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A Brief Review of Nitric Oxide Synthase

Shyanher Wang

Nitric oxide (NO) is a free radical and yet an important intercellular signaling messenger. It plays a role in many physiological and pathological processes including relaxation of smooth muscle, transduction of intercellular signals, killing of invading organisms and tumors, and damage of various cell components. NO is synthesized by the nitric oxide synthase (NOS). NOS uses *L*-arginine and molecular oxygen as substrates to synthesize NO and *L*-citrulline. There are three isoforms of NOS: neuronal constitutive NOS (ncNOS or type I NOS), inducible NOS (iNOS or type II NOS), and endothelial constitutive NOS (ecNOS or type III NOS). Both ncNOS and ecNOS are constitutive isoforms and are Ca^{2+} and calmodulin-dependent enzymes. In contrast, iNOS is a Ca^{2+}-independent inducible isoforms in which the calmodulin molecule is tightly bound to the enzyme as a subunit of iNOS. Since *L*-arginine is the substrate to synthesize NO, most NO synthetic inhibitors are analogues for the amino acid, *L*-arginine, and are either nonselective or are more selective for constitutive NOS than iNOS. Alternatively, some NO synthetic inhibitors are not amino acids but are analogues for the guanidine group on *L*-arginine. Those inhibitors are more selective for iNOS than constitutive NOS.
(Tungs' Med J 2008; 2: 63-68)

Key words: nitric oxide, nitric oxide synthase, *L*-arginine, guanidine, constitutive, inducible.

INTRODUCTION

Nitric oxide (NO), a free radical, had been considered as a toxic air pollutant until 1987 when it was proved to be the same as the so-called endothelium derived relaxing factor (EDRF)[1,2]. Since then, thousands of studies have been done to understand this dramatic chemical compound. Now it is a general concept that NO is an important signal messenger. It plays a role in many physiological and pathological processes including relaxation of vascular and bronchial smooth muscles, transduction of signals between neurons and various cells, killing of the invading organisms and tumors, and participation in various cell damages. NO is synthesized by the enzyme, nitric oxide synthase (NOS). NOS uses *L*-arginine and molecular oxygen as substrates to synthesize NO. And *L*-citrulline is the by-product of this reaction (figure 1)[3,4,5,6].

Nitric Oxide Synthase

There are three isoforms of NOS (table 1): neu-

NOS = Nitric Oxide Synthase

$$\textit{L}\text{-arginine} + O_2 \xrightarrow{\text{NOS}} \textit{L}\text{-citrulline} + NO$$

Fig. 1 Nitric Oxide（NO）Synthesis

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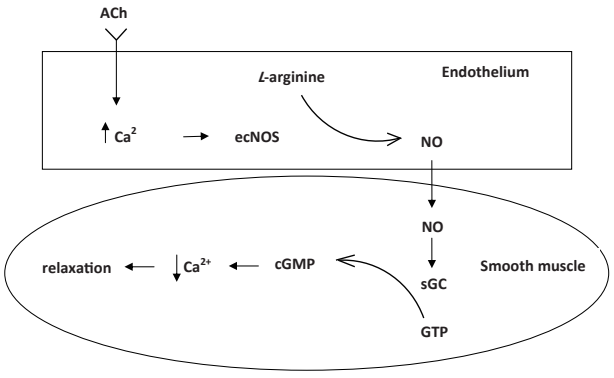
Table 1. Isoforms of Nitric Oxide Synthase (NOS)
CaM = Calmodulin

Type I	ncNOS	neuronal constitutive	Ca^{2+}/CaM-dependent
Type II	iNOS	inducible	Ca^{2+} - independent
Type III	ecNOS	endothelial constitutive	Ca^{2+}/CaM-dependent

ronal constitutive NOS (ncNOS or type I NOS), inducible NOS (iNOS or type II NOS), and endothelial constitutive NOS (ecNOS or type III NOS) [7]. Both ncNOS and ecNOS are constitutive isoforms and are Ca^{2+} an calmodulin-dependent enzymes. In contrast, iNOS is a Ca^{2+}-independent inducible isoforms in which the calmodulin molecule is tightly bound to the enzyme as a subunit of iNOS[8]. The ncNOS is present primarily in neurons and epithelia, the iNOS in stimulated macrophages and vascular smooth muscles, and the ecNOS in vascular endothelia.

The constitutive NOS is rapidly activated by Ca^{2+} mobilizing agents and rapidly inactivated when these agents are removed. For example, ecNOS can be activated by acetylcholine, which increases the intracellular Ca^{2+} concentration through stimulation of type III muscarinic receptors on endothelial cells (figure 2)[9]. Also, ncNOS can be activated by the stimulation of Ca^{2+} influx to the nonadrenergic, noncholinergic nerve cells. In contrast, activation of iNOS requires several hours of exposure to an appropriate agent such as IL-1β and is blocked by the inhibitors of translational or transcriptional processes like cycloheximide or actinomycin-D, respectively. That is, the expression of iNOS involves an induction of *de novo* protein synthesis and gene induction.



ecNOS = endothelial constitutive nitric oxide synthase
NO = nitric oxide
sGC = soluble guanylate cyclase
GTP = guanosine triphosphate
cGMP = cyclic guanosine monophosphate

Fig. 2 Acethylcholine (Ach) induces endothelium-dependent vascular relaxation by activation of ecNOS.

However, the general concept that the iNOS is not constitutively expressed in normally unstimulated cells has been challenged by observations in airway epithelial cells[10] and platelets[11,12]. In these cells, iNOS has been shown to be present constitutively and co-localized with constitutive NOS. Moreover, pulmonary vascular endothelium has been stained positively with anti-iNOS antibody in human and rat lungs[10], and both calcium-dependent and calcium-independent synthesis of NO have been reported in native porcine aortic endothelial cells[13].

Since *L*-arginine is the substrate to synthesize NO, most NO synthetic inhibitors described in the literature are analogues for the amino acid, *L*-arginine, such as N^{ω}-nitro-*L*-arginine (LNA) (figure 3), N^{G}-methyl-*L*-arginine, and N^{G}-amino-*L*-arginine[13]. Most of these inhibitors are either nonselective among the three isoforms of NOS or are more selective for constitutive NOS than iNOS[4]. Alternatively, some NO synthetic inhibitors are not amino acids and are analogues for the guanidine group on *L*-arginine, such as mercaptoethylguanidine (MEG)[14] and aminoguanidine[15] (figure 3). These two inhibitors have been shown to be selective for iNOS. For example, MEG at concentrations up to 10^{-4} M has no effect on the acetylcholine-induced endothelium-dependent relaxations in rat aorta but reverses the sepsis-induced vascular hypocontractility in endothelium-removed rat aorta[14]. These observations have led to the speculation that the binding site for the guanidino group might be different between the inducible and constitutive isoforms of NOS and that MEG and aminoguanidine are selective for iNOS.

Expression of iNOS in vascular smooth muscle cells by IL-1β appears to require protein tyrosine phosphorylation. For example, increases of cyclic guanosine monophosphate （cGMP）and nitrite (NO_2), a stable NO metabolite, in cultured rat aortic smooth muscle cells exposed to IL-1β are inhibited by tyrosine kinase inhibitors such as genistein, geldanamycin, and herbimycin[16]. These tyrosine kinase inhibitors do not affect ecNOS activity, because basal or Ca^{2+} agonist stimulated NO release from cultured bovine aortic endothelial cells are not altered

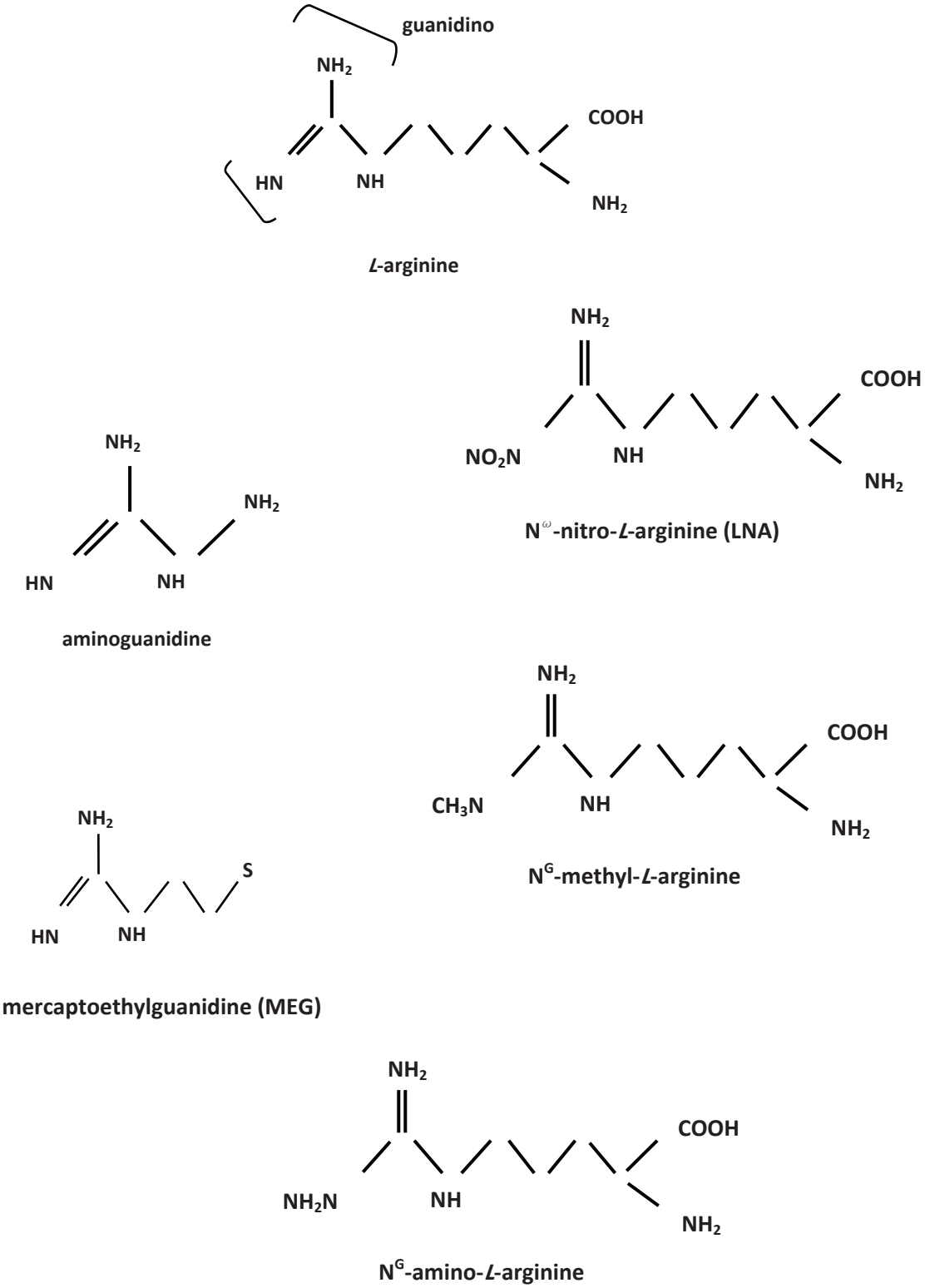


Fig. 3 Structures of *L*-arginine and its competitive antagonists

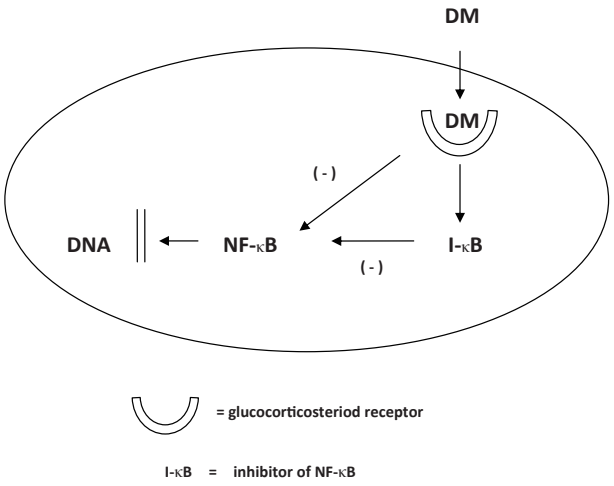


Fig. 4 Dexamethasone (DM) inhibits nuclear factor-κB (NF-κB) activity.

by these inhibitors[16]. Also, expression of iNOS appears to require activation of nuclear factor-κB (NF-κB), a transcriptional factor. For example, the increase of NO2 and nitrate (NO3) production in cultured rat aortic smooth muscle cells induced by IL-1β is inhibited by dexamethasone and is independent of protein kinase C phosphorylation[17]. Dexamethasone, a glucocorticoid, inhibits activation of NF-κB either by direct inactivation[18,19] or by induction of the inhibitor protein, I-κB (figure 4)[20,21,22]. The effect of dexamethasone is thought to be mediated *via* activation of a cytosolic receptor. Also, the inhibitory effect of IL-1β on vascular contractility is reversed by the antioxidant pyrrolidine dithiocarbamate (PDTC), a reported NF-κB inhibitor, in endothelium-removed rat aorta[23].

The activated or induced NOS produces NO, which is a very short-lived and freely diffusible molecule. NO, in turn, mediates various physiological and pathological reactions. For example, NO reduces vascular tone by activating soluble guanlyate cyclase (sGC) to increase levels of cyclic guanosine monophosphate (cGMP)[3,4,5,6]. Increased levels of cGMP are thought to cause relaxation of vascular smooth muscle by decreasing the intracellular calcium concentration[4,5,6].

Summary

The discovery of its various physiological and pathological roles had made NO being viewed quite differently. NO has showed its characteristic as an important biochemical compound in the body instead of just a notorious toxicant in the air. Its synthesizer, NOS, also attracts scientists' attention by the various functions and mechanisms. The studies of the three isoforms of NOS and their downstream pathways have lead to the production of many new chemical compounds. Some compounds are clinically applicable and have been used to treat illness. A more understanding of this small molecule, NO, and its producer, NOS, a more appreciation of the life science will be.

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一氧化氮合成酶之簡要回顧

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一氧化氮 (NO) 是細胞之間極為重要的訊息傳遞者。它參與了許多的生理與病理反應，例如，平滑肌的放鬆以及細菌或腫瘤的消除等。NO 是由一氧化氮合成酶 (NOS) 所合成。NOS 使用 *L*-arginine 和氧分子為基質，合成 NO 和 *L*-citrulline。 NOS 可分為三種型態：ncNOS（type I）、iNOS（type II）和 ecNOS（type III）。ncNOS 和 ecNOS 兩者為常態結構型，酶的活性和細胞內鈣離子濃度有關。相反地，iNOS 為引發生成型，酶的活性和細胞內鈣離子濃度無關。NOS 的抑制劑可分為 *L*-arginine 的相似胺基酸和 guanidine 分子的相似物兩大類。前者為 *L*-arginine 的競爭型抑制劑，通常對三種 NOS 之間比較不具選擇性或者對 ncNOS 和 ecNOS 比較有作用。相反地，後者對 iNOS 的選擇性作用較高。
（童綜合醫誌 2008; 2: 63-68）

關鍵詞：nitric oxide, nitric oxide synthase, *L*-arginine, guanidine, constitutive, inducible

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Calcium Metabolisms in Children with Nephrotic Syndrome

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Background: Calcium metabolism was abnormal in patients with nephrotic syndrome. The aim of this study was to evaluate the alteration of calcium and vitamin D (Vit. D) metabolisms in children with nephrotic syndrome, but with normal renal function.

Methods: Twelve nephrotic syndrome children with normal GFR were enrolled in this study. Blood and urine procured were assayed for albumin, protein, calcium, phosphate, PTH, 25(OH)D and $1,25(OH)_2D$ during the episodes of active and of the remission of nephrotic syndrome.

Results: Decreased calcium and vit. D levels in serum and urine, and elevated blood PTH level are the hallmarks of nephritic syndrome in active phase. These abnormalities resume after remission of disease.

Conclusions: Distant dysregulation of calcium and vitamin D metabolisms were evident in these patients with active nephrotic syndrome and normalized following their remission. These results suggest that urinary 25(OH)D substrates were progressively lost in these patients with active nephrotic syndrome.
(Tungs' Med J 2008; 2: 69-73)

Key words: nephrotic syndrome, calcium metabolism, vitamin D, renal function

INTRODUCTION

Hypocalcemia has long been recognized[1], but it was usually ascribable to the hypoalbuminemic condition[2]. Leonard et al, found that abnormalities of bone mineralization in groups who had continuous derangements in calcium and vitamin D metabolisms of children with nephrotic syndrome[3]. For further understanding the abnormalities of calcium and vitamin D metabolism in children with normal renal function, we conducted our experience on some aspects of mineral metabolism in children with normal GFR during active stage and during remission of nephrotic syndrome.

MATERIALS AND METHODS

Twelve children (2 to 10 years old) diagnosed of having nephrotic syndrome with normal renal function were studied, Nine were male and 3 female, all the cases were studied during active nephrotic syndrome and during remission. Active nephrotic syndrome was defined by increased 24-hour proteinuria (>40mg/m^2/h) and decreased serum albumin concentration (<2.5gm/dl). Remission was defined by the absence of proteinuria (<4mg/m^2/h) and normal serum albumin concentration (>3.5gm/dl). All the patients received no steroid or other medications known to affect calcium and vitamin D metabolisms before the test. All the patients received a physical examination, including body weight and blood pressure

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measurements. Blood samples were obtained for total serum calcium, phosphate, albumin, creatinine, PTH, 25(OH)D and 1,25$(OH)_2$D. A 24 hours urine, for the assays of creatinine, calcium and protein was collected from each patient. All the parents were given detailed instructions on the technique of urine collection. To insure the completeness of urine collection, 24 hours urinary creatinine excretion was corrected by the subject's body weight and then calculated[4]. All routine chemical analysis were performed by autoanalyzer in the biochemical laboratory. Serum parathyroid hormone was measured by radioimmunoassay[5]. Circulating 25(OH)D[6] and 1,25$(OH)_2$D[7] were measured by binding assay. In all of these patients received conventional low-dose prednisolone (2mg/kg/day) therapy after test. The remission was found within 4-8 weeks of prednisolone therapy.

Statistical analysis

Data were expressed as mean±SD. Statistics were calculated by Sin test, and Pearson's correlation. Differences between groups were considered significant at $p<0.05$.

Results

Mean values for age, body weight, blood pressure, glomerular filtration rate, and mean values for 24-hour proteinuria, 24-hour calcium, and plasma concentrations of albumin, calcium, phosphate, PTH, 25(OH)D and 1,25$(OH)_2$D during active nephrotic syndrome and during remission of nephrotic syndrome were presented in Tables 1 and 2 respectively. Mean values of glomerular filtration rate (98±19 vs 103±24 ml/min/1.73m2), systolic blood pressure (84 ±8 vs 86±10 mmHg), diastolic blood pressure (56±5.8 vs 58±7.6 mmHg), and plasma creatinine levels (0.59 ±0.11 vs 0.56±0.14 mg/dl) were not significantly different in active nephrotic syndrome and in remission. As expected, in all the patients who had significant hypoalbuminemia, proteinuria and body weight gain during active nephrotic syndrome. Generalized edema and proteinuria disappear, serum albumin level returned to normal range during their remission. Plasma albumin concentration and 24-hour urinary excretion of protein were significantly different ($p<0.01$) in active nephrotic syndrome compared to those in remission. Mean 24-hour urinary excretion of calcium were significantly lower in active nephrotic syndrome ($p<0.01$). Total plasma calcium concentration was significantly lower ($p<0.01$) and plasma phosphate concentration was higher ($p<0.05$) in active nephrotic syndrome. Plasma PTH concentration was slightly higher in active nephrotic syndrome ($p>0.05$). Conversely, the plasma 25(OH)D and 1,25$(OH)_2$D levels were significantly lower in active nephrotic syndrome ($p<0.01$).

During active nephrotic syndrome, 24-hour proteinuria was found to be correlated inversely with both plasma 25(OH)D ($r=-0.49$, $p<0.01$) and plasma 1.25$(OH)_2$D ($r=-0.45$, $p<0.01$) respectively. Plasma albumin correlated directly with both plasma 25(OH)D ($r=0.59$, $p<0.01$) and 1,25$(OH)_2$D ($r=0.51$, $p<0.01$). plasma calcium directly with plasma 1,25$(OH)_2$D ($r=0.70$, $p<0.01$). Plasma 25(OH)D concentration directly with that of 1,25$(OH)_2$D ($r=0.68$, $p<0.01$), and PTH inversely with plasma 1,25$(OH)_2$D ($r=-0.09$). In remission, no significant correlation were found on all the parameters being measured.

Table 1. General data in patients with active phase and remission of nephrotic syndrome (N=12)

	Active phase	Remission	P value
Age（Yr）	5.52±2.4	5.92±2.1	NS
Body weight（kg）	19.3±1.5	17.5±1.3	0.01
Blood Pressure (mmHg)			
Systolic	84±8.2	86±10.3	NS
Diastolic	56±5.8	57±7.5	NS
plasma creatinine	0.59±0.11	0.58±0.14	NS
GFR（ml/min/1.73m^2）	98±19	103±24	NS

NS = not significant

Table 2. Biochemical data in patients with active phase and remission of nephrotic syndrome (N=12)

	Active phase	Remission	P value
Urine protein（g/day）	2.81±1.38	0.07±0.11	0.01
Urine Calcium（mg/kg/day）	0.72±0.19	1.19±0.25	0.01
Albumin（g/dl）	2.08±0.31	3.61±0.52	0.01
Calcium（mg/dl）	8.03±0.42	9.47±0.59	0.01
phosphate（mg/dl）	5.58±0.71	4.74±0.65	0.05
PTH（pg/ml）	75±40	65±31	NS
25(OH)D（ng/ml）	9.5±6.8	34±14	0.01
1.25$(OH)_2$D（pg/ml）	13±10	49±26	0.01

NS = not significant

DISCUSSION

Hypocalcemia frequently occurred during the active nephrotic syndrome. Plasma calcium concentration was less than 8.5mg/dl in our cases during active nephrotic syndrome. Studies in adults, and in nephrotic children had shown that this reduction in total serum calcium reflects a decrease in serum ionized calcium.[8] In fact, total serum calcium concentration tends to overestimate the ionized fraction even after correction for the decrease in the serum protein concentration.[9] The reduction in total plasma calcium concentration during active nephrotic syndrome returned to normal values in all instances during remission. The results of transiently altered calcium balance resulted from defective intestinal absorption of calcium.[10] This explanation could be supported by decreased 24-hour urinary excretion of calcium during active nephrotic syndrome compared with those during remission in the study.

Secondary hyperparathyroidism had seldom been recognized in nephrotic children.[8] There were elevation of plasma PTH concentration during active nephrotic syndrome, but it was not statistically significant. The values of plasma PTH were elevated as well in three of these patients during remission. The lack of consistent hyperparathyroidism during active nephrotic syndrome despite hypocalcemia had been noted in adults and in children.[10-11] Undetected elevation in circulating PTH,[12] excessive urinary losses of carboxyl-terminal hormonal fragments with concurrent proteinuria, or unknown factors may be interfering with normal calcium-PTH feedback or with the peripheral metabolism of hormone that can explain those existed discrepancies.

25(OH)D was the main type of vitamin D in circulation.[13] Approximately 98% of 25(OH)D was attached to vitamin D binding protein.[14] The molecular weight was similar to that of albumin.[15] In this study, the plasma levels of 25(OH)D were strikingly decreased during active nephrotic syndrome, probably as a result of urinary losses.[15-18] The explanation was supported by the inverse correlation between proteinuria and plasma 25(OH)D, the direct correlation between serum albumin and 25(OH)D values in active nephrotic syndrome, and the absence of these correlation on disappearance of proteinuria.

Plasma $1,25(OH)_2D$ levels were low during active nephrotic syndrome in most patients. Only two of our patients had normal plasma $1,25(OH)_2D$ levels. Some investigators had reported low plasma $1,25(OH)_2D$ values,[10.16] albeit in some patients and in rats,[20] plasma $1,25(OH)_2D$ were normal during active nephrotic syndrome. Levels of $1,25(OH)_2D$; nevertheless, could be normal or elevated.[21] Circulating levels should be reviewed in relation to those factors that regulated the renal production and plasma concentration of $1,25(OH)_2D$.[22-23] Both hypocalcemia and elevated PTH stimulated $1,25(OH)_2D$ synthesis, whereas the concentrations of phosphate in plasma and in renal tubular cells[22-24] contributed to the renal synthesis of $1,25(OH)_2D$. Low phosphate stimulated and high phosphate decreased synthesis. In our patients, hyperphosphatemia did not occur, and glomerular filtrate rate was normal. Most of those parameter including calcium, phosphate, PTH, and renal functional mass could not explain the relative deficiency in $1,25(OH)_2D$ concentration. Therefore adequate synthesis of $1,25(OH)_2D$ was apparently dependent on sufficient availability of its endogenous precursor 25(OH)D[13] as suggested by our data. Furthermore, low $1,25(OH)_2D$ levels had been observed in nephrotic syndrome when 25(OH)D levels were substantially low. That $1,25(OH)_2D$ levels may ultimately be related to those of 25(OH)D was supported by the direct relationship between these metabolites observed in our patients during active nephrotic syndrome. In remission the plasma $1,25(OH)_2D$ concentrations were appropriate for the prevailing levels of serum calcium and PTH. This suggested normal renal synthesis of this vitamin D metabolite.

Glucocorticoid administration for more than one year had been associated with diminished circulating levels of $1,25(OH)_2D$ and bone mineralization.[25] However most of our patients received only short-term (2-4 months) conventional low-dose (1-2mg/kg/day) prednisone therapy. As to children with nephrotic syndrome, particularly those children with a protracted or frequently relapsing course. However, a question as to whether it would be at risk[26-27] for developing bone disease with normal GFR, needs to be further addressed.

In conclusion, several abnormalities of calcium and vitamin D metabolisms were observed in our study with children having acute nephrotic syndrome. Our data suggest that urinary losses of vitamin D binding protein in active nephrotic syndrome may lead to insufficient 25(OH)D substrate and relative

inadequacy of 1,25$(OH)_2$D which was caused by defective intestinal calcium absorption and diminished bone sensitivity to the calcemic action of parathyroid hormone. Consequently, this leads hypocalcemic condition.

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腎病症候群兒童鈣代謝之分析

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背景：鈣代謝也是小兒腎病症候群眾多異常代謝中之一項。為進一步對正常腎功能情況下之腎病症候群病童之有關鈣及 Vitamin D 之代謝狀況之瞭解而進行了本分析。

方法：12 例被診斷為腎病症候群之病童，且其腎臟功能均屬正常者為分析對象。收集其急性期與康復期之血液及尿液標本，分別進行血液中鈣、磷、白蛋白、肌酸酐、PTH、25(OH)D 及 $1,25(OH)_2D$ 之測定，以及尿液中鈣、蛋白質及肌酸酐之測定，並對該些檢測值在急性期與康復期作一分析與比較。

結果：結果顯示；這些急性期之腎病症候群病童不僅有血鈣之降低，PTH 有增加，及 25(OH)D 之減少外，且也有尿鈣與血中 $1,25(OH)_2D$ 之減少。但這些異常值在其康復期，又均回復正常。

結論：在急性期之腎病症候群病童之異常鈣與 Vitamin D 代謝而在康復期均又回復正常代謝之結果，在本研究中也獲得證實。該結果反應出急性期之腎病症候群病童，其血中活性 Vitamin D 之前驅物 25(OH)D 之不足，這或許與其在尿液中之流失有關。
（童綜合醫誌 2008; 2: 69-73）

關鍵詞：腎病症候群、鈣代謝、維他命 D、腎功能

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降低檢驗報告錯誤率之措施評估

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危及病人安全的醫療錯誤最常肇因於一連串不能預期的疏失。有鑑於此，我們自 2006 年 6 月至 2006 年 12 月藉由品管圈的運作，公開以非懲罰性內部通報方式收集本實驗室生化、血清、血液、血庫及急診檢驗等單位錯誤的報告，改善前先由品管圈成員共同腦力激盪，整理出檢驗錯誤的原因，再用柏拉圖及特性要因圖做真因探討與驗証。從中，我們發現報告錯誤的真因以人為疏失佔最大比率 (38.9%)，其次為異常報告未複檢 (22.2%)，再其次為病人身份識別錯誤 (12.5%) 及採檢 檢體識別錯誤 (9.7%)。上述問題點我們以戴明循環：P、D、C、A 概念討論出攻堅對策，並在考量病人安全的重要性之後，將總體改善目標值設定為 75%（即降低檢驗錯誤率至 9 件 / 月）。改善過程，我們不斷加強內部溝通並辦理人員教育訓練，且利用電腦資訊輔助管理。實施至 2007 年 12 月為止，已讓錯誤的報告數從改善前 36 件 / 月降至改善後 8 件 / 月，目標達成率 103.8%，總進步率為 73.3%，總體改善目標已達到降低檢驗報告錯誤率 80% 的滿意值，效果持續維持中。
（童綜合醫誌 2008; 2: 74-77）

關鍵字：檢驗報告錯誤率、病人安全

前　言

醫療疏失是世界共同關心的議題，根據 2000 年美國國家科學院附屬醫院研究院的文獻調查報告，在美國，每年約 44000 人至 98000 人死於醫療疏失，遠高於因交通意外事故、乳癌、愛滋病等死亡人數 [1]，台灣地區雖無正式文獻數據，但據丹麥醫師會會長 Dr. Jesper poulson 估計，台灣地區因醫療疏失而致死的人數每年約在六千到二萬人之間，他強調，假如不是醫療人員的敬業，醫療疏失致死的病患一定會更多。基本上，造成醫療疏失的因素主要有：人為因素、技術錯誤、系統錯誤及環境因素等 [2]，其中以人為因素佔率最高，人為犯錯的範圍包括：混亂、疏忽、違反作業規範、知識不足及沒有這個能力等 [3]。

有鑑於醫療疏失將造成病人傷害，行政院衛生署於 2003 年 2 月成立病人安全委員會，其目的在於眞正落實以病人為中心的醫療照護，並將民眾當作是建立安全醫療環境的伙伴，積極推動保護病人安全之各項政策與年度工作目標。安全工作目標推動優先工作有：了解國內存在的醫療疏失到底有多少？又有多少是可以預防？最常發生的原因有哪些？原因何在？該如何改善？及如何預防再發生。

為了配合行政院衛生署安全工作目標，我們特別成立品管圈專案改善小組，針對本實驗室最常發生的檢驗告錯誤利用資訊管理技術以期降低錯誤比率 [4]，並積極辦理病人安全相關訓練，讓同仁學習如何在醫療團隊中成為主動的一員及如何通報異常等 [5]，使同仁可以在「理所當然」的情況下通報異常事件，建立從「錯誤中學習」的機制 [6]，共同為病人安全把關。

研究材料及方法

本主題採用品管圈手法進行改善程序，改善共分三階段，2006 年 6 ～ 8 月為計畫期（改善前），9 ～ 10 月

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爲執行期（改善中），11 ～ 12 月爲評值期（改善後），數據收集執行期從 95 年 7 月 1 日起至 95 年 8 月 31 日止，品管圈採用非懲罰性內部通報方式 [7]，收集了 72 件錯誤報告事件，錯誤報告的類別包括血液、生化、血清、血庫及急診檢驗等。同時段內檢驗總件數是 90968 件，其中生化 39551 件，血液 26281 件，血清 8003 件，血庫 3190 件及急診檢驗 13943 件等。

改善幅度目標值設定爲 75%，亦即將檢驗報告錯誤件由 36 件 / 月降至 9 件 / 月，此目標值之設定除了參考國內相關醫學實驗室文獻數據外 [7]，更考量病人安全之重要性，嚴格要求。改善目標件數的設定計算公式是：改善目標件＝檢驗錯誤件數－（檢驗錯誤件數 × 改善重點 × 圈改善能力），其中圈改善重點設定爲 83.3%，圈改善能力設定爲 90%。

改善策略方法包括建立電子檔檢驗項目採檢說明、異常報告重測／通報系統、電腦 delta check 警示、電腦雙向連線、溶血及脂血檢體品質註記與檢驗報告整批查檢功能等六項。其中電子檔檢驗項目採檢說明內容包括：檢體種類、採血量、試管種類、報告時間及採檢注意事項等。而異常報告重測／通報系統是將原有的通報系統修正，必需重測後再通報，且強制規範通報時除了要輸入員工代號外須再輸入密碼確認，以防止假性或惡性通報。

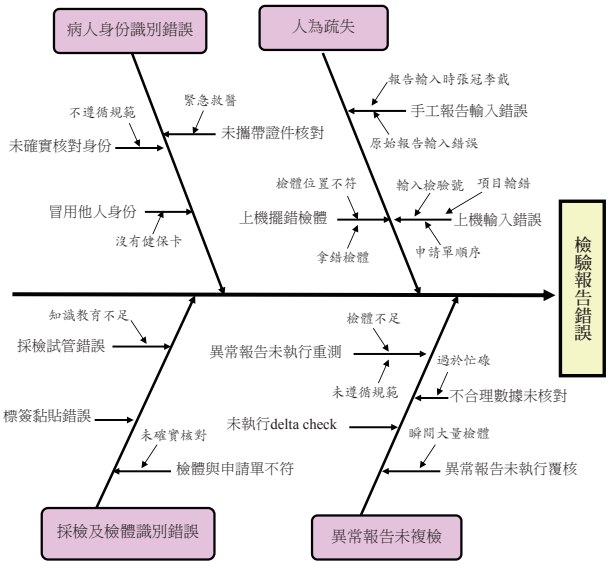

圖 1　檢驗報告錯誤要因分析

結　果

以柏拉圖分析執行期中檢驗報告錯誤的原因，發現以人爲疏失佔最多 (38.9%)，異常報告未複檢其次 (22.2%)，病人身份識別錯誤 (12.5%) 與採檢、檢體識別錯誤 (9.7%) 分居第三及第四，錯誤要因如圖 1 所示。

在人爲疏失的管控上，我們完成了資訊管理輔助系統，包括電腦 delta check 警示功能及電腦雙向連線等，此些功能主要用於自動化操作及異常或不合理數據之警示及控制，警示功能可以比對前次資料以協助判斷數據之合理性，而雙向連線可以避免人工抄寫或輸入的錯誤。

在異常報告未複檢的管理上，我們完成了異常報告複核及異常報告通報管理系統，複核系統可以強制異常報告複檢，確認爲危險值後直接以簡訊方式自動通報開單醫師。

在身份識別和檢體識別錯誤的管理，我們建立了身份識別及檢體識別作業程序，除了作業程序，更製作了簡易圖片檔說明，並在院內及單位內各舉辦了三場教育訓練，充分溝通。

經由上述各項對策之實施，人爲疏失引起的檢驗報告錯誤量由改善前的 28 件降至改善後的 6 件，進步率 78.5%，異常報告未複檢的錯誤量由改善前的 16 件降低至改善後的 3 件，進步率 81.3%，病人身份識別錯誤量由改善前的 9 件降低至改善後的 1 件，進步率 88.8%，採檢及檢體識別錯誤量由改善前的 7 件降至改善後的 2 件，進步率 71.4%，總體的目標達成率爲 103.8%，進步率爲 77.8%，如圖二及圖三所示。

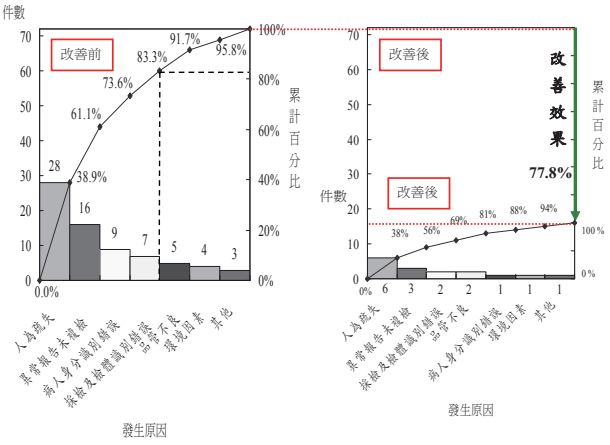

圖 2　改善前每月錯誤件數 36 件，改善後 8 件，進步率 77.8%，目標達成率 103.8%。

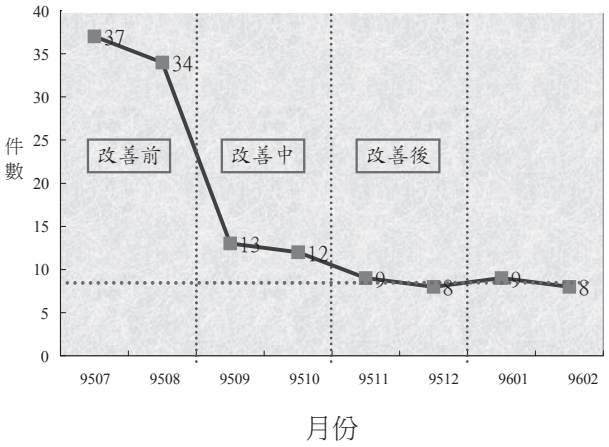

圖3 改善前報告錯誤通報件每月約36件，改善中約12件，改善後降爲 8 件，進步率 73.3%。

討　論

持續降低檢驗報告錯誤的過程中，品管圈面臨最大的困難度是如何突破同事間相互坦護隱匿不報的心態，此一心態幸賴院方實施非懲罰性的通報制度加以扭轉，特別是在幾近錯誤的異常或錯誤事件，院方對主動通報者非但不罰，還有獎勵。非懲罰性通報制度解除了同事間互相坦護的錯誤觀念，更建立了正確的通報文化，確實做到爲病人就醫安全而努力的檢討改善。

電腦未全面自動化雙向連線前，人爲疏失大都和人工輸入錯誤相關，主要的人工輸入錯誤有：上機時輸錯檢驗項目或輸錯受檢者的基本資料。輸錯檢驗項目，常見的結果是該有報告的沒有數據，而不該有報告的卻有結果；而在基本資料輸錯方面，則會產生受檢者名字張冠李戴或報告極不相符合的錯誤。爲了解決這些問題點，我們以人工方式編序並逐筆核對申請單和報告單，且對特殊檢驗項目如血型等，更採取第二人覆核方式，以確保檢驗之正確性。

所有檢驗報告錯誤事件中最容易影響病人安全的，以危險數據和不合理數據未複檢就直接傳輸的錯誤最爲嚴重，受檢者及單位人員的傷害也最深，如何有效解決又如何預防再發生，列入我們最優先改善的標的。不合理的數據包括不可預期的超高或超低值或危險值，超低值常發生於儀器吸量不足或測試件濃度過高，而超高值常見於檢體溶血或檢體不良或病人本身的異常，不合理偏低或偏高的數據，我們以檢體品質註記或以電腦 delta check 警示功能把關，非經確認不會發出報告，且確認後危險值會經由檢驗危險值通報系統傳出，不但可確保通報又可避免通報錯誤，及時保護病人安全。

病人身份識別錯誤，最常發生於前線採檢單位，以美國紐約州統計輸血錯誤的調查報告爲例，病人身份識別錯誤佔輸血錯誤最大的比率（43%）[8]，因此落實三讀五對政策以確保病人身份正確性，是避免病人身份識別錯誤最重要的程序。

結　論

檢驗報告的錯誤通常是可以避免的，但卻難以達成，原因是檢驗流程的各項環節和過程都可能出錯，爲達到病患就醫安全之目標，設計嚴謹的關卡以降低檢驗報告錯誤，保護病人安全，是我們改善最優先的重點。然而，高品質的醫檢服務有賴於人員、技術、流程及制度四要素的充分配合，在人員和技術能力的提昇方面，我們強化不符合或異常事件的發掘和處理，更加強教育訓練以彌補認知的不足。而在減少檢驗報告錯誤的流程和制度上，則依認証規範建立相關政策及作業程序，異常的問題點在經過一段時間的矯正管理後仍遺有錯誤時，必需以戴明 PDCA 循環再評估改善。爲了持續改善我們自 2007 年元月起，將本改善主題加入台灣醫療照護品質指標系列 (THIS) 中持續追蹤，以期能做得更對、更好，共同爲病人安全努力。

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A Method for Reducing the Rate of Laboratory Report Error Evaluated

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It is consensus that a plethora of unpredictable negligences or mistakes is often associated with the erronous laboratory reports that can jeopardize the safety of the hospitalized patients. For this reason, we conducted an intralaboratory Quality Control Circle (QCC) starting from June through December, 2006, aiming to collect the data on the frequencies of reporting errors in five subdivisions of Clinical Laboratories including Chemistry, Serology, Hematology, Blood Bank and STAT Lab in a non-penalty and voluntarily fashion for the purpose of knowing the seriousness of the problem in our hospital. Trough the group discussion of the QCC board members, innovative measurements for preventing laboratory errors can be generated and put into practice. We then used Pareto' s Cause and Effect Diagram to review and analyze the reasonings for eommitting errors. Trough this effort, we identified the reasonings for committing laboratory report errors in descending order are: (1) human error (38.9%); (2) abnormal results without follow-up checking (22.2%); (3) patient' s identify recognition error (12.5%); and (4) specimen collection and identification error (9.7%). We then applied the concepts of Deming Cycle: Plan, Do, Check, Act, to discuss and come up with a corresponding strategy for correcting the problems mentioned above. We then set an improvement goal to 75% (i.e., to reduce laboratory error ratio to 9 cases/month). To achieve this goal, we tried to enhance intralaboratory communication, and laboratory staff education and training. Meanwhile, we used computer delta check system to assist in data management. Because of this implementation effort, the report error ratio of our laboratories has been reduced from 36 cases/month to 8 cases/month. This represents an accomplishment rate of 103.8% and an overall improvement rate of being 73.3%. Taken together, through the implementation of our QCC program, we have been able to reduce laboratory report errors by 80% and have so far maintained the same level of efficiency.
(Tungs' Med J 2008; 2: 74-77)

Key words: laboratory error rate, patient safety

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The Coincidence of Acute Myocardial Infarction and Scrub Typhus: A Case Report

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Scrub typhus (tsutsugamushi disease) is associated with many serious complications including myocarditis. Major symptoms and signs of myocarditis are chest pain, dyspnea, ST-T change and the elevation of CK activities. These attributes are very similar to acute myocardial infarction (AMI) and may lead to a possibility of misdiagnosis. Our patient, a 45-year-old male with a history of hyperlipidemia, hypertension, hyperuricemia and hepatitis B carrier, visited our hospital owing to the occurrence of chest tightness for one-day and a fever for 7-day. Triple vessel coronary artery disease with non-Q MI and with a proven scrub typhus were noted. The patient recovered well after cardiac catheterization with coronary angioplasty and tetracycline treatment. Owing to a simultaneous presence of scrub typhus and chest pain may easily be misdiagnosed for having myocarditis, we thus report this case for the purpose of reminding that a patient with scrub typhus along with chest pain can either result from myocarditis or acute coronary syndrome.
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Key words: Scrub Typhus, Chest Pain, Acute Myocardial Infarction, Myocarditis

INTRODUCTION

Scrub typhus is an acute febrile infectious disease cause by *Orientia tsutsugamushi*[1]. The clinical manifestation of scrub typhus is greatly diversified due to its multiple organ involvement. The most common clinical symptoms included fever, myalgia, macular rash, and headache. Myocarditis is a rare serious complication of scrub typhus. The symptoms and signs of myocarditis are very similar to acute myocardial infarction. Acute onset of chest pain in patients with scrub typhus may be regarded as scrub typhus in relation to myocarditis, not acute coronary syndrome. The misdiagnosis of acute coronary syndrome will result in high morbidity and mortality rate. We report here a case in which acute myocardial infarction and scrub typhus can be occurred simultaneously. This can serve to remind us that a possibility of coincidence of acute coronary syndrome and scrub typhus can be existed.

CASE HISTORY

A 45-year-old male worker with a history of cigarette smoking, hyperlipidemia, hypertension, hepatitis B carrier and hyperuricemia was admitted to our hospital because of persistent chest pain for one day and fever for one week. He is an aborigine of Taiwan and has been lived in Pu-Li, which is the endemic area of scrub typhus.

He had suffered from an episode of chest pain, and ischemic heart disease that was diagnosed by

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practitioner one year ago. He also had several episodes of mild chest discomfort during last year. Fever, chills, chest discomfort, skin rash, and headache occurred one week prior to admission. Acute onset of chest tightness with cold sweating developed one day prior to admission. He visited another hospital and the Electrocardiogram (ECG) showed ST segments elevation over V1 to V4 leads. Elevated cardiac enzyme was also disclosed. He received heparin intravenous bolus 10,000 units, nitroglycerin intravenous continuous infusion, morphine 5mg intravenous drip and aspirin 300mg by mouth, and then was referred to our emergency room with a tentative diagnosis of acute anteroseptal myocardial infarction.

In our emergency room, chest tightness, fever, chills, headache, and mild dyspnea persisted. His mental status was normal. The initial blood pressure was 110/70 mm Hg; body temperature, 38.4℃; heart rate, 120/min; respiration rate, 20/min with normal respiration pattern. The findings of physical examination were normal except for systolic murmur grade III/VI over apex and left sternal border. There was no eschar or lymphadenopathy. The 12 leads ECG still showed ST segment elevation over V1 to V4 leads. The initial laboratory data was following: peripheral blood hemoglobulin, 14.3gm/dl; platelet count, 186000/μl; white blood cell count, 12700/μl with 91.3% neutrophil and 3.26% lymphocyte. The serum level of blood urea nitrogen was 13 mg/dl; creatinine, 1.1 mg/dl; SGOT 76 IU/L, SGPT 28 IU/L, sodium, 132 mmol/L; potassium, 3.3 mmol/L; CK, 1081 IU/L; CKMB, 40.1 U/L; Troponin I, 16.0 ng/ml; and C-reactive protein, 15.34 mg/dl. Heparin continuous infusion, nitroglycerin continuous infusion, cephradine 1gm intravenous every 6 hours, and gentamicin 60 mg intravenous drip every 8 hours were given under the diagnosis of acute anteroseptal myocardial infarction and fever of unknown origin. The levels of follow-up CPK/CKMB were 976 IU/L and 29.8 U/L 8 hours later. Due to rising SGOT and temperature and living in endemic area of scrub typhus, tetracycline 500mg per oral four times per day for one week had been given. Fever subsided on the fourth hospital day.

Initial echocardiogram showed fair left ventricle performance, mild hypokinesis over apex and anterior segment, moderate tricups regurgitation, and mild mitral regurgitation. Chest tightness recurred on sixth hospital day, so coronary angiography was done on the next day and revealed 50% segmental stenosis of middle left anterior descending artery (LAD), and 89% segmental stenosis over middle portion of

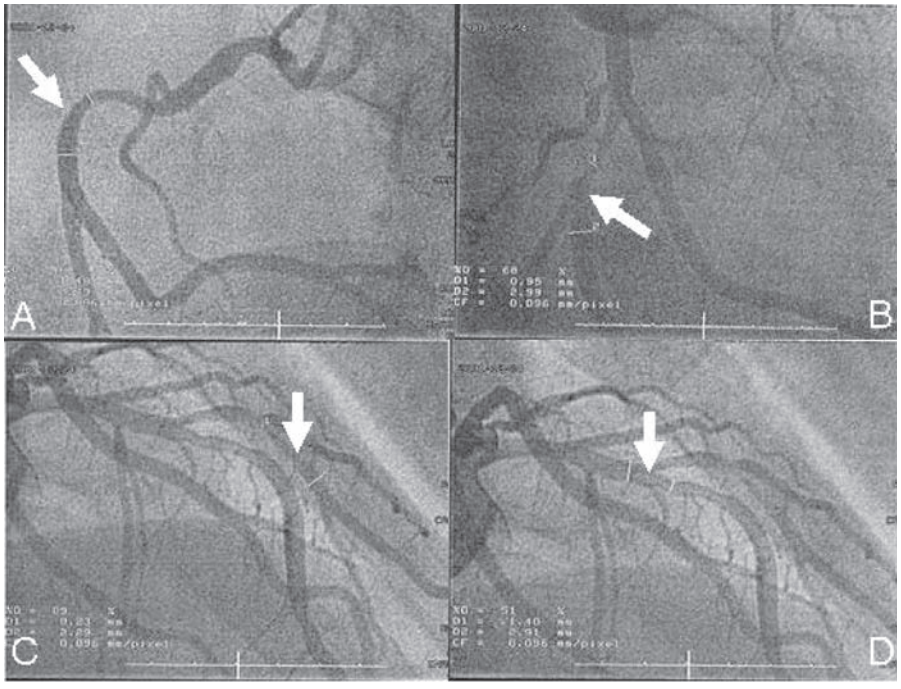

Fig. 1. Coronary angiography showed a 46% segmental stenosis at right coronary artery (A), 68% segmental stenosis at distal left circumflex artery (B), 89% segmental stenosis over middle portion of second diagonal branch of left anterior descending artery (C), and 50% segmental stenosis of middle left anterior descending artery (D).

second diagonal branch. There was 68% segmental stenosis at distal left circumflex artery and 46% segmental stenosis at right coronary artery (fig 1). Percutaneous transluminal coronary angioplasty to diagonal branch of LAD was done. He was discharged uneventful on the ninth hospital day.

The initial IgM titer of *O. tsutsugamushi* was positive. The IgG titer of *O. tsutsugamushi* has fourfold elevation 2 weeks later.

DISCUSSION

Scrub typhus is an acute febrile infectious disease caused by *O. tsutsugamushi*, an obligate intracellular bacterium, formerly *Rickettsia tsutsugamushi*. The clinical manifestation of scrub typhus is greatly diversified due to its multiple organ involvement. More common clinical symptoms were fever, myalgia, and headache. Rash and eschar are the most common signs[2]. Physical examination may reveal lymphadenopathy, splenomegaly and relative bradycardia.

The reported serious complications included pneumonitis, acute respiratory distress syndrome (ARDS), acute renal failure, septic shock[3], encephalitis, and meningitis[4]. Myocarditis is also a rare complication of scrub typhus[3]. The earlier report of an autopsy series showed 80% patients of scrub typhus have myocardial lesions. The vasculitis and perivasculitis result in hemorrhage and edema of interstitial tissue of myocardium[5]. Patients have scrub typhus with cardiac involvement can have ST-T change, PR prolongation, and mild mitral regurgitation[6]. These symptoms are very similar to acute myocardial infarction. Prudent physical examination of the patient heart function and electrocardiogram are necessary in every case of scrub typhus[7].

To our knowledge, this is the second reported case, which acute myocardial infarction (AMI) associated with scrub typhus. The AMI of the first reported case developed one week after scrub typhus symptoms disappeared[8]. However, the AMI of our case developed during the acute stage of scrub typhus. Despite many vasculitis related disease can involve the heart and artery[9], no evidence can prove the association between acute myocardial infarction and scrub typhus of our patient.

This case reminds us that chest pain in patients with scrub typhus can result from not only myocarditis, but also acute coronary syndrome, especially those have the risk factors of coronary artery diseases, such as smoking, diabetes mellitus, and hypertension. For scrub typhus patients with chest pain, the careful evaluation of heart function should be done. If local hypokinesis of heart and refractory congestive heart failure are discovered, coronary angiography and follow-up echocardiogram are also necessary.

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急性心肌梗塞及恙蟲病同時發生：個案報告

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恙蟲病是一種急性發熱性疾病，它可以引起很多嚴重併發症，其中包括有心肌炎。心肌炎的主要症狀包括有胸痛、呼吸困難、ST-T 改變及 CPK 值的上升。這些症狀非常類似心肌梗塞，可能造成臨床醫師把急性冠狀症候群誤認為恙蟲病合併心肌炎。這個 45 歲男性，先前有高血脂症、高血壓、高尿酸及 B 型肝炎帶原者的病史。病人因為胸痛一天及持續發燒 7 天而轉至本院。經心導管檢查及血清學試驗證實病人同時有 non-Q 心肌梗塞及恙蟲病。在接受心導管動脈氣球擴張術及 tetracycline 的治療後，病人復原良好。因為恙蟲病病人發生胸痛或胸悶可能被認為心肌炎。因此我們報告這個案例提醒大家，恙蟲病病人出現胸痛，有可能為心肌炎或急性冠狀症候群。
（童綜合醫誌 2008; 2:78-81）

關鍵詞：恙蟲病，胸痛，胸悶，急性冠狀症候群

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Psychoanalytic treatment of an adult woman experiencing childhood sexual abuse: A case report

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Background: Very few literatures have reported clinical vignette of psychoanalytic treatment of a female adult with childhood sexual abuse in a context of an oriental culture. Some descriptive studies have reported the long term sequelae of childhood sexual abuse. There are variations in the clinical manifestation of these patients. Influencing factors include the age at which abuse occurs, the relationship of the perpetrator with the victim, early childhood development and mainly the quality of the relationship with his or her primary objects, etc. In-depth exploration of the clinical dilemmas that are present in the psychoanalysis of the patient may shed light on the psychopathology of these clinical manifestations.

Case reports: Mrs. X, a forty-year-old married mother of two, sought treatment because of episodic depression that incapacitated her to the extent of being bedridden for as long as 3 months with each episode during the past 15 yrs. From the age 6 to 10, a veteran who was a stranger to her sexually assaulted her. She kept the abusive relationship secret to all until the psychoanalytic treatment sessions. In the early phase of the treatment, she repeatedly mentioned her feeling of fear and conflict with the therapist. Frequently dreaming of the therapist helping or abandoning her. Trials of interpretation were fruitless and she seriously considered withdrawing from the therapy after a seductive behavior being confronted by the therapist. However, important progress occurred 6 months after treatment had begun which was heralded by empathic interpretation of the trust and safety issues. She was reported to be more assertive and stable emotion in dealing with the abusive husband. Without any psychotropic medication, she remained symptom free throughout the two years when she was in therapy albeit abuse by her spouse was ongoing.

Conclusion: Reenactment of childhood trauma along with the primitive aspects of personality was mobilized in the treatment, which seemed to be overwhelming if the abuse had been persistent or parental and spouse abuse present. Taken together, we suggest that the developmental arrest resulted from early childhood trauma can be reawakened and revived with symptom relief through psychoanalytic psychotherapy in the context of an oriental culture.
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Key words: Psychoanalytic treatment, Childhood sexual abuse

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Background

Mrs. X, a forty year old women, was self referred because of tinnitus, hightened anxiety and dizziness for 2 months, and the fear of taking public transportation for decades. She was married, a homemaker, living with her husband and two sons. Her husband was a manager in a franchise corporation.

At the initial evaluation interview, she appeared mildly overweight and a sense of sadness was noted during an eye contact. She wore make-up lightly and had long perm hair. Her motivation, fluency and college education were her psychological strengths.

She also reported to have recurrent depressive episodes twice annually since she gave birth to her eldest son 18 years ago and at that time abuse from her husband began. During depressive episodes, she was totally incapacitated, being bedridden with little food intake. Intravenous fluids were a life –saving necessity during the episodes. The husband was described as a macho kind of person who always demanded extreme tidiness and orderliness at home. Stinginess, lack of mercy and self-centeredness were the husband's traits as described by her.

She stated that male chauvinism was professed in the husband's family tradition, which demanded total obedience and subordination of the women.

It was some time into the therapy when she disclosed having experience of being sexually assaulted by a veteran during her childhood apart from being physically abused by the adoptive mother. Long term feeling of uncertainty and emptiness that were relentlessly in recent years prompted her to seek help.

Adoption

Mrs. X was adopted by her parents when she was two months old. She was brought up in a rural area, in a middle-class family consisting her adoptive parents and a step-brother 6 years older than her. Her biological parents were never known to her.

The adoptive father

Mrs. X's father was born in China, came to Taiwan in 1949 and married her adoptive mother who was a widow living with her son. Because of the infertility of the adoptive mother, the father decided to adopt a child. The father was a religious man with strong faith in Christianity. He was pictured as gentle, righteous and caring for her emotionally although always not at home due to business reasons. She was his "little princess". The father was one of few persons that she could depend on emotionally in the past decades before the therapy began.

The adoptive mother

The mother was described as a beautiful woman who was very concerned about her biological son. In contrast, Mrs. X stated that she was frequently abused by her both emotionally and physically. She suffered physical abuses quite frequently and sometimes so severe that the neighborhood came to the rescue. She was always ridiculed as "a stupid, ugly and lazy whore" both in private and public by the adoptive mother. She remembered being left all alone at the corner shivering in wet clothes while her mother was gambling in a typhoon night. The mother had slipped up her unpleasant life partly due to her husband's sexual impotence. Actually, the mother herself had had experiences of being neglected as a child, according to Mrs. X. However, the mother seemed to take pride in her biological son—Mrs. X's step brother.

The family in the past

The relationship between her parents was perceived as distant and tense, uneventful at the surface and tense underneath. In the family, she was facing two worlds in great contradiction: the world of the father and the world of the mother. She was a "little princess" in the presence of the father and a "poor orphan" in his absence. The step brother was an "accomplice" with the mother, letting her down in her desire and striving for sibling intimacy. The parents had been on the brink of divorce several times during Mrs. X's childhood. She had been acting as a mediator to make peace in her parent's impending divorce out of fear of being abandoned if the parents had broken up.

The family in the present

Mrs. X's husband was described as domineering and controlling as her mother. She stated that the same quality of abuse was received from the husband as from the mother in the past. The physical abuse went to such an extreme that she was once badly hurt due to kidney hemorrhage after the physical abuse. Coercive sex occurred quite often as well. It was not until a trust relationship was established that Mrs. X began revealing the family violence in which her sons were also the victims. The husband set up stringent

family rules that whoever violated them will be punished.

Victimization

Mrs. X was tailed by a pedophilic veteran and was sexually assaulted at age of 7-8.The pedophilic veteran kept pursuing and sexually harassing her for the next 2 years. The recollection of the trauma was so vivid in detail that she was emotionally overwhelmed during that session. Hatred of marked intensity toward the perpetrator and the parents were revealed at that session as well. The sexual abuse was deemed as the most pivotal turning point in her life.

Treatment modality

The treatment was psychoanalytically oriented with the patient talking about whatever came to mind as facilitated by the therapeutic relationship.

The main focus of intervention was to deal with the factors that accounted for the formation of symptoms and disturbances in object relations, namely, the fear and anxiety associated with childhood trauma and the disturbances in primary object relation.

Trauma and defense

Janet[1] proposed that the unbearable emotional reaction to traumatic events exert a disintegration side effect on the mind. The traumatic emotions that seemed to hibernate may be acting through the defense of dissociation to cause physical symptoms. Breur and Freud[2] had discovered that the reawakening of the past traumatic memories and discharge of the repressed emotions associated with the trauma yielded symptom relief. Van der Kolk[3] states that once a patient starts remembering the trauma and is able to understand the connection between the events and the subsequent emotional experiences, there is a gradual reduction in the intensity and frequency of the intrusive nightmare, reenactment, or anxiety and panic states. The theories seemed relevant in this case during the course of psychoanalytic treatment. The patient reported to have more harnessing ability over her own emotions and family conflict as the traumatic events were recalled, processed and integrated in the therapy.

Dissociation and trauma

Mrs. X recalled the day when the sexual abuse first occurred. She was brutally hurt by the pedophilic veteran with painful swelling and bleeding over her private part. After returning home, she was numb and immobile on her bed. She felt detached from the outside world. Her mind gradually “turned off”, refusing any attention from the father who was ignorant of the severe event. She said that within a matter of one day she decided not to trust any person in the world anymore. Her mind was sealed off the outside world. The “original me” was dying and was replaced by “another me”, as she said in the session. The sexual trauma was never disclosed to anybody until in the therapy with me.

Mrs. X during several treatment sessions was noted to lapse into her childhood scenes in which she could see herself at age 3 and 7 years. She felt touched by the 3-year-old scenes but when it came to the 7-year-old scenes, she felt like crying began shivering and was agitated. In the scenes, “spring of tears” was flowing like a waterfall. Her body and mind seemed to be torn apart from each other, as she described it. She was noted to be absolved in the dreamful scenes with a frozen facial appearance, weeping with mute.

The shattering experiences that account for the dissociation seemed to have its origins at the time of the trauma when the cognitive and affective processing were blocked by the shock. The reenactment, integration and reprocessing of the traumatic memory and affect seemed to exert a symptom reducing effect in this patient[4,5,6,7].

Object relation and transference

Mrs. X reported one of her most frequent dreams throughout her life, consisted of scenes of the skinny shadow of a little girl being dragged along the trail toward her father’s office. The trail seemed endless and the goal seemed too far to reach. Early in treatment, she reported a dream in which she was falling down a well and the therapist reached out his hand to her rescue. Suddenly she was shocked to find the outreached hand melting like wax. The dream that seemed to bother her the most was the scene of incest with the father. Mrs. X recalled one of her favorite childhood activities was to suck the nipple of the father who allowed her to do so.

The disturbance in internalized object and ego identity was affected by the early childhood trauma and perpetuated by the spouse abuse. Due to the lack of stable and adequate parental attention, the object constancy and stable object relation were poorly de-

veloped leading to problem of trust and identity diffusion. She reported having long period of neutral dressing in her adolescent years.

The treatment of this patient seemed relevant to the notion made by Mendelberg[10] who stated that the treatment of trauma intertwined with the poorly developed object relation required more than release of the pent-up emotions. The treatment need to be done in a context of a holding environment[8]. The therapist' s containing and soothing in a vicarious introspective[10] manner seemed to provide an opportunity for the self to grow with improving ego mastery[9]. Thus the positive transference and the build up of trust in the therapeutic relationship become the pivotal therapeutic factors.

Intimate relations inevitably aroused dangerous and conflicting emotions which was originated from the disrupted primary object relations. ie. the abusing mother and the inconsistent father. Theses emotions seemed reawakened during the treatment as manifested in the erotic transference resistance which was evidenced by the dilemma of dropping out as proposed by her in the middle phase of treatment.

She had several dreams with themes of the therapist being removed involuntarily from the office by the superior etc. She was also very concerned about the physical health of the therapist just in case it might jeopardize the therapy.

Psychoanalytic treatment setting unveiled the archaic need for object attachment and to be loved that were conflicting with feelings of being bad and undeserving and with the expectation of being rejected and abandoned. The resistance and negative transferences were confronted and interpreted. She came to the realization of her expectations that I would be despising and victimizing her like her mother and inconsistent and unprotective like her father. Later, we also came to the realization of the contrast of the past with the present, of the previously helpless child with the present mature adult.

From trauma to recovery

After two years of once a week sessions, without any psychotropic agents, she was free from any depressive episodes that she had experienced twice annually before the therapy. She reported to be her real self again after decades of falsehood. Her friends also noted her burgeoning changes and commented on her as being more “amiable and energetic “ than ever before. Although a number of regressions were noted when spouse abuse recurred, she seemed to master them in a more efficient way and more able to pull herself together again. She said that she would work harder to save her children from the same victimization she had had before. She also anticipated the option of divorce when the reality allowed in the future. Toward the end of therapy, she started to read the psychoanalytic books written by Karen Horney and Carl Jung.

Conclusion

The importance of this case report is to present the clinical evidence of effectiveness of psychoanalytic treatment modality based on the theoretic model of object relations. Namely, the developmental arrest resulted from early childhood trauma can be reawakened and revived with symptoms relief through psychoanalytic psychotherapy in the context of an oriental culture.

The finding of this case report seemed replicate the notes made by Dr. Ralph R. Greenson (1960) " The psychoanalyst does not have the right to impose any brand of morality or values of any kind upon his patient. It is our duty only to free the patient from his irrational unconscious and tyrannical past. If we succeed in doing this, and our patient has achieved some maturity, he should be free then to choose the kind of morality, standards and values that suit him." The patients of any cultures and religions could be benefited from the psychoanalytical treatment because the inner psychic trauma is universally affecting his life which go beyond his morality or values of different cultures or religions.

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幼年時期受性虐待東方成年女性之精神分析治療：一例報告

李豪剛

目的： 某些描述性研究顯示幼年時期受性虐待導致日後長期之後遺症，其臨床表徵有個別之差異性，影響因素包括受虐待時的年齡、加害人與受虐者之關係、受虐者幼年早期之心性發展以及其與主要客體關係之品質等等。對精神分析治療中之困境加以深入剖析，有助於了解其臨床表徵之各個面向；國內外極少有受性虐待東方成年女性之精神分析治療報告，其治療過程及效果值得探討。

個案報告： X 女士，40 歲，已婚育有兩子。主訴有間歇憂鬱發作甚至癱瘓在床長達三個月；在六歲至十歲之間她曾被一位陌生老榮民性侵及騷擾多次，一直到精神分析治療中才吐露出來。在治療早期她重複提及對治療者之害怕及矛盾，常常夢到治療者幫助她及放棄她，嗣後雖經解析仍無進展之後她鄭重考慮退出治療。在治療六個月之後，就信任及安全之主題予以同理解析之後，獲得重要進展，在與施暴丈夫之互動中情緒更加沉穩及自我肯定。雖然婚姻暴力仍然持續，在接受精神分析治療兩年期間未服用任何精神科藥物情形之下其憂鬱發作未再出現。

結論： 幼年時期創傷伴隨人格之原始面貌會在精神分析治療中發動再現，其強度似乎與受虐之持續性與否、父母配偶是否為加害人有關；在東方文化的背景下，經由精神分析治療，個案中止發展之人格可以甦醒、復活，臨床症狀獲得舒解。（童綜合醫誌 2008; 2: 82-87）

關鍵詞：精神分析治療，幼年時期受性虐待

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Cardiac Myxoma with Malignant Glandular Component and High Serum CA125: Immunohistochemical Finding of One Case and Literature Review

Tang-Yi Tsao[1*], Ching-Wen Wu[2], Jeng Wei[2]

Cardiac myxoma is the most common primary cardiac tumour in adults, typically arising from the left atrial wall in middle-aged women. For all practical purposes cardiac myxoma are considered benign tumours, although disputed sporadic case reports existed for malignant cardiac myxoma. A striking observation, seen in approximately 1–5% of cardiac myxoma, is the occurrence of glandular component embedded within the myxomatous stroma.We report a case of 69-year-old man who presented with chest discomfort for several days. Echocardiography demonstrated a 7.0 × 3.0 cm echo-dense mass in left atrium. He also had high serum level of CA125. Histologically, the general pattern was typical for cardiac myxoma. The tumor was embedded with groups of glandular component which showed cribriform with prominent nucleoli, apoptotic bodies, occasional mistoses, and signet ring cells differentiation. Immunohistochemically, glandular components were immunoreactive for EMA, pancytokeratin (AE1/AE3), CK7, CK8, CK18, CK19, CA-125, Mucin-carmin, Alcian blue (PH=2.5), and negative for CK5,CK20, CD34, smooth muscle actin, NSE, synatophysin, TTF-1, and calretinin.
(Tungs' Med J 2008; 2: 88-94)

Key words: cardiac myxoma, glandular component, Mucin-carmin and Alcian blue (PH=2.5) stains.

INTRODUCTION

Cardiac myxomas are the most common primary cardiac tumor in adults and account for approximately 75 to 80% of cardiac tumor in surgical series[1], and typically arising from the left atrial wall in middle-aged women. Microscopically, glandular, hematopoietic, chondroid, and thymic tissues may be found within cardiac myxomas[3]. For all practical purposes cardiac myxoma are considered benign tumors, although disputed incidental case reports existed for malignant cardiac myxoma[5,6,7]. A striking observation, seen in approximately 1–5% of cardiac myxoma, is the occurrence of a glandular component embedded within the myxomatous stroma[4,7,8]. We present a case of cardiac myxoma with malignant glandular component and high serum level of CA125 with special references to the morphologic features and immunohistochemical profiles.

CASE REPORT

A 69-year-old man who presented with chest discomfort for several days was admitted to the Car-

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diovascular Clinic of Tungs' Taichung MetroHarbor Training Hospital. On physical examination, there was no evidence of enlarged lymph node or edema in the lower extremities. No signs of tumor were detected in lungs and mediastinum by chest X-ray. Echocardioraphy demonstrated a 7.0 × 3.0 cm echodense mass in left atrium, with mild mitral regurgitation and tricuspid regurgitation(Fig 1). Surgery was performed under the diagnosis of cardiac myxoma. During the surgical resection, the myxoma appeared to have long pedicle that was attached to the myocardium at the interatrial septum. The mass was removed along with the pedicle. Afterwards, pathologists submitted a preliminary report on the next day. The subseguent laboratory tests showed a high serum CA125 level (135 U/mL) but normal CEA and PSA serum levels. Grossly, the left atrial myxoma was polypoid and loosely lobulated with a smooth and glistening surface, measuring 7.8 x 6 x 3.7 cm in size and 51 gm in weight. The fragile tumor was red to white-gray in color with incomplete capsule and with a long pedicle measuring 3.0 x 1.5 cm in size. On the cut surface, the tumor was gelatinous and semitransparent with partially hemorrhagic and cystic areas (Fig.2). Microscopically, the myxoma surface was lined by a single layer of flat cells. The predominant component was like a classical myxoma with stellate or spindle-shaped "myxoma cells" lying in a myxoid background, with oval nuclei and a moderate amount of eosinophilic cytoplasm. Short cords of myxoma cells were occasionally detected. Numerous capillaries scattered among the typical areas and the myxoma cells were evenly distributed with sporadic perivascular aggregates. The myxoid background had additional focal hemorrhage fibrin mixed with hemosiderin and blood cells such as erythrocytes, neutrophils, and lymphocytes. Atypia, hyperchromatism, or mitoses were not observed in these "myxoid cells. The stalk area was free of myxomatous tissue. The glandular components were irregular and tubular glands lined by a single layer of cuboidal to tall columnar cells mixed with some goblet cells. The epithelial cells had basally-oriented round nuclei with prominent nucleoli and eosinophilic cytoplasm and apical mucinous bubbles.(Fig.3). Some glands had angulated contours and cribriform architecture. The latter structures were composed of cells with irregular hyperchromatic nuclei of varying sizes and shapes, with distinct large nucleoli and signet ring cells differentiation. Within these glands apoptotic bodies, mitoses were readily identified (Fig.4). Selective sections were stained with Mucin-carmin stain and Alcian blue (PH=2.5). Both histochemical stains had strongly positive reaction in the glandular components (Fig.5 & Table 1). In addition, the myxomatous stroma component also had moderately positive reaction for Alcian blue (PH=2.5) stain. Immunohistochemical staining was performed by avidin–biotin complex peroxidase complex meth-

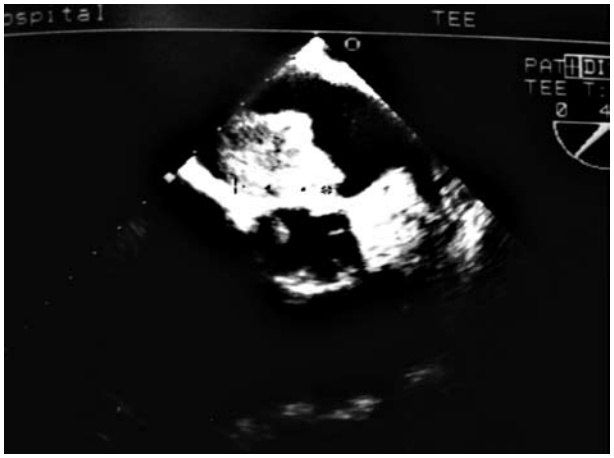

Fig. 1 Echocardiography demonstrated a 7.0 × 3.0 cm echodense mass in left atrium. Myxoma was considered.

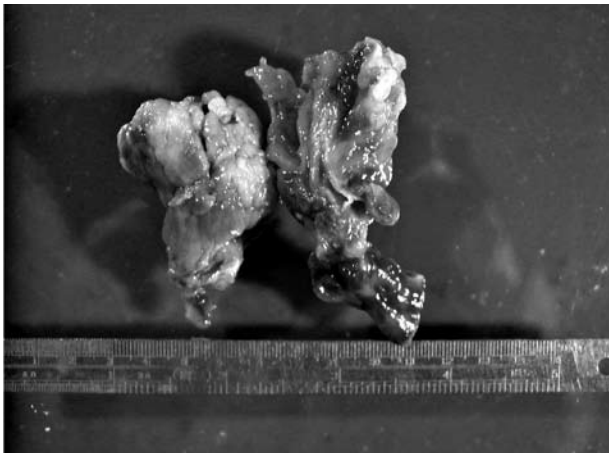

Fig. 2 Grossly, the left atrial myxoma was polypoid and loosely lobulated with smooth, and glistening surface measuring 7.8 x 6 x 3.7 cm in size and 51 gm in weight. The fragile tumor was red to white-gray in color with incomplete capscule and with a long pedicle measuring 3.5 x 1.5 cm. On the cut surface, the tumor was gelatinous and semitransparent with partially hemorrhagic and cystic regions.

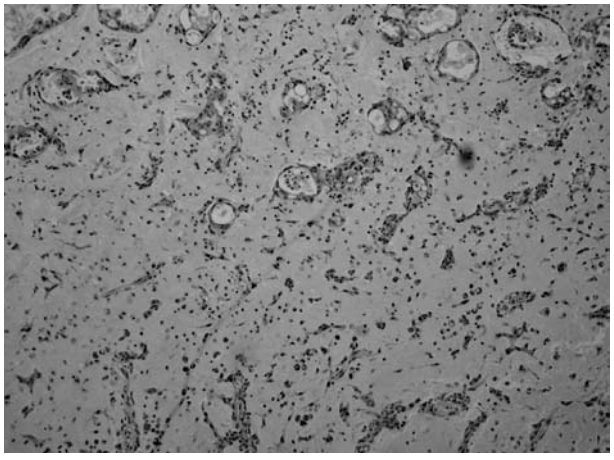

Fig. 3 Microscopically, the general pattern was typical for a cardiac myxoma with small stellate cells forming strands and perivascular circular structures. Atypical hyperchromatism or mitoses were not observed in these stellate cells. Within the tumor, glandular structures were focally present in groups. (Hematoxylin- eosin stain, X 100).

od according to the manufacturer's instructions. The immunohistochemical stains utilized the antibodies against pancytokeratin (AE1/AE3), CK5, CK7, CK8, CK18, CK19,CK20, EMA, CA125, calretinin, NSE, Synatophysin, TTF-1, smooth muscle actin, and CD34. Immunohistochemical staining showed CD34 and smooth muscle actin positive in myxoma cells as well as vascular endothelial cells and the capsular

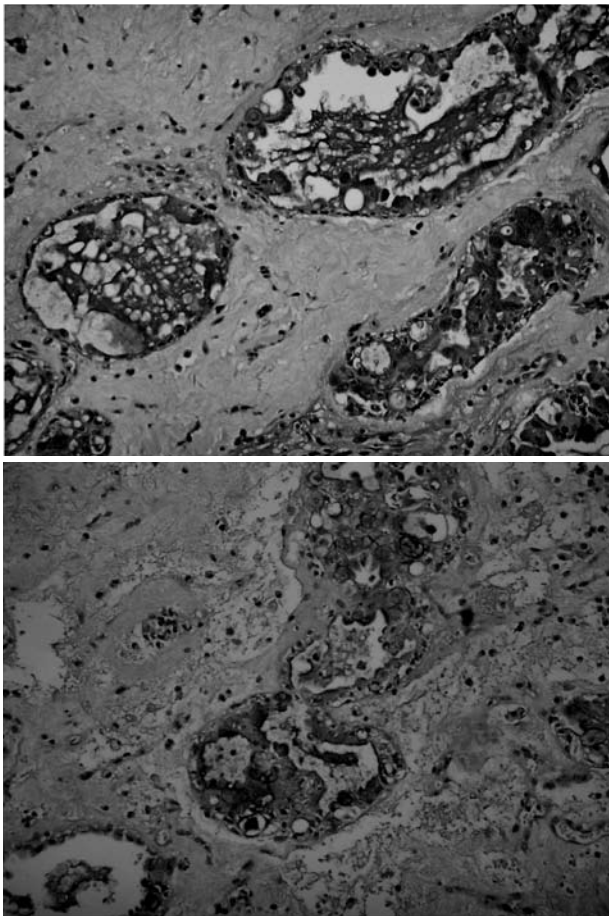

Fig. 5 Both Mucin-carmin (left:4A) and Alcian blue (PH=2.5)(right:4B) histochemical stains were strongly positive in the glandular components (Histochemical stain, X 200).

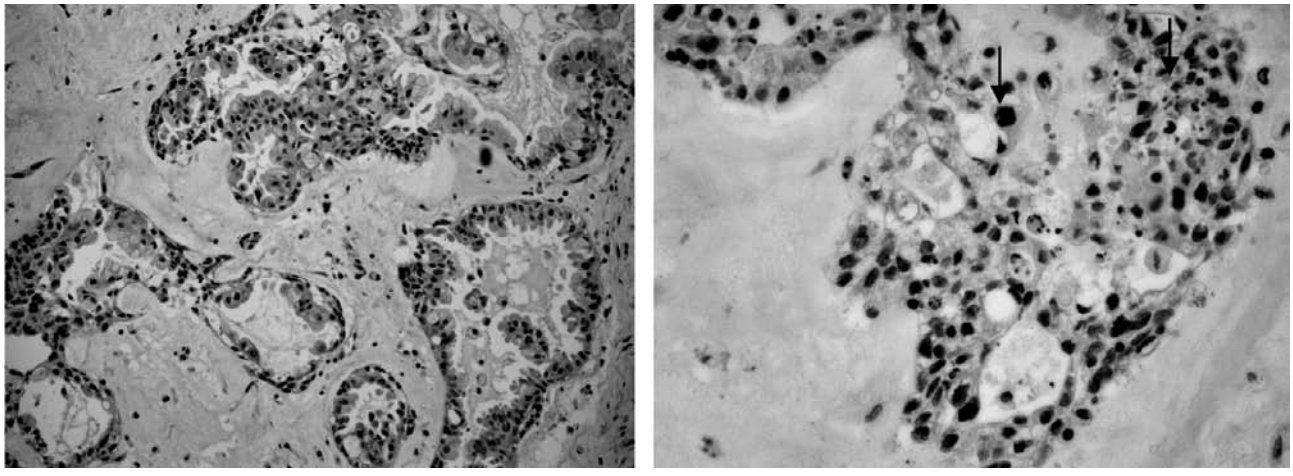

Fig. 4 The glangular components (left:4A) were composed of cells with irregular and hyperchromatic nuclei of varying sizes and shapes, distinct large nucleoli with cribriform growth pattern, and signet ring cells differentiation that were readily identified. Apoptotic bodies and mitoses (arrow)(right:4B) were also easily found (Hematoxylin-eosin stain, X 200 and X 400).

Table 1. Histochemical and immunohistochemical stains findings in cardiac glandular myxoma.

Stains Tumor component	Mucin-carmin	Alcian-Blue (pH=2.5)	CD34	Actin (SM)	CA125	EMA/ CK	CK5/ CK20	CK7/ CK19	CK8/ CK18	TTF-1/ calretinin	NSE/ synatophysin
1.Myxoid cells	-	-	+++	+++	-	-	-/-	-	-/-	-/-	-/-
2.Endothelial cells	-	-	+++	+++	-	-	-/-	-	-/-	-/-	-/-
3.Myxomatous matrix	-	++	-	-	-	-	-/-	-	-/-	-/-	-/-
4.Capsule lining cells	-	-	+++	++	-	-	-/-	-	-/-	-/-	-/-
5.Glandular component	+++	+++	-	-	+,focal	+++/ +++	-/-	+++/ +++	+/+	-/-	-/-

Note: degrees of positive stains. +: slight, ++:moderate, +++:marked

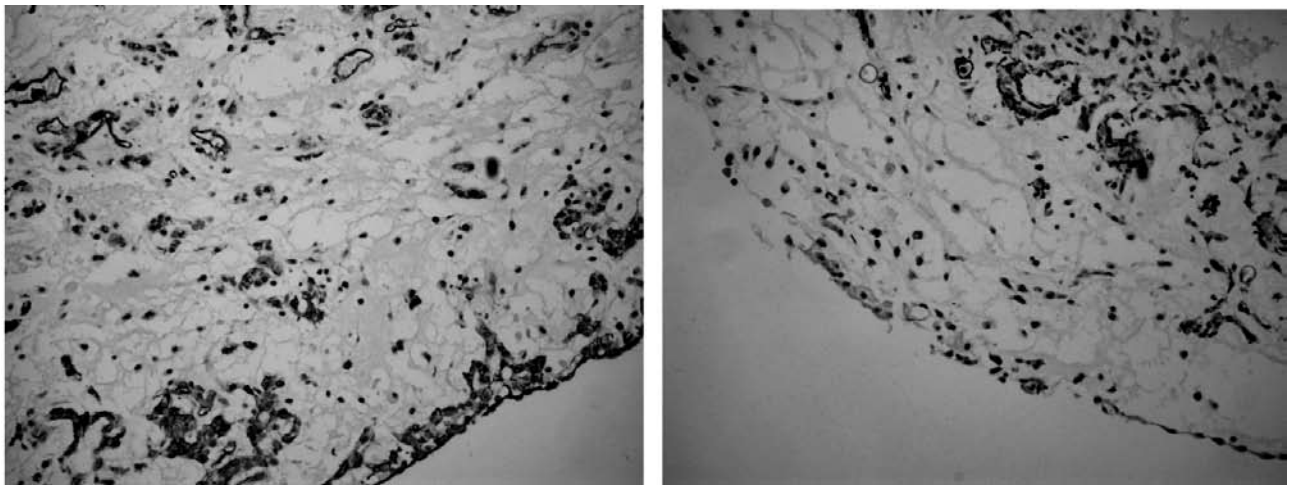

Fig. 6 Immunohistochemical staining showed CD34 (6A:left) and smooth muscle Actin (6B:right) positive in myxoma cells as well as vascular endothelial cells and capsule lining cells. (PAP stain, X 200).

lining cells (Fig 6 & Table 1). The glandular components were strongly and diffusely immunoreactive to EMA, pancytokeratin (AE1/AE3), CK7, CK19(Fig 7), weakly and focally immunoreactive to CK8, CK18, and CA125, and negative immunoreactive to calretinin, CK5, CK20, NSE, Synatophysin, and TTF-1 (Table 1). The histopathology of the present case was compatible with the current literature[3,6,7]. But the high serum level of CA125 in the present case has never been reported before. After surgery, the patient received endoscopic examination of the stomach and colon, and computed tomography of the chest and whole abdomen. They all showed negative finding. Simutaneously, the serum CA125 level returned to normal one week after the left atrial tumor removal. In our case, there was no any other primary tumor found. Therefore, metastatic adenocarcinoma to the cardiac myxima was unlikely. The tumor was diagnosed as "cardiac myxoma with maligant glandular component". There has been no evidence of recurrence of the myxoma or metastatic carcinoma during the 20-months follow-up period up to now.

DISCUSSION

Cardiac myxomas are the most common primary cardiac tumor in adults and account for approximately 75 to 80% of cardiac tumor in surgical series[1], and typically arising from the left atrial wall in middle-aged females, occasionally with a familial

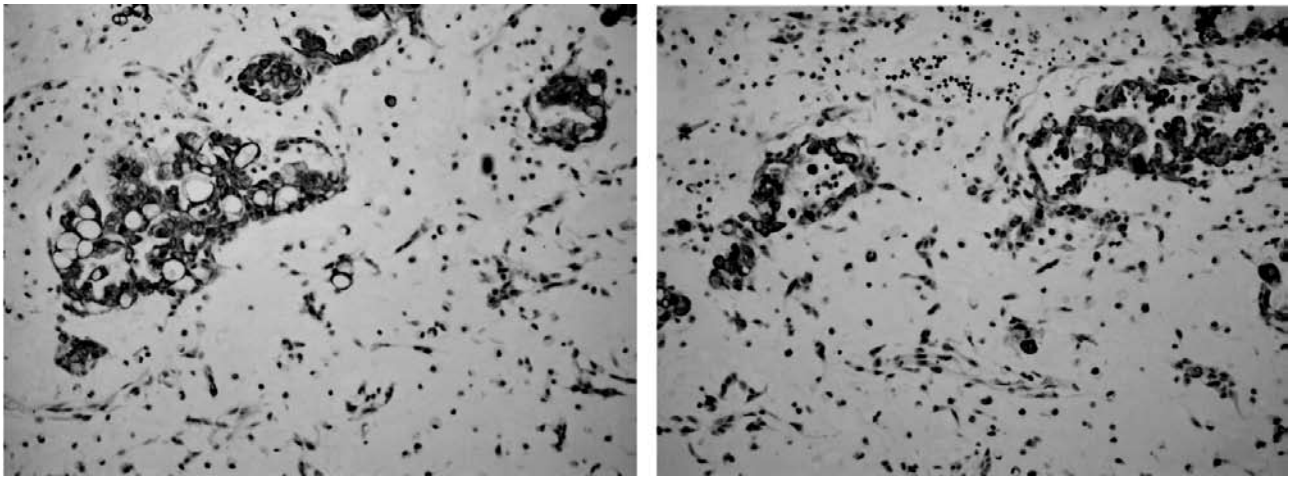

Fig. 7 Both CK7 (left:7A) and CK19 (right:7B) immunohistochemical stains were strongly positive in the glandular components (PAP stain, X 200).

background. They can manifest with a variety of signs and symptoms, including palpitation, shortness of breath, syncope, and heart murmurs. These symptoms, usually based on the location of the tumor, vary with its size, shape, and also with the pedicle length. In almost all of the patients, preoperative diagnosis of intracardiac myxoma was sufficiently established by echocardiography. The morphologic characteristics in diagnosis of classical cardiac myxoma is the stellate or spindle-shaped "myxoma cells" lying in a myxiod background Most authors now believe that cardiac myxoma is a neoplastic lesion derived from "embryonal nests", and the presence of various mesenchymal cells, smooth muscle cells, fibroblasts, myofibroblasts, and chondroid cells represents divergent differentiation[4-8]. Microscopically, glandular, hematopoietic, chondroid, and thymic tissues may be found within cardiac myxomas[3]. Glandular differentiation is a rare feature, and constitutes approximately 3.7% or less of all cardiac myxomas[9]. The histogenesis of glandular component in cardiac myxoma is enigmatic. Derivation from foregut remnants, bronchial or alveolar epithelium, mesothelium, or germ cells has been suggested but none has been conclusively identified as the origin of the gandular component. The glands were predominantly mucous-secreting and well-differentiated, which were frequently found at the base or the pedicle of the myxoma. The intracellular mucin was composed of both neutral (Mucin-carmin positive) and acid mucin (Alcian blue positive). So the light microscopic appearance of the glandular epithelium, including the histochemical and immunohistochemical patterns, suggests the gastrointestinal or enteric nature of the epithelium. In Goldman's study,[2] electronic microscopic observation of one cardiac myxoma demonstrated well-formed glands with basement membranes, junctional complexes, and apical secretory granules. These findings indicated the capacity for true epithelium differentiation of cardiac myxoma. For many decades, the presence of heterotopia in cardiac myxoma has given credence to the theory of a pluripotent "vasoformative reserve cell" line of origin for cardiac myxomas. These pluripotent cells are thought to arise from embryonic rests aberrantly retained during early developmental migration events when the embryonic foregut and cardiac anlage are juxtaposed[3]. In Chopra's study, the epithelial differentiation seemed to be an expression of the multipotentiality of the progenitor cells in cardiac myxoma, and was enteric in nature[10]. In our present case, it showed CD34 and smooth muscle actin positive in "myxoma cells" as well as vascular endothelial cells and the capsular lining cells that provided evidence to the theory of a pluripotent "vasoformative reserve cell" line of origin for cardiac myxomas. Simultaneously, the glandular components were strongly reactive for Mucin-carmin, Alcian-blue (PH=2.5), EMA, pancytokeratin (AE1/AE3), CK7, and CK19, and negative for CK20, TTF-1 and calretinin. These findings also indicated the true glandular differentiation, and

implied the gastrointestinal (foregut) nature of the epithelium devoid of neuroendocrine differentiation (negative for NSE and synatophysin), and it did not derived from hingut (negative for CK20), bronchial, alveolar epithelium (negative for TTF-1), or mesothelium (negative for CK5 and calretinin). For all practical purposes, cardiac myxomas are considered benign tumors, although disputed incidental case reports existed for malignant cardiac myxoma[5, 6, 7]. In our present case, the glandular components were composed of cells with irregular hyperchromatic nuclei of varying size and shape, distinct large nucleoli with cribriform growth pattern, and signet ring cells differentiation. Within these glands, apoptptic bodies, mitoses were readily identified. Simutaneously, the case also had a high serum level of CA125. These findings indicated the malignant glandular differentiation. Finally, recognition of the glandular element in classical myxoma background is important because it mimics metastasis from an adenocarcinoma[10]. In our case, there was no any other primary tumor found, and the serum level of CA125 returned to normal after the tumor removal. Therefore, metastatic adenocarcinoma to the cardiac myxoma was unlikely. After surgery, the patient was generally asymptomatic and had an uneventful life. The influence on the prognosis of the occurrence of glandular differentiation has no statistical data available because of its low incidence, especially for the malignant glandular differentiation of cardiac myxoma. But metastasis has been reported in literature.[5] In brief, long-term postoperative follow-up and serial echocardiography are advisable especially for atypcial or malignant glandular component cases, and the follow-up of the serum CA125 may be useful in our case.

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心臟黏液瘤合併惡性腺體成份及血中 CA125 濃度上升免疫化學染色特徵—病例報告及文獻回顧

曹唐義[1*]　吳清文[2]　魏　崢[2]

心臟黏液瘤是成人心臟中最常見的腫瘤，尤其是好發在中年女性的左心房，心臟黏液瘤均為良性的，但也有幾例爭議性的惡性黏液瘤報告過，心臟黏液瘤合併腺體存在相當少見，大約為 1 ～ 5% 的發生率。本文報告一位 69 歲男性主訴胸部不適數日，在心臟超音波檢查時發現在左心房有一腫瘤，同時血中 CA125 上升。在組織學上，此腫瘤為一典型黏液瘤。在腫瘤內混以成群的腺體成份，這些腺體呈現明顯的核仁、凋亡小體，偶見分裂像，以及呈現戒指環細胞的分化，在免疫染色上，腺體部份對 EMA、pancytokeratin(AE1／AE3)、CK7、CK8、CK18、CK19、CA125、Mucin-carmin、Alcian blue(PH2.5)，均呈陽性反應，但對 calretinin、CK5、CK20、CD34、Smooth muscle actin 、NSE、Synatophysin 及 TTF-1 均呈陰性反應。

（童綜合醫誌 2008; 2: 88-94）

關鍵詞：心臟黏液瘤、腺體成份、 Mucin-carmin stain、Alcian blue(PH=2.5) stain

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A Successful Experience for the Reversal of Acute Respiratory Failure Ascribable to Re-expansion Pulmonary Edema Via Extracorporeal Membrane Oxygenation Therapy: A Case Report and Review of the Current Literature

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The literature has documented that various clinical conditions including hemopneumothorax, large pleural effusion, pnemothorax,and after lobectomy (or even one-lung ventilation), can lead to re-expansion pulmonary edema (REPE), an uncommon complication and yet potentially life-threatening condition.We describe herein a successful experience for the reversal of post-operative REPE case associated with video-assisted thoracoscopic surgery of massive spontaneous hemothorax due to acute hypovolemia occurred following the evacuation of an hemothorax with rapid re-expansion of a collapsed lung. This patient was successfully treated by application of extracorporeal membrane oxygenation (ECMO).
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Key words: Reexpansion Pulmonary Edema, Extracorporeal Membrane Oxgenation, Spontaneous Hemothorax, Acute Respiratory Failure

INTRODUCTION

Reexpansion pulmonary edema (REPE) is characterized by development of pulmonary edema in the lung that has been rapidly re-inflated following a variable period of collapse secondary to pneumothorax or pleural effusion. However the etiology of REPE remains elusive, despite being thought to be caused by increased pulmonary capillary permeability. The clinical presentation can be subtle or a life-threatening event involving acute respiratory failure with circulatory shock[1].

Extracorporeal membrane oxygenation (ECMO) is a life-saving procedure in patients with acute, reversible cardiac or respiratory failure that are unresponsive to conventional therapy[2,3]. It is commonly used in the neonatal and pediatric populations and are being used with increasing frequency in adults. The major function of ECMO is to allow the lungs to heal by avoiding high oxygen concentration and high peak inspiratory pressures that associated with conventional ventilation and resulted in further lung injury.

CASE REPORT

A 16 year-old boy (body weight 50 kg, height 170 cm) presented with acute-onset breathlessness and right-sided chest pain on the day of admission. Initially, he noted the symptoms of vigorous coughing upon awakening. The patient had no history of chest

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trauma. The patient has not received any surgical treatment in the past. Vital sign were: blood pressure 100/60 mmHg, pulse rate 100 beats/min, respiratory rate of 20 breaths/min with a pulse oximeter reading of 93-95%. No breath sounds could be heard in the right hemithorax. Chest radiography showed massive right side opacity (Fig. 1). A thoracostomy tube was placed at the emergency room immediately. About 2 liters of blood was noted thought drainage. He was transferred to the surgical intensive care department for further care. Due to worsening hypoxemia and serious condition , emergency operation for thoracoscopy was arranged. General anesthesia was induced with midazolam 5 mg , fentanyl 100 ug, citosol 200 mg intravenous supplemented with rocuronium 40 mg. The trachea within the left main bronchus were intubated with a left-sided, double-lumen bronchotracheal tube. Anesthesia was maintained with sevoflurane and oxygen, rocuronium was injected intravenously to maintain muscle paralysis and facilitated with controlled mechanical ventilation. Video-assisted thoracoscopy was performed under left-lung ventilation to minimize transpulmonary bleeding. After the removal of blood clot and bleeding checked which was completed 120 min later. During the time, the right lung was deflated and opened to room air. The blood loss content was approximately 2.2 kg of blood clot with 1 liter of fresh blood (active bleeding of small lung vessel about 1 mm in diameter) were found near the apex of the right-sided pleural cavity, therefore blood transfusion with packed RBC 6 units, whole blood 6 units, fresh frozen plasma 8 units and a total 1.5 liter crystalloid were given during the procedure. Progressive swelling of the lung parenchyma was found after the removal of blood clot. Before closure of the thorax, the right lung was reinflated to examine for air leakage, and the both lungs were expanded with manual positive-pressure ventilation with a 20 cm H_2O peak inspiratory pressure. Unilateral rhonchi was audible during auscultation and a frothy serosanguinous fluid greater than 3.0 liters was suctioned from the right -sided endobronchial tube. After the next 15 min, the patient's blood pressure dropped to 72/48 mmHg, but returned to 90 mmHg systolic after administration of 8 mg intravenous ephedrine and 200 ml crystalloid, and oxyhemoglobin saturation was decreased from 99 % to 80% abruptly, even with an FiO_2 of 1.0. His clinical conditions deteriorated very rapidly. REPE occurred subsequently with a high airway pressure (> 50 cmH_2O) under ventilation. Vital signs were not be able to maintaine by inotropic agents and conventional ventilation. Under the impression of an acute onset REPE , the patient then received veno-arterial mode extracorporeal membrane oxygenation(ECMO) because of unstable hemodynamics and poor oxygentaion(Fig. 2). Postoperatively, the patient was admitted to the intensive care department for further management. ECMO was removed after running for 96 hours (Fig. 3). He was extubated 2 days after the removal of ECMO and discharged 13 days after the operation with improved pulmonary function (Fig. 4)

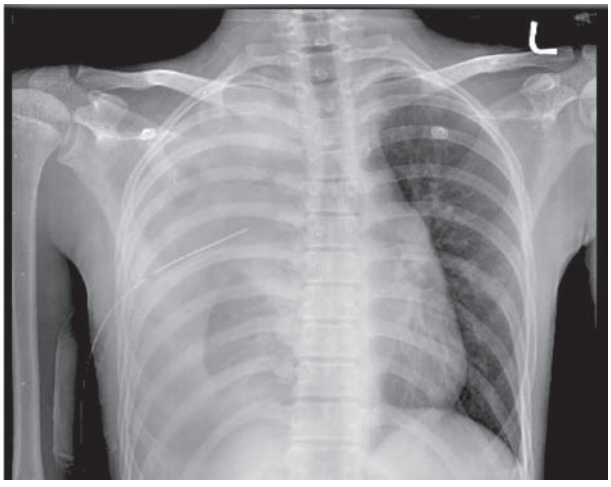

Fig. 1 Hazziness over right lung fields and atelectasis of RUL, RML and RLL.

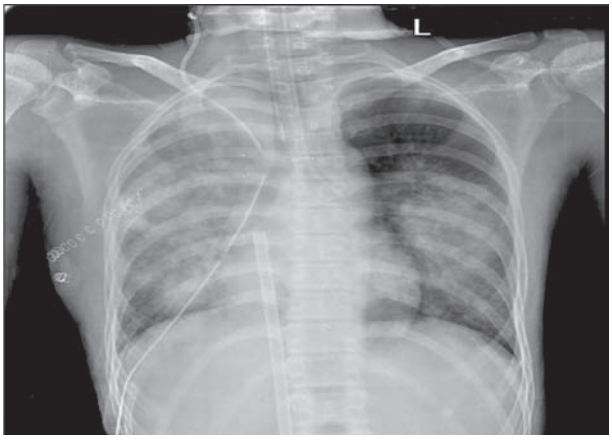

Fig. 2 Post-ECMO chest x-ray demonstrating pulmonary edema.

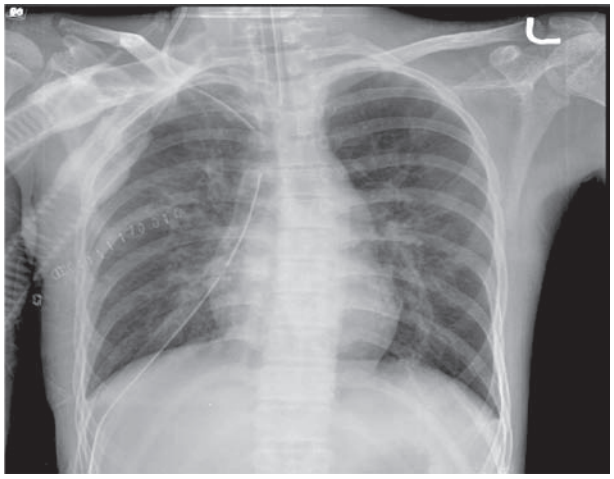

Fig. 3 Chest x-ray after removal of ECMO.

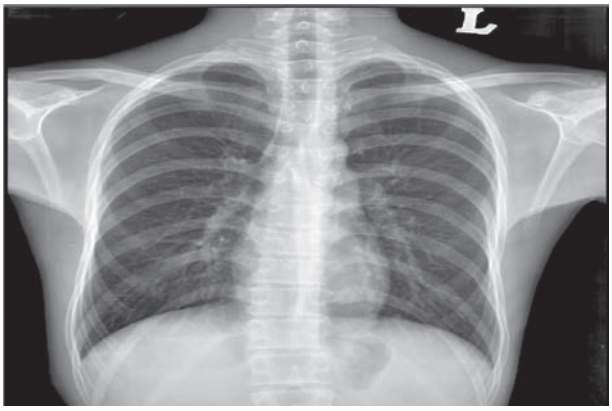

Fig. 4 Follow–up chest x-ray showing resolution of patchy infiltrates in both lungs.

DISCUSSION

REPE is a rare, but well-known complication that occurs after rapid re-expansion of collapsed lung following drainage or evacuation of pleural disease, such as a large pneumothorax or a large hemothorax[4,5]. The edema is usually on the ipsilateral side, but can be contralateral or bilateral[6,7]. Clinical presentation ranges from asymptomatic chest radiology to severe cardiorespiratory insufficiency and possibly death. Early recognition of REPE is important because the disease may prove fatal in up to 20% of the cases[8,9].In about two thirds of reported REPE cases develops rapidly within hours and typically occurs following lung collapse of three days duration or more[9]. The pathophysiology of REPE is complex and still not completely understood. Multiple factors may involved in the process, especially pulmonary collapse with more than 72 hours of evolution. This component apparently generates permeability alternation and lung capillary pressure. An inflammatory response occurs when the lung re-expands. This response is believed to be secondary to expansion-related mechanical injury to the alveolar-capillary membrane and reperfusion injury as blood flow return to the now fully expanded lung[10,11].Therefore, we can define re-expansion edema as being caused by two main entities : alternation of capillary permeability, the most important in this process and the increase of hydrostatic pressure. On re-expansion and reintroduction of oxygen to the relatively hypoxic lung, oxygen-derived free radicals are thought to damage the alveolar epithelial and endothelial cells and may cause increased vascular permeability. Hypoxemia and capillary lesion produce the release of inflammatory mediators (IL-8,nitric oxide, polymorphonuclear and free radical), which perpetuate the microvascular lesion, also may alter the capillary permeability[12,13,14,15]. Pulmonary re-expansion results not only in alveolar alternation, but it also makes the great and fast blood flow to increase the lung capillary pressure leading to increase hydrostatic pressure. Vascular permeability, altered by capillary and alveolar lesion and associated to the increased hydrostatic pressure, lead to liquid and protein overflow into the interstitial and alveoli, thus characterizing REPE[9,10].

Therapeutic strategies for REPE consists of a supporting measure and is based on oxygen supplementation, as well as in ventilatory support, associated to hemodynamic supporting strategy of using inotropic agents and even diuretics[4,5,6].

Our case received veno-arterial mode ECMO because of poor oxygenation and unstable hemodynamics. There are several forms of ECMO, the two common of which are veno-arterial and veno-venous mode. In both modalities, blood drained from the venous system is oxygenated outside the patient's body. Veno-arterial ECMO can provide sufficient oxygenation for several days, allowing lungs to heal while the potential additional injury of aggressive mechanical ventilation is avoided[2,16,17]. ECMO is a highly invasive treatment commonly used as a rescue therapy in critically ill patients. Systemic heparinization is a

mainstay of ECMO therapy because of platelet activation in the circuit. Mechanical complications and significant bleeding can occur in up to one quarter of patients, requiring close attention and prompt intervention should they occur[3].

We conclude that early diagnosis for REPE is crucial, since prognosis depends on early recognition and prompt treatment. The selective use of ECMO for REPE will increase survival rates in this case, over conventional mechanical ventilation. Patients with REPE usually respond favorably to various forms of mechanical ventilation with PEEP, permissive hypercapnia, and inhalation pulmonary vasodilators. Using these methods, survival rates greater than 60% have been documented[3,11]. There remains, however, in a small number of patients with REPE whose pulmonary gas exchange cannot be improved by above mentioned methods. ECMO may be a therapeutic option during the acute phase of REPE[16,17].

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自發性血胸病患在胸腔鏡手術後發生再張性肺水腫繼而引起急性呼吸衰竭：使用體外葉克膜維生系統之經驗 - 病例報告及文獻回顧

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再張性肺水腫是一種罕見的手術後併發症，如果沒有早期的診斷及有效的治療，它是會危及生命。其繼發生於任何原因所致的肺部擴張不全之後，在肺部再膨脹時或擴張後發生急性肺水腫，多見於治療氣胸後或單側肺部麻醉之後再膨脹時。我們報告一位 16 歲男性因自發性右側大量血胸，在胸腔鏡清除胸腔內血塊後單肺麻醉再膨脹時發生再張性雙側肺水腫合併急性呼吸衰竭。病患生命徵象與血中含氧量在強心劑與呼吸器使用下，仍無法維持穩定情況時，在運用體外葉克膜維生系統治療下，成功搶救病人的生命。臨床上發生再張性肺水腫合併急性呼吸衰竭在常規支持和輔助治療無效後才會考慮使用體外葉克膜維生系統，此技術被認為是一項安全且有效維持生命的臨時救治手段。

(Tungs' Med J 2008; 2: 95-99)

關鍵詞：再張性肺水腫、體外葉克膜維生系系統、自發性血胸、急性呼吸衰竭

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Spinal Cord Tumor Manifesting with Chest Pain: A case report

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A thorough literature search reveals that hitherto only three case reports describing patients with cervical or thoracic spinal cord presenting with mainly chest pain have been reported. We report herein a case of thoracic spinal cord tumor also manifesting with chest pain. The patient was characterized as having dull pain, with sensation of heaviness and tightness. The pain was confined to both anterior and posterior chest that lasted for a whole day. No concomitant shortness of breath or cold sweating was noted. MRI of the lower cervical and upper thoracic spine showed an intradural extramedullary lesion at the right side, T1-T2 level of the spinal cord. The pathological diagnosis was schwannoma. After surgery, the patient's chest pain subsided.
(Tungs' Med J 2008; 2: 100-103)

Key words: chest pain, spinal cord tumor, schwannoma

INTRODUCTION

The common clinical presentations of thoracic spinal cord lesion include neck pain, back pain, focal or limb weakness, paresthesia or hypoesthesia, and urine retention. Nevertheless, it is uncommon for patients to complain of chest pain. There are hitherto only three case reports of spinal cord tumor manifesting with chest pain documented in the literature[1-3] (Table 1). Herein, we report the fourth case with review of the literature.

CASE REPORT

A 43-year old male patient was admitted to our hospital with the chief complaint of anterior and posterior chest pain for 9 months. The pain was characterized as dull, with sensation of heaviness and tightness that lasted for a whole day. There was no concomitant shortness of breath or cold sweating. In addition, the patient was unable to flex his neck. No prior history of neck injury was noted. There were no sphincter disturbance or apparent limb weakness

Table 1. List of literature reported cases of spinal cord tumor manifested with chest pain

Case no	Author (yr)	Age(y/o)	Sex	Location	Symptoms	Treatment	Pathology
#1	H Akiyma et al (1994)	47	F	C5~C6	Chest pain	Laminectomy	Ependymoma
#2	GL Marseglia et al (1995)	9	M	T2~T3	Chest pain	Surgery	Meningioma
#3	T Harakuni et al (2001)	49	M	C4~C5	Chest pain	Laminectomy	Schwannoma
Present case	CC Yang et al(2008)	43	M	T1~T2	Chest pain	Laminectomy	Schwannoma

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albeit mild unsteady gait was noted. A series of cardiovascular examinations done elsewhere, including EKG, treadmill test and cardiac echo, showed negative results. The patient had a history of hypertension and DM. Neurological examination showed a subjective feeling of neck flexor weakness, absent DTRs in both arms (which could be due to normal variation), positive bilateral Babinski sign, and impaired pinprick sensation below the level of T5 bilaterally. No definite weakness of both arms and legs was noted. MRI of the lower cervical and upper thoracic spine showed a strongly enhancing tubular mass measuring 4.5 x 1.0 x 1.5 cm with signal-void central portion and on intradural location at the right side of T1 to T2 level was noted, displacing the cord to the left side. No widening of the right neural foramen was noted(Fig.

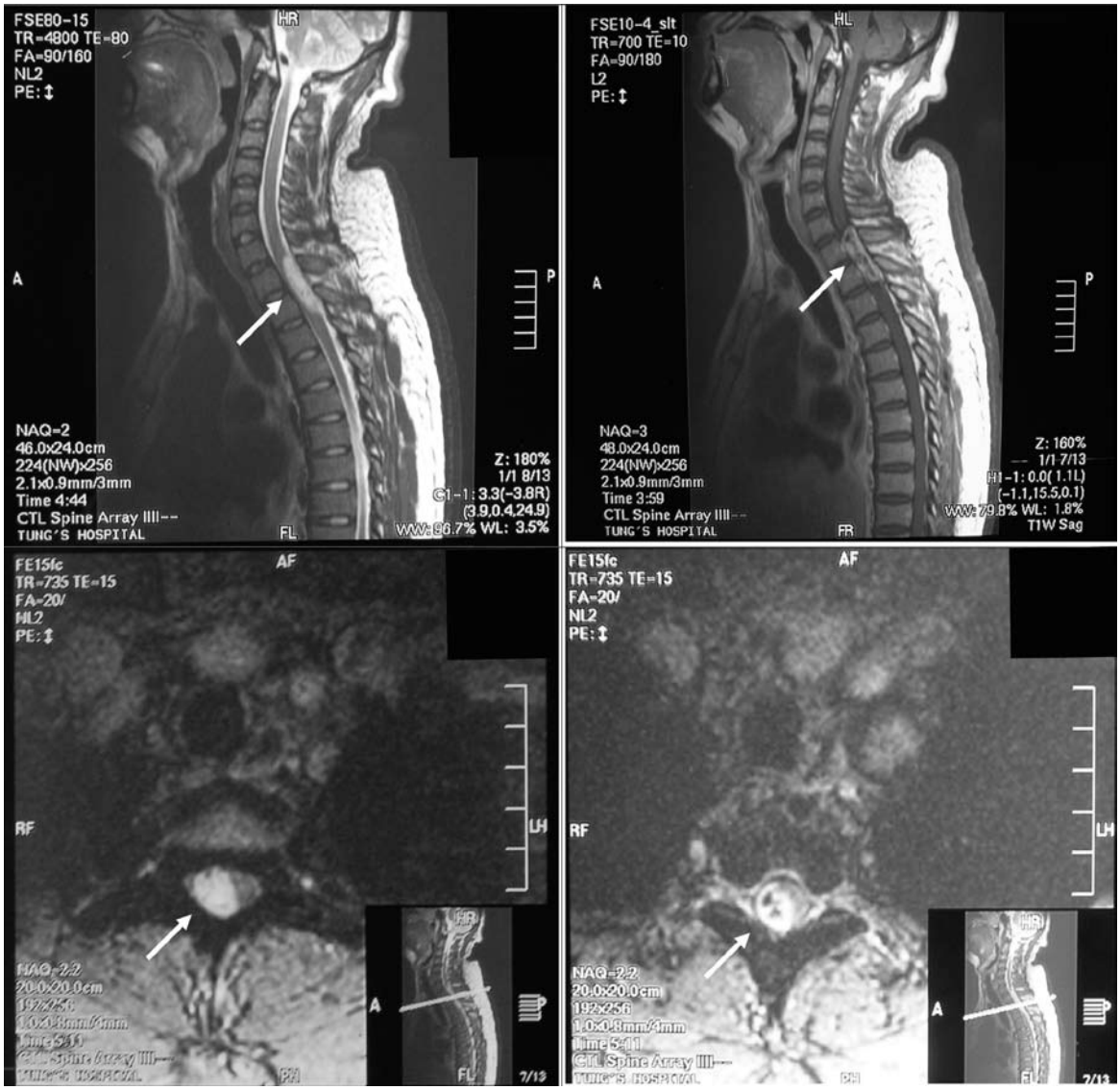

Fig. 1 MRI examination of the patient before surgery A strongly enhancing tubular mass measuring 4.5 x 1.0 x 1.5 cm with signal-void central portion and on intradural location at the right side of T1 to T2 level was noted, displacing the cord to the left side.

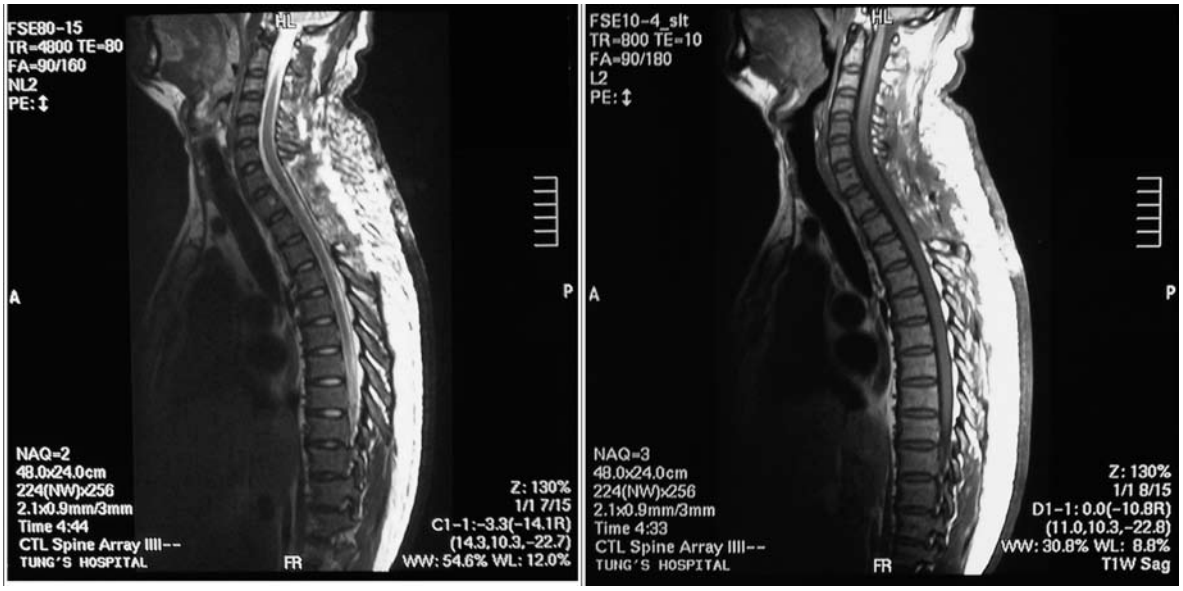

Fig. 2 MRI examination of the patient after surgery revealed no spinal cord tumor

1). The pathological diagnosis was schwannoma. After surgery, the patient's chest pain subsided. Follow-up MRI was done 19 days after surgery which revealed no more spinal cord tumor (Fig.2). Patient had been followed up at neurosurgery department for one year after surgery and no tumor recurrence or chest pain was noted.

DISCUSSION

A chief complaint of chest pain usually will lead the physician to initially suspect of cardiovascular origin. However, the pain may occasionally be due to spinal cord in origin, such as spinal cord infarction[4].

From the study of neuroanatomy, the dermatomal distribution of the chest and the upper back is usually from T2 to T6. The network of nerves that service all parts of the body originates in the spinal cord. The spinal cord runs through the spinal canal inside the spine. Smaller nerves branch off the spinal cord at various points along the neck and back and exit through openings along the spine. If one of these nerves becomes pinched or partially blocked where it exits the spine, pain can result. Somatic fibers enter the spinal cord at specific levels and tend to produce symptoms that follow a dermatomal pattern. The chest pain of our patient may be due to referred pain from stimulated or compressed spinal roots or spinal tract fibers. The nature and character of chest pain and the associated symptoms, including shortness of breath, cold sweating, radiation, etc. should be noted carefully because a detailed history taking can be helpful in the differential diagnosis of chest pain. In addition, a detailed neurological examination is also utmost importance to arrive at a correct diagnosis.

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以胸痛為表現的脊髓瘤

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臨床上，以胸痛為主訴的頸或胸椎脊髓瘤非常少見，經查文獻，以文字發表的僅有 3 例。我們報告的這位 43 歲男性患者，是患胸椎脊髓瘤，臨床上，以胸痛為主訴，此胸痛分佈於前後胸，並持續整天，胸痛的同時並無呼吸困難，盜汗或其他冠心病的症狀。經頸、胸椎磁振造影檢查在 T1-T2 間右側顯示有一硬腦膜內、脊髓外的病變，病理檢查證明為神經鞘瘤，手術後，患者的胸痛明顯消失。

（童綜合醫誌 2008; 2: 100-103）

關鍵詞：胸痛、脊髓瘤、神經鞘瘤

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童綜合醫學雜誌投稿相關規則

本雜誌刊載與醫學有關之論述，包括原著論文、臨床病理討論、病例報告等論述及特別約稿之綜論（review article）、special article、Editorial（編著的話）等。惠稿請送 43503 台中縣梧棲鎮中棲路一段 699 號童綜合醫學雜誌編審委員會。

壹、投稿前注意事項

1. 投稿時，需附原稿三份（一份原稿和兩份複印稿，但圖片應用三份原圖）並以電腦打字（請以 MS WORD 文書處理格式，中文字型以標楷體，英文字型以 Time New Roman 12 號字大小，稿紙之左右緣爲 2.54 公分，上下緣爲 3.17 公分），請勿裝訂，同時須提供最後版本之電子檔一份，若圖片或照片有電子檔提供者，請以附檔 jpg 的形式提供。
2. 文件內容需清晰，內容與原稿一致，若複印稿與原稿有差異或遺漏，由作者自行負責。著作中若牽扯到版權所有之內容，作者需取得其使用權，法律責任由作者負責。
3. 投稿請參照稿件核對表準備所需項目，同時附上著作權讓與同意書。所有作者必須實際參與並同意該論述。本院於接受稿件且印刷完成後，將贈送 20 份抽印本給通訊作者，如需額外抽印本請於校稿時言明，並酌收成本費用。第一作者若需抽印本可提出申請，依份數酌收成本費用。
4. 本刊對於原稿經徵得著者之同意得伸縮或修改之。如不合本刊宗旨者，得退還之。
5. 凡刊載於本雜誌之著作，若涉及「研究用人體檢體採集」及「人體試驗」等情事，應遵守該注意事項，以落實保障受檢人權益。詳文請參考須附上相關審議認可之文件。
6. 論文中如涉及使用脊椎動物進行科學應用計畫者，應檢附該計畫業經所屬機構動物實驗管理小組審議認可之文件，以落實實驗動物之人道管理。

貳、寫作原則

1. 原著論文按下列順序撰寫：摘要、前言、材料與方法、結果、討論與結論、誌謝、參考文獻、附表、圖片說明、圖片（含照片）。
2. 病例報告按下列順序撰寫：摘要、前言、病例、討論、參考文獻、附表、圖片說明、附圖、照片。
3. 病例報告，每篇以五頁以內爲限（即約 9,000 字），依題目、所屬機構、作者姓名（作者以 5 人爲限）、病例之病史經過及重要之診療資料、主要之臨床問題、討論或分析、結論、推薦讀物等順序繕寫。凡病患顏面部位之相片必須遮去眼睛部位，表示尊重隱私。診療資料或臨床經過之圖表，原則上均限六個月以內。
4. 綜說不必按原著論文格式撰寫，但必須列出參考文獻。
5. 其他類文章連圖表，以不超過四頁（每頁約 2,000 字）爲原則，但特約稿例外。學術文章，題目、姓名均須以中文書寫。
6. 其他細節，請參閱國際指導委員會（International Steering Committee）發表之生物醫學雜誌稿件統一規格（Uniform Requirements for Manuscripts Submitted to Biomedical Journals，見 The New England Journal of Medicine 336: 309-315, 1997）。

參、投稿須知

一、稿件須符合「生物醫學雜誌投稿之統一規定」[1]，請以電腦隔行 double space 書寫並編頁碼。

二、第一頁爲標題頁，須列出中文及英文之論文題目、簡題（running title）、中英文作者姓名、所屬機構及單位之中英文稱號（分屬不同單位，請以阿拉伯數字標出作者與單位）、聯絡人姓名、電話及中英文通訊錄。

三、第二、三頁爲中文及英文之摘要及關鍵詞 (請提供 3 至 5 個關鍵詞或簡短片語)，中英文摘要須完全相同，英文摘要不超過 250 字，中文摘要不超過 500 字，摘要分段撰寫，依序爲背景及目的（Background and purpose）、方法（Methods）、結果（Results）及討論（Discussion）。

四、請附三份原稿（一份原稿和兩份複印稿，但圖片應使用原圖），包括附表、附圖及照片。圖表應專業製作，一張紙僅一個附圖或附表，依引用順序以阿拉伯數字標出排列。附表須有標題及說明。照片須 5 × 7 吋光面黑白，背面以鉛筆編號，附圖須有簡單說明（Legend），並另頁撰寫。光學或電子顯微鏡照片，請註明擴大倍率或比例。

註：[1] 根據「生物醫學雜誌投稿之統一規定」第五版，刊載於 Annals of Internal Medicine 1997; 126(1): 36-47.

肆、參考文獻

未經發表之論文或摘要不得列爲參考文獻，但可於本文中說明並註明「未發表」（unpublished observations）。博碩士論文可引用。已被任何雜誌接受刊發但仍未發表之著作，請列出雜誌名稱及年份，並註明「in press」。

原著論文、臨床病理討論、病例報告等論述及特別約稿之綜論（review article）按下列格式撰寫：

一、雜誌名稱之簡稱須按照 Index Medicus 型式，作者人數小於 6 位時，詳列所有作者姓名，超過 6 位時，只須列出前 6 位，其它以「等」（et al）代替。

例：Bhasin S, Storer TW, Berman N, Callegari C, Clecenger B, Phillips J, et all. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996; 335: 1-7.

二、本文內引用時，若兩名以下作者請列出姓氏。兩名以上則列出第一名之姓氏，其他以「等」（et al）代替，並以阿拉伯數字方括弧表示於引用之後。

例：One of the first well documented reports of ECH poisoning with fatality in young children was reported by Miller et al. in 1970[2].

例：Boulet 等人 [3] 報告氣喘患者接受衛教後的知識改變量不受個人因素影響。

三、參考範例

A. 期刊：[作者姓名：題目。雜誌簡稱　年代；卷數（期數）：起迄頁數]

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