. Although the value of a sputum culture in determing the cause of bacterial pneumonia is controversial, a culture of this type may be positive for salmonella pleuropulmonary infection, as in our case.

Although a salmonella infection causing enterocolitis alone is self-limited, patients with serious underlying disease may benefit from

antimicrobial therapy. The major therapeutic agents have been choloramphenicol 50 mg/kg BW/day in four divided doses orally or IV, or ampicillin 2 gm IV q6hr. Trimethoprim + sulfamethoxazole IV can be substituted at 10 mg/kg/day for five days. Third generation cephalosporin, such as cefotaxime, ceftriaxone, ceftizoxime, ceftazidime, and fluroquinolone are effective as older drugs and resistance is less likely. Therapy is continued for 2 weeks for enteric fever and for much longer with localization to the bone, aneurysm, heart valves, and various other sites.

In the literature, overall mortality has been from 28% (4) to 63%[6]. Patients who died and those who survived did not differ with respect to mechanism of acquisition of infection or underlying disorders. The mortality in patients younger than 60 years or without underlying pulmonary diseases was lower than that in those older than 60 years or with previous pulmonary abnormalities. Patients treated with antimicrobial agents active against nontyphoid Salmonella seemed to fare better than did those who were inadequately treated[5]. In our case, despite appropriate antibiotics and surgical drainage of the lung abscess and empyema, the patient died on the 31st day of hospitalization due to secondary infection and candida sepsis.

The diagnosis of salmonella infection is made by detecting the organism from cultures of blood, urine, sputum, local abscess aspiration, or synovial fluid aspiration. If no clinically localized of infection is available, a Gallium-67 citrate scan may be helpful[19].

In conclusion, although pulmonary manifestations of salmonella infection are rare, we must consider that salmonella infection may be the causal organism, especially in immunocompromised patients and those with preexistent pleuropulmonary disease. Efforts should be made to isolate this organism from sputum and blood cultures. Leukocytosis was absent in the majority of patients with salmonella pulmonary infection[5], but a WBC count over 10x $10^3/\mu$ l cannot rule out salmonella infection, as in our case. Pleuropulmonary infection due to nontyphoid strains of salmonella is a serious disease with high mortality, especially in the immunocompromised host. Increasing awareness of the role of nontyphoid salmonella as a causative agent of pneumonia will help to increase our knowledge of this infection and the need for early treatment.

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轉移性乳頭狀的甲狀腺癌症病患併發沙門桿菌肺膿瘍及膿胸—病例報告

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沙門桿菌屬所引起的肺部感染是非常少見的。而其中以鼠傷寒桿菌(S. typhimurium)和豬霍亂桿菌(S.choleraesuis)所引起的肺部感染是較為常見的。它們通常發生在那些具有潛在嚴重的系統性疾病、肺部或肋膜有結構性的異常、或者是免疫系統受到抑制的人身上。由 nontyphoid Salmonella 所引起的肋膜肺部感染的確實發生率目前並不清楚。但據我們的了解，由 nontyohoid Salmonella (Salmonella enteritidis 腸炎桿菌)在癌症病人身上，所造成的肺氣腫和肺膿瘍，目前還沒有被報導過。我們在這裏報告一個病例，這是一位七十一歲的女性病人，她原本就有轉移性乳頭狀的甲狀腺癌症，被發現有肺氣腫和肺膿瘍產生。從肺氣腫和肺膿瘍所形成的痰和膿液培養出 Salmonella enteritidis。一開始先用 ceftazidime 治療，後來再改用 cefatriazone 治療，但是最後病人還是因為併發無法控制的二度感染、敗血症和多發性器官衰竭而死亡。*(胸腔醫學 2000; 15: 90-96)*

關鍵詞：沙門桿菌肺膿瘍，膿胸，腸炎沙門桿菌，轉移性乳頭狀的甲狀腺癌症

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支氣管肺泡灌洗術在石綿症診斷的應用—病例報告

邱昭華　張西川

詳實的暴露史在間質性肺病變的診斷流程中，扮演相當重要的角色，職業史對職業性肺病診斷的確立更是一必要條件。然而，有時或因醫生的疏忽，或是病人對工作或周遭環境的認知不夠，因此無法得到正確或有意義的暴露史資料，此時一個客觀評量物質暴露的方法就有其重要性。本篇提出一56歲男性病例，藉由支氣管肺泡灌洗術（bronchoalveolar lavage，BAL）檢查中發現病人肺泡有大量石綿體，進而確定石綿症的診斷。在告知病人石綿症的預後以及抽菸對其罹患肺癌危險性有加成作用後，病人已戒菸，並規則在門診追蹤。BAL在間質性肺病診斷的重要性已無庸置疑，吾人若能熟悉石綿體在一般細胞學檢查的特殊發現，雖然沒有可靠暴露史的幫助，也能客觀而快速的確立病人的診斷。*（胸腔醫學2000; 15: 97-101）*

關鍵字：石綿，石綿症，石綿體，支氣管肺泡灌洗術

前　言

細心且詳實的病史詢問，是正確診斷疾病的第一步；職業暴露史更是診斷職業性肺病的必要條件。然而，有些物質的暴露和疾病的發生雖然有因果關係，但從初次暴露到產生症狀的時間卻不一定。例如石綿症便可長達二、三十年以上，以致病患不見得能記得，而使診斷延遲或甚至錯誤。此外，暴露史常是主觀的，而職業病的確立又常牽涉到補償問題；因此，客觀評量暴露史的方法，自有其臨床重要性。本文提出一案例，簡要回顧石綿症，並說明支氣管肺泡灌洗術（bronchoalveolar lavage, BAL）在石綿症診斷的應用。

案　例

華先生，56 歲本省籍男性，因乾咳及活動性呼吸短促數週，至本院門診求治。病人一天抽半包菸約 40 年，現職爲陽明山國家公園管理員。病人一般健康情形良好，無使用輔助性呼吸肌肉的情形，理學檢查除發現雙側下肺野有細囉音（fine rales）及喘鳴音（wheezing）外，其餘均無異常。在第一次門診時，胸部 X 光顯示兩側肺野有瀰漫性的間質浸潤增加，在兩側肺尖有肋膜增厚情形（圖一），肺通氣功能檢查顯示 FEV1 爲 1.27 升（45% predicted），FVC 爲 1.98 升（54% pred.），FEV1/FVC 爲 64%，TLC 爲 5.18 升（96% predicted）。在間質性肺病的臆斷下，安排胸部高解像度電腦斷層檢查（high resolution computed tomography，HRCT），發現廣泛性的肺小葉內及肺小葉間間隔增厚、支氣管管壁增厚、以及肺尖輕度肋膜肥厚情形（圖二）。病人在第二次門診複檢時，接受動脈血氣體分析以及氣體瀰散功能檢查，PaO2 爲 74.1 mmHg，PaCO2 爲 42.2 mmHg，DLCO 爲預測值的 77%。同時，當天進一步的病史詢問發現，病人在 1969 到 1977 年間，曾經在石綿加工廠工作 8 年，工作內容主要是石綿布料剪裁。爲確立診斷，病人接受氣管鏡檢查和 BAL。總共 150cc 生理食鹽水，在室溫下每次以 50cc 灌入右中葉內側支（medial segmental bronchus of right middle lobe）然後迅速回收，施行三次的 56cc 回收液全部都納入分析；另外在右下葉底前支（anterior basal segmental bronchus of right lower lobe）施行經支氣管肺切片（transbronchial lung biopsy）。我們將 BALF（bronchoalveolar lavage fluid）分成兩部份，一部份將雜質過濾後，計算細胞總數及分類數目，其中細胞總數爲 4×10^6/cc，巨噬細胞佔 87.5%，淋巴球佔 8%，嗜中性白血球佔 3%，嗜伊紅性白血球佔 1.5%；另一部份送常規細胞學檢查，包括 Papanicolaou's stain 及 Liu's stain，其中並無惡性細胞，但發現許多『鼓槌狀』異物，經特別鐵染色（iron stain），確定爲石綿體（asbestos body，AB）（圖三和四），而其濃度大約是 10 AB/cc。肺病理切片則可以在肺間質及肺泡中

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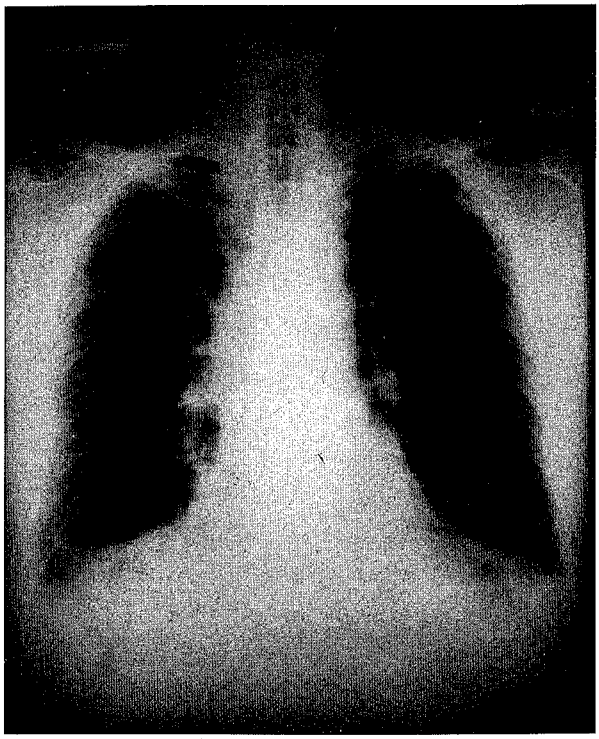
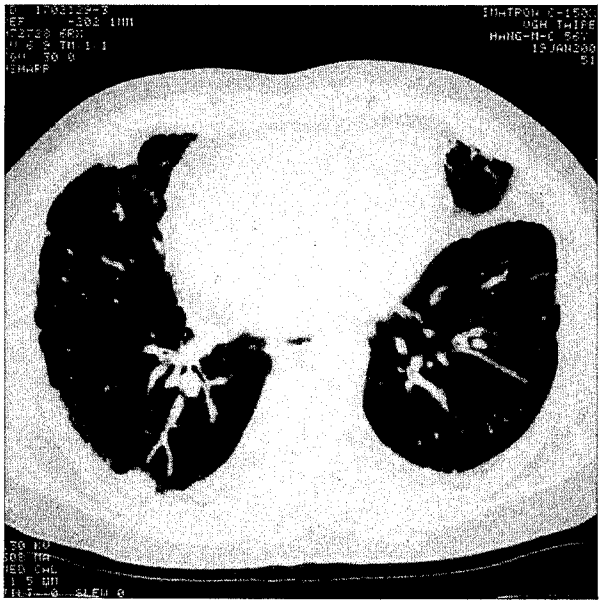
發現許多典型的石綿體，並且有明顯的肺間質纖維化現象。在向病患詳細解釋病情後，勸他戒菸，並給予吸入性支氣管擴張劑，病人症狀已有改善，目前在門診定期追蹤。



圖一 胸部 X 光片顯示兩側肺野有瀰漫性的間質浸潤增加，在兩側肺尖有肋膜增厚。



圖二 胸部高解像度電腦斷層(lung window)顯示廣泛性的肺小葉內及肺小葉間間隔增厚，以及支氣管管壁增厚。

討 論

石綿（asbestos）爲一群纖維性礦物質的總稱，組成包含基本的矽石（silica）加上各種金屬離子，包括鎂、鈣、鈉及鐵。英文"asbestos"源自拉丁文，原意爲「無法摧毀的」。它除了能耐酸耐熱，還有堅韌及可塑的特性。中文「石」「綿」兩字剛好表現出此種物質的兩大特徵。因此，當它被我們吸入肺內後，極難被分解，容易造成纖維化病變。石綿在 20 世紀初開始被廣泛運用，在 80 年代初期達到高峰，後因發現它的毒性及致癌性，消耗量漸漸減少。台灣自 1950 年代開始引進，目前每年的消耗量約 3 萬噸[1]。

石綿可分爲蛇紋石（serpentines）及角閃石（amphiboles）。工業上使用的蛇紋石只有白石綿（chrysotile）一種，它是彎曲的纖維，因此適合做紡織品。角閃石包括青石綿（crocidolite）及褐石綿（amosite）等，它們是筆直的纖維，適合做耐酸耐熱的建築材料。因爲物理特性的不同，角閃石比較容易致病，其中青石綿及褐石綿的致癌性又特別強。石綿症的致病機轉目前仍不是很明白，可確定的是它和石綿的暴露量及時間有關，目前的看法是肺內自由基（free radical）過剩所造成的傷害[2]。另外，若同時暴露於其他危險因子，例如吸菸，可增強其致癌力。有研究顯示，吸菸者得肺癌的機會約增11倍，石綿症增加5倍，吸菸的石綿症患者的危險性則高增加爲55倍[3]。除了暴露史外，接觸者本身的特性及免疫力，也是決定是否患病的因素之一；有研究顯示，BALF若持續出現嗜中性或嗜伊紅性白血球增加者，其肺功能較容易惡化；若是淋巴球增加者，則較不易發生肺纖維化及肋膜間皮瘤（mesothelioma）[4]。

石綿在肋膜可造成肋膜積水、局部或廣泛性肋膜增厚、肋膜斑、以及良性或惡性肋膜間皮瘤；事實上，石綿是肋膜間皮瘤最重要的原因之一。石綿在肺內可以造成石綿症、圓性肺塌陷（round atelectasis）、肺癌或其他較少見的情況如肉芽腫性炎症、BOOP（bronchiolitis obliterans organizing pneumonia）及LIP（lymphocytic interstitial pneumonitis）等。另外，石綿也可以在呼吸道及淋巴結，甚至腹腔內臟器官造成疾病。

石綿症的診斷主賴可靠的暴露史，典型的胸部X光變化，肺功能異常以及理學檢查發現。然而暴露史常是主觀的，會受病人的記憶力和求醫動機所影響，而且石綿症的發生常有一段長達二三十年以上的潛伏期，甚至在停止暴露後數十年才發生；另一方面，石綿在日常生活的使用相當廣泛，因此石綿的暴露不限於石綿工人，在詢問病史時，病人也許不知道曾經接觸過石綿。自從1970年代末

期，就有人用BAL當作客觀評估石綿暴露的方法。De Vuyst等人曾經做過一大規模的研究，包括232個對照組的563份樣本，發現BALF中石綿體的濃度和受檢者的石綿暴露史有相關性，雖然正常人的BALF也有可能發現石綿體，但每一毫升很少會超過一個，而在確定有暴露的石綿工人中，96.8%人的BALF發現有石綿體，其中濃度大於1AB/cc者有84.3%的 [5]。Sebastien等人則分別檢查石綿症患者的BALF和經開胸切片或屍體解剖的肺組織中的石綿體數目，發現兩者有很好的相關性。經過估算，由BAL得到的石綿體，大概佔該部份肺組織的2%，而1AB/cc的灌洗液濃度所推算出肺組織中石綿體的濃度大概介於1050 到 3010 AB/g（95%信賴區間）[6]。根據前人經由手術或屍體解剖的經驗，每克淨肺組織中（dry lung tissue），若含超過1000個石綿體，代表了病人曾經接受了有意義的石綿暴露[7]，Sebastien等人認爲1AB/cc的灌洗液濃度表示肺組織中的石綿體數目超過1000AB/g，意味著病人的石綿暴露量是不可忽視的[6]。

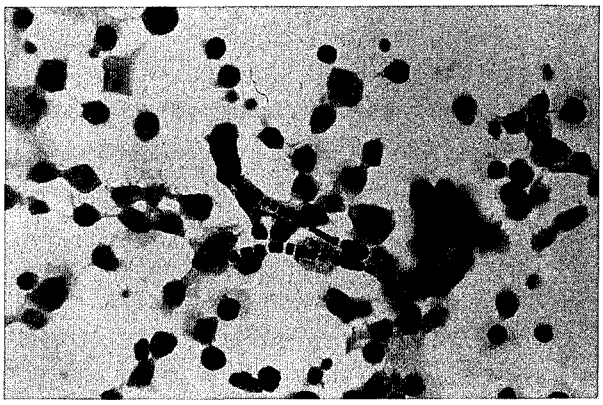
在此之後，大多數的研究都指出肺泡灌洗液中石綿體的濃度和病人的石綿暴露史有相關性[8-10]，但和病人的症狀、肺功能以及影像學檢查（包括CXR和HRCT）則不見得有相關性。然而，Schwartz等人的研究則持負面看法，結果顯示不只臨床的相關性不佳，連和暴露史也沒有一致性[11]。推究其因，大概有以下幾點：

1.真正致病的是石綿纖維（uncoated fiber）而非石綿體。

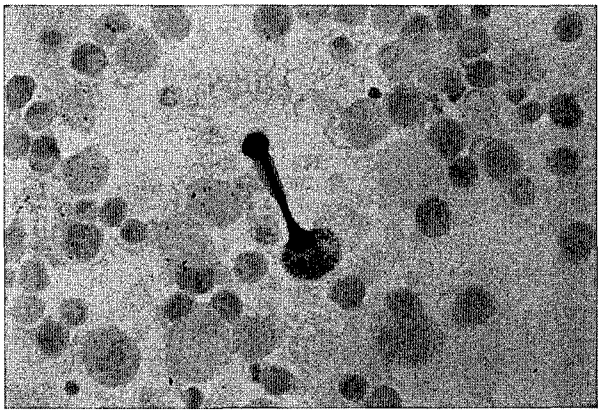
2.每種石綿形成石綿體的能力都不相同，白石綿比角閃石不容易形成石綿體，因此對主要暴露在白石綿的工人而言，會被低估。

3.到目前爲止，BAL還沒有一個標準程序。各實驗室灌洗液標本的處理方法不同，選擇檢查的位置也不同。事實上，一個對不同肺葉施行BAL的實驗顯示，石綿症在肺的侵犯不是均勻的。兩邊BALF中的石綿體都呈現隨肺由上向下而數目遞增的情形，但左右相對應的肺葉則大致差不多[12]。

當病人有明確的石綿暴露史合併典型胸部X光所見，石綿症的診斷大致可以成立。但若暴露史沒有或不明確，此時BALF中的石綿體便可作爲一個客觀的評估證據。雖然多少濃度的臨床意義仍有爭議，但大多數人都同意大於1AB/cc的濃度不容易在一般環境暴露中發生，因此代表病人的石綿暴露量是有意義的。當石綿症診斷確立後，我們應告知病人其危險性，尤其是吸菸對發生肺癌的加成效應；另一方面，我們也應注意病人的家屬，尤其是負責清洗病人工作衣物的親人，他們也是石綿暴露的高危險群。



圖三 BALF中的石綿體(Papanicolaou's stain，放大400倍)。



圖四 BALF中的石綿體(iron stain，放大400倍)。

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Application of Bronchoalveolar Lavage in the Diagnosis of Asbestosis—A Case Report

Jau-Hwa Chiou, Shi-Chuan Chang

Thorough exposure history plays an important role in establishing a diagnosis of interstitial lung disease. Furthermore, occupational history is one of the criteria for the definite diagnosis of occupation lung disease. However, either the carelessness of the doctor or the ignorance to the working environment or living place of the patient, exposure history may be unavailable or unreliable sometimes. Therefore, an objective measurement of exposure is of clinical importance in this circumstance. We present a case of a 56 year-old man here. After identification of significant amount of asbestos bodies in the recovered bronchoalveolar lavage (BAL) fluid, we confirm the diagnosis of asbestosis. We have informed the patient about the outcome of asbestosis and the addictive effect of smoking on lung cancer. Then the patient has quit smoking and is regularly followed up at our OPD. The role of BAL in the diagnosis of interstitial lung disease is clinically considerable. If we are familiar with the characteristic finding of asbestos body in routine cytology smear of BAL fluid, we can make sure the asbestos exposure history rapidly and objectively even without the help of a reliable exposure history. ***(Thorac Med 2000; 15: 97-101)***

Key words: asbestos, asbestosis, asbestos body, bronchoalveolar lavage

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Acute Respiratory Failure as an Initial Manifestation of Motor Neuron Disease – A Case Report and Literature Review

Gwo-Shu Wang, Kuang-Yao Yang, Reury-Perng Perng

Respiratory failure usually occurs late in the course of motor neuron disease (MND), but it can present very rarely as an initial manifestation of the disease. We report a patient with MND who presented with acute respiratory failure, recurrent atelectasis of the left lower lobe, and difficulty in weaning from the ventilator. After excluding other causes of respiratory failure, motor neuron disease was diagnosed based on the clinical manifestations and the electrophysiological study. Several therapeutic strategies were undertaken including the use of mechanical ventilation with a high tidal volume and high positive end-expiratory pressure (PEEP), and endobronchial room-air insufflation, but none of them was effective. After tracheostomy, he was transferred to a chronic respiratory care center for further management. We herein review the literature and discuss this unusual initial manifestation of motor neuron disease, as well as its management. Based on this case report, we would suggest that a patient with recurrent lung atelectasis and acute respiratory failure may be exhibiting an early presentation of motor neuron disease. ***(Thorac Med 2000; 15: 102-109)***

Key words: motor neuron disease (MND), respiratory failure, atelectasis, endobronchial room-air insufflation

Introduction

The causes of respiratory failure are generally divided into hypoxemic and hypercapnic categories, and constitute a long list that includes primary lung disorders, cardiovascular disorders, endocrine disorders, electrolyte imbalance, and neuromuscular disorders. Among these, motor neuron disease (MND) is uncommon and hard to diagnose, especially when respiratory failure develops early in the disease course, because other common causes should be considered first.

MND is one of the most common neurodegenerative diseases of adult onset. It predominantly occurs in people of middle or old age with a mean age of 55 years[1]. The precise cause of the neurodegenerative process remains unknown. This disease may cause progressive cell injury and the cell death of lower motor neurons, as in the spinal cord or the brain stem, and/or upper motor neurons, as in the motor cortex [1]. The average survival is only about 2 to 3 years from the start of symptoms [1,2], and 17 months from the need for mechanical ventilation [3].

Respiratory failure usually occurs late in the course of MND, and is the most important

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Table 1. Past serial pulmonary function evaluation

Variables	1995-8-11	1998-4-21
FVC (L, % pred)	3.07 (89%)	2.12 (64%)
FEV1 (L, % pred)	1.92 (79%)	1.81 (78%)
FEV1/FVC(%)	62	85
TLC (L, % pred)	4.78 (87%)	4.71 (87%)

FVC: forced vital capacity.

FEV1: forced expiratory volume in one second.

TLC: total lung capacity.

factor in terms of morbidity and mortality. However, in some patients, respiratory failure might occur early and present as an initial manifestation [4-12]. Clinicians should be alert to this condition and choose the most appropriate treatment modality, such as prevention of infection, early tracheostomy, negative-pressure ventilation, or nighttime ventilation, rather than let the patient suffer from repeated and unnecessary episodes of intubation and weaning failure. The patient's quality of life and complication rate may be improved if we can make an accurate diagnosis and provide an adequate management program.

We report a patient with MND, who presented with acute respiratory failure earlier than other manifestations. The clinical course, diagnosis, and management of MND are reviewed and discussed.

Case Report

A 77-year-old man was admitted to our ward from July 31 to October 25, 1999, because of acute hypercapnic respiratory failure requiring intubation and mechanical ventilatory support. He had been relatively healthy before, except for a mild chronic obstructive ventilatory impairment in 1995. He had a 30-pack-a-year history of cigarette smoking. His serial pulmonary function is shown on Table 1. Five days prior to admission, he visited the Emergency Department because of a productive cough, dyspnea, and body weight loss. Laboratory data that included a complete blood count, blood chemistries, and cerebrospinal fluid analysis, were all within normal limits. The chest radiograph showed atelectasis of the lower left lobe (LLL). In the beginning, bronchodilator inhalation therapy and non-invasive pressure support ventilation (bilevel positive airway pressure, Bi-PAP) were used, but in vain. Four days later, he was intubated with mechanical ventilation because of progressive hypercapnia and a change of consciousness, then transferred to the respiratory intensive care unit (RICU). The serial arterial blood gas values are shown in Table 2.

After admission to RICU, the $PaCO_2$ value returned to normal and the F_IO_2 went down rapidly from 1.0 to 0.4. His sensorium became clear the next day. He could communicate with people by writing and gestures, but was still ventilator- dependent. Follow-up chest radiographs showed a persistent atelectasis of the LLL, thus the PEEP level was increased to 10~12 cmH_2O and the tidal volume to 0.65~0.70 liter, but this proved ineffective.

To rule out an endobronchial lesion, a diagnostic bronchoscopy on August 6 revealed a sputum impaction over the LLL bronchus. Suction and bronchoalveolar lavage (BAL) were performed to clear the sputum impaction, but, the follow-up chest X-ray (CXR) showed little improvement. An interventional bronchoscopy

Table 2. Serial arterial blood gas (ABG) values

	2 days before admission	1 day before admission	3 days after admission	10 days after admission
supply of oxygen	Nasal prong, 2 L/min	Bi-PAP,15 L/min	A/C ventilator,40%	A/C ventilator,21%
pH value	7.340	7.283	7.603*	7.563*
$PaCO_2$ (mmHg)	67.3	102.9	24.6*	28.0*
PaO_2 (mmHg)	64.3	67.8	85.7	51.8
HCO_3 (mmol/L)	32.6	41.5	24.6	24.7

*Respiratory alkalosis and hypocapnia, which might be due to the maneuvers of increased ventilation (high PEEP and tidal volume) to re-expand the collapsed lung.

A/C: assist/control mode

was done on August 18, and included bronchoalveolar lavage and selective intrabronchial air insufflation via the orifices of LB8, 9 and 10. A partial re-expansion of the LLL was achieved, but atelectasis recurred progressively over the next several days. The same procedure was tried again on August 26, but the effect lasted for only a few days. The serial chest radiographs are shown in (Figure 1.)

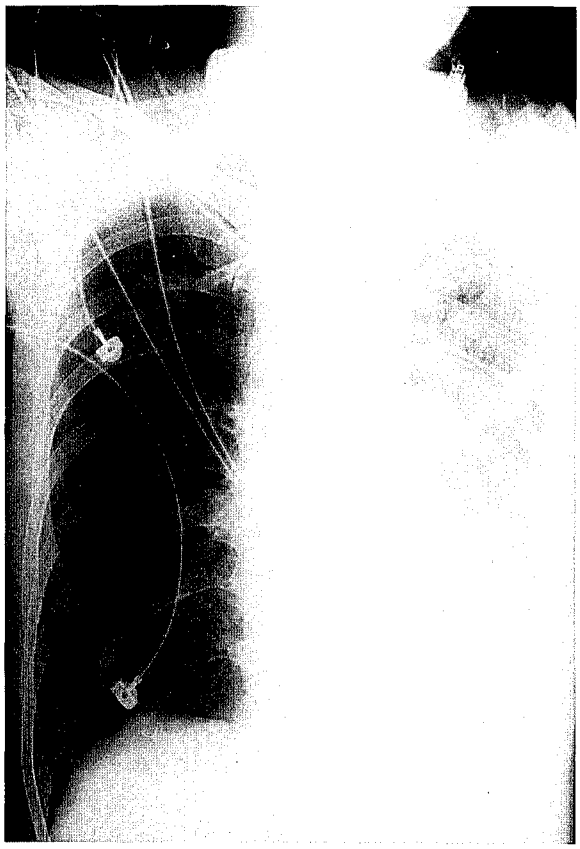
The chest computerized tomography (CT) scan disclosed a patchy density with partial collapse of the LLL, in favor of an inflammatory process. No lung parenchymal tumor or mediastinal lymphadenopathy was found. With an aggressive weaning, he was successfully extubated on September 2 and kept on non-invasive positive-pressure ventilation (Bi-PAP therapy). Unfortunately, he was re-intubated on September 7 because of a recurrence of severe hypercapnic respiratory failure and the total collapse of the left lung.

For the recurrent LLL atelectasis and refractory respiratory failure, other examinations were performed. His serum thyroid-stimulating hormone (TSH) was 0.261 μ IU/ml (normal range, 0.4-4.0), free thyroxine (T4) 0.72 ng/dl (0.8-1.9), diurnal serum cortisol 8.6 μ g/dl (morning, 5-25) and 6.9 μg /dl (evening, <5), and the serum acetylcholine receptor antibody (AchRAb) was 0.10 nmoles/L (<0.5). The TSH and free T4 level returned to a normal range 10 days later (0.67 ng/dl and 1.64 μ IU/ml, respectively). The bronchoalveolar lavage fluid studies were negative for both tuberculosis and cytology.

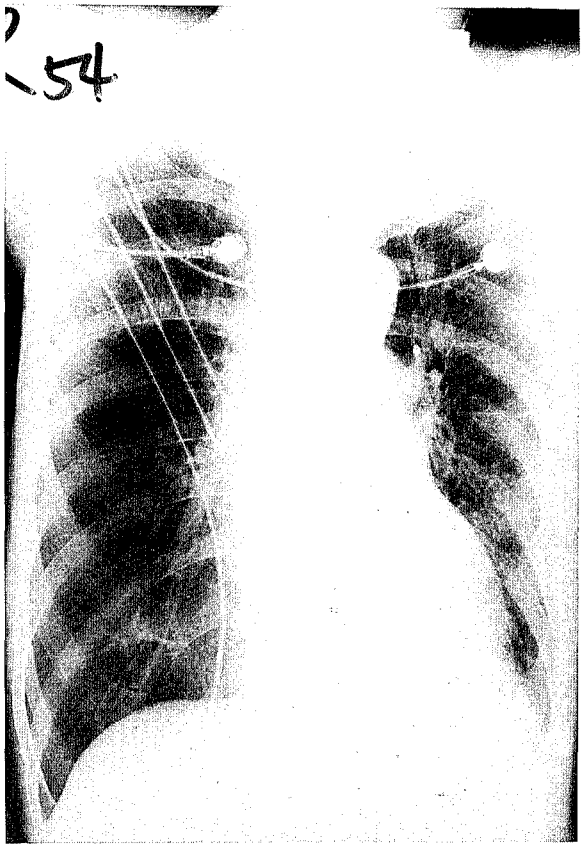
On neurological examination, he showed diffuse muscle wasting, especially of the distal extremities, symmetric tendon reflex, equivocal Barbinski's response, and a minimal muscular fasciculation of the bilateral lower legs. The nerve conduct velocity (NCV) study showed a normal sensory and reduced motor nerves conduct velocity of both the arms and legs. The needle electromyography (EMG) study of the sampling muscles, including bilateral paraspinal muscles, showed acute denervation. Finally, MND was diagnosed according to the above electrophysiological findings and clinical manifestations. Because of his ventilator-dependent condition, he was transferred to a chronic respiratory care center for long-term management.

Discussion

MND was diagnosed based on the refractory respiratory failure, persistent atelectasis of the lung, clinical manifestations, and electrophysiological studies. The time interval



(A)



(B)

(C)

Fig. 1. The serial chest radiographs.

(A) August 4, 1999. 4 days after admission. The chest radioraph revealed increased opacity and volume reduction over lung suggesting LLL atelectasis the left lower.

(B) August 19, 1999. After the first bronchoscopic positive-pressure room air insuffation therapy. This film revealed partial re-expansion of the LLL.

(C) September 9, 1999. After the 2nd bronchoscopic positive-pressure room air insufflation therapy (August 26) and extubation (September 2). He was treated with Bi-PAP thereafter, but unfortunately, re-intubated on September 7. This film showed similar findings with (A), LLL atelectasis recurred

from admission to diagnosis was 31 days in our case. The average time from the presentation of respiratory failure resulting from MND to definite diagnosis, although not clearly defined, is about 11 to 13.5 months in the literature [2,9].

In the past 20 years, fewer than thirty cases of MND presenting with acute respiratory failure have been reported [4-12]. This is a rare mode of initial presentation, but MND must be considered in any patient with unexplained respiratory insufficiency or difficulty in weaning from a ventilator [9], and when other common causes of respiratory failure, such as lung parenchyma disorder, cardiovascular disorder, hypothyroidism, adrenal insufficiency, or electrolytes imbalance, have been excluded. It is also important to differentiate this disease from other neuromuscular diseases, especially myasthenia gravis, since the latter is a treatable condition [6]. Myasthenia can be differentiated, however, by a careful clinical survey, muscle biopsy, and the presence of acetylcholine receptor antibodies.

The electrophysiological findings of MND revealed a reduced motor conduction of the limbs with a relative sparing of sensory conduction, and an active denervation of the bilateral paraspinal muscles. Because diaphragm sampling was not available in this case, the involvement of paraspinal muscles may represent the involvement of the ventral horn at the C3-C5 level [4,5] — where the phrenic motor neurons originate.

Atelectasis has for many years been recognized as a complication of neuromuscular disease (NMD) [12]. In a small series, 85% of the patients with neuromuscular respiratory failure requiring assisted ventilation developed atelectasis in their disease courses [13]. Most of them had major atelectasis, involving at least one lobe of the lung, which tended to occur early and persist despite positive pressure ventilation, chest percussion, and postural drainage. The atelectasis is located most commonly in the lower lobes of the lungs, especially the lower left lobe [13]. In patients with NMD, this condition is most likely due to muscle weakness and frequent infection, as it occurs less frequently among unselected cases treated with mechanical ventilation, and its frequency dose not differ substantially when comparing the modern era (with positive-pressure ventilators, endotracheal tubes, intensive care units, and other new respiratory care and treatment techniques) with earlier reports [13]. These findings suggest the importance of the early prevention of infection, including timely intubation, an aggressive search for the earliest signs of infection, appropriate antibiotics therapy and, most importantly, bronchial hygiene therapy and volume expansion therapy performed by a well-trained therapist to prevent atelectasis. Major atelectasis, once established, is difficult to correct and often persists until spontaneous respiratory efforts resume.

A new method of bronchoscopic washing and intrabronchial insufflation of room air to re-expand the collapsed lung was developed in the 1990s [14-16]. The results were encouraging, as the success rate for complete plus partial re-expansion was as high as 70% - 100%. However, the reported cases were collected mostly from surgical intensive care units, and almost all the causes of lung collapse were related to post-operation, chest trauma, infection, or head injury. In this case, BAL with intrabronchial room air insufflation was performed twice, and the collapsed lung re-expanded partially after each attempt, albeit temporarily. The role of BAL with intrabronchial room air insufflation in patients with respiratory failure combined with collapsed lungs due to neuromuscular disease, including MND, is uncertain.

So far, there has been no effective treatment to slow down the progression of MND. The treatment for MND patients is mostly conservative, and assisted ventilatory

support is applied when the patient develops respiratory insufficiency. Non-invasive ventilations, including negative pressure modes (iron lung, Porta-Lung, chest shell), abdominal displacement modes (rocking bed, pneumobelt), and the positive pressure mode (Bi-PAP), have been proven effective in the respiratory insufficiency of NMD patients [17-19]. These techniques may be used for patients who have developed severe respiratory muscle weakness before the onset of significant bulbar involvement, however, most patients will require tracheostomy and mechanical ventilation, since MND is a progressive disease. As the patient's consciousness is often clear when respiratory insufficiency appears, ethical considerations are very important [2,19]. When symptoms such as pain, dyspnea, and insomnia develop, active treatment, including opioids, may be reasonable [2]. Pain is a common problem in MND patients, and is described as aching, cramping, burning, shock-like, or indescribable. This pain can occur at multiple sites, and is frequently worse at night. The precise etiology of the pain is not well known, but joint stiffness, muscle cramps, and skin pressure may all contribute [2]. In a small subset of patients who had a bulbar form of MND and other motor functions that were stable, specific inspiratory muscle training offered a partial but significant improvement of ventilation [9].

MND patients with impaired respiratory function may present symptoms of chronic hypoventilation, i.e. daytime hypersomnia, sleeping disturbance, fatigue, irritability, and a decreased intellectual function. Failure to recognize these may lead to severe sequelae, even cardiorespiratory arrest. External negative pressure-assisted ventilation at night may enable such a patient to return home and lead an independent life [7]. On the other hand, assisted mechanical ventilation during sleep has prevented the central chemoreceptors from accommodating to the high carbon dioxide level [10].

In conclusion, MND must be considered in patients with unexplained refractory respiratory failure and atelectasis of the lung. Before the diagnosis is made, other possible causes need to be excluded. Once the diagnosis is established, early intervention to prevent infection should be initiated. Non-invasive ventilation, including negative pressure modes, may be used initially for patients with respiratory insufficiency. Nighttime assisted non-invasive ventilation is indicated for ambulatory patients with symptoms of chronic hypoventilation. Of most importance, ethical considerations should always be kept in mind when choosing the therapeutic modality.

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運動神經元疾病以急性呼吸衰竭爲起始表現－病例報告及文獻回顧

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呼吸衰竭通常出現在運動神經元疾病(motor neuron disease, MND)的病程晚期；隨著疾病的進展，罹患運動神經元疾病的病患會逐漸發展出呼吸衰竭的症狀。但是，有非常少數的病人在病程早期便出現此情況。我們報告一位以急性呼吸衰竭來表現的病人，在病程中並有持續性的左下肺葉萎陷(atelectasis)及呼吸器依賴，最後在住院 31 天後經由神經傳導及肌電圖檢查確定診斷為運動神經元疾病。此病人接受過正壓呼吸器(positive-pressure ventilation)，大潮氣容積(tidal volume)，高吐氣末陽壓(PEEP)，及支氣管內空氣灌注法(endobronchial room air insufflation)治療，但是情況並未改善。由於需要長期依賴呼吸器治療，最後他接受氣管造口術並轉至慢性呼吸照護中心繼續治療。我們將就其病程、診斷、及治療加以討論，並回顧相關的文獻報告。經由此病例，我們建議臨床醫師對於無法解釋的急性呼吸衰竭病人應考慮運動神經元疾病的可能性，而儘早給予適當的診斷及治療。如預防感染及早期使用非侵襲性呼吸器等，以改善生活品質及避免嚴重的後果。 ***(胸腔醫學 2000; 15: 102-109)***

關鍵詞：運動神經元疾病，呼吸衰竭，肺萎陷，支氣管內空氣灌注

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