Vol. 11 No. 1 January-June 2017

Tungs' Medical Journal

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Editorial

Medical Education Shifts for Twenty-First Century Physician's Training

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Received: Jun. 05, 2017; Accepted: Jun. 07, 2017

Abstract

Healthcare delivery changes rapidly in the twenty-first century. Medical education shifts are needed to prepare medical school students for their future practice. Each phase of medical education has revised their curriculum and training focuses to accommodate the current and future needs of patient care. As the result, three important shifts in medical education have occurred across each stage of physicians' training. Interprofessional-based education (IPE) curriculum has grown twice in the recent decade; and competency-based medical education (CBME) and assessment has become the mainstream approach to enhance physicians' clinical skills. Additional, technology is now commonly integrated into simulation session and e-learning. Effective use of technology in medical education can not only enhance learning, but also improve patient safety. As a medical residency training institution, we are responsible for shifting our program focus to promote learning outcome and optimize the capabilities of our medical team in order to provide high quality healthcare.

Key words: IPE (Interprofessional-based Education), CBME (Competency-based Medical Education), Technology

The needs of healthcare faced by twenty-first century physicians are rapidly changing from the last century. Medical education requires a comprehensive forward-looking perspective in order to prepare these physicians for the future needs of patient care. In general, medical education includes a series of phases, such as medical school education, internship, residency, fellowship or practice. In traditional medical education, each phase of education is treated as a separate–stage. However, instead of treating each of these stages as a discrete part, physicians will benefit if these stages actually share a uniform perspective and approach [1]. Changing is a challenging task for many professional fields. This paper discusses the trends of medical education, emphasizing the shifts in the following three aspects across each stage including team-based learning, competency-based medical education (CBME) and assessment [1] and use of e-learning.

Based on Ausubel's and Piaget's learning models, people learn better through a learning setting between language and context; and develop knowledge and skills from being actively involved in their learning activity. Team-based learning and interperfessional team work can help doctors transfer their knowledge to various situations to resolve patients' issues; and foster communication skills to meet the public expectation of physicians. Nowadays, health care does not only involve providing medical treatment for a patient; but also requires physicians to build a positive relationship with their patients, patients' families, and other medical colleagues. Physicians are expected to be partners with their patients to make sure patients are engaged in medical decision with clear communication. The Institute of Medicine (IOM) has found that health care professionals working collaboratively in a team will increase patient safety and promote health care quality [2].

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The purpose of Interprofessional education is to train medical students to work in an interprofessional team effectively and apply what they learned from the team-based working experience into their medical practice. A survey by the Liaison Committee on Medical Education indicated that interprofessional education increased from 44 percent to 88 percent in the recent decade [2].

Competency-based medical education (CBME) and assessment is another main shift in medical education. In traditional medical education, the sequence of curriculum design is subject-based and time-based. Most assessments are summative and focus more on assessing isolated knowledge rather than holistic ability. Therefore, some physicians might have adequate medical knowledge but lacks the mastery of basic clinical skills or other soft skills to perform efficiently in their practice. Thus, Accreditation Council for Graduate Medical Education (ACGME) and American Board of Medical Specialties (ABMS) started to create a competency framework based on a set of essential outcomes for medical education. From this framework, the Association of American Medical College (AAMC) identified a list of required skills for physicians. There are eight domains in this list; and many post-graduate medical education and residency training programs apply this framework of competency-based learning to their curricula and program. The eight domains of CBME are patient care, knowledge for practice, practice-based learning and improvement, interpersonal and communication skills, professionalism, systems-based practice, interprofessional collaboration, and personal and professional development [3]. Trainings that are competency-based are also focused on learners' understanding and experience, as opposed to traditional lectures and presentations [1]. In order to effectively implement CBME, medical school instruction and the subsequent training programs need to shift from the existing lecture-oriented approach to a focus on skill-based and case-based learning activities. Competency is an observable and measurable ability in a professional field. In terms of assessment, multiple formative assessments are recommended instead of single summative assessment during learning periods. In addition, constructive feedback is strongly encouraged following each competency-based formative assessment.

Different phases of medical education are also now integrating and requiring different types of technology to enhance learning [4]. The two most common technological usage are simulator and e-learning. Since patient safety is a priority in many medical centers, sufficient experience with simulators will reduce unprofessional performance in medical treatment procedure during residency training. In many U.S medical institutions, simulation technology is widely provided for competency-based training and assessment. Those institutions use models or dummies attached to simulators to direct medical students' skill learning and practice. In addition to the usage of simulators, e-learning has been commonly used in different types and levels of education. The benefits of e-learning include flexible accessibility for self-pacing, synchronous learning for different location participants, and increase in the interaction and feedback among instructors and trainees. In fact, Web-based standardized patients have been used in both medical education training and assessment. For example, the Objective Structured Clinical Exams (OSCE) also have used the Web-based standardized patients as an evaluation tool to assess medical doctors' essential clinical skills.

It is crucial that medical education curricula and training programs provide proper learning experience for medical students to fully prepare for their practice. The way of healthcare is different from past. To satisfy the demands of twenty-first century healthcare, medical education must shifts away from a sole attention to knowledge acquisition [5]. The trend of medical education is to highlight interprofessional and team-based learning, and competency-based assessment by broadly using learning technologies. Medical schools and residency training institutions need to adapt changes in its current education process to help prepare physicians for future challenges in their practice.

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二十一世紀醫學教育的變遷

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受文日期：民國 106 年 06 月 05 日；接受刊載：民國 106 年 06 月 07 日

摘要

隨著二十一世紀的來臨，醫療照護的需求及方法也隨之改變。醫學教育也須有所改革，以培養能勝任未來醫療需求的醫師，因而醫學教育每一階段的訓練機構也需調整他們的課程內容及訓練的方向以應對未來醫療照護的需求。有鑑於此，許多醫學院及住院醫師訓練醫院已開始各項改革。其中最顯著的改革有三項，跨領域的專業教育課程在近十年內呈倍數成長，能力本位的教學及評量在醫學教育上已成一大主流。除此之外，科技也已廣泛的運用在醫師的訓練方面，尤其是運用在醫療技術的模擬訓練及數位教學上，不但能提升學習成效，也兼顧到病人安全，因此醫院針對新進人員的醫療教育，需要以上述的方法予以推動，將醫學教育目標提昇至團隊能力為本的教育。

關鍵詞：跨領域的專業教育、能力本位的教學、科技

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Review Article

Hormone Replacement Therapy and Quality of Life: A Systematic Review

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Received: Apr. 30, 2015; Accepted: Mar. 2, 2016

Abstract

Background : Hormone replacement therapy is widely used for controlling menopausal symptoms.
Objective : To assess the effects of hormone replacement therapy on the quality of life of postmenopausal women.
Search strategy : We searched the following databases for relevant articles published between 2003 and 2014: Cochrane Central Register of Controlled Trials, PubMed, and Google Scholar.
Selection criteria : We selected randomized controlled, double-blind trials evaluating hormone replacement therapy versus placebo for postmenopausal women. Hormone therapy included administration of estrogens, with or without progestogens, via the oral route.
Main results : Three trials involving 20,561 postmenopausal women were included. None of the studies reported any significant benefit on the quality of life.
Authors' conclusions : Although combined hormone replacement therapy is involved in the treatment of menopausal symptoms, there is no evidence that it improves the quality of life.

Key words: Hormone replacement therapy, menopause, quality of life

Background

Over two-thirds of perimenopausal women experience menopausal symptoms, which may persist for years. Women's quality of life could be impaired due to menopausal symptoms, such as hot flashes, night sweats, and sleep disturbances. Reportedly, hormone replacement therapy for controlling menopausal symptoms may be beneficial for the quality of life [1]. However, in 2002, the Women's Health Initiative clinical trial reported that substantial risks for cardiovascular disease and invasive breast cancer must be considered when prescribing combined hormone therapy for preventing chronic diseases [2]. Therefore, the routine use of hormone replacement therapy for preventing chronic conditions in postmenopausal women is not recommended.

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Objectives

Our objective was to conduct a systematic review of the existing literature on the effects of hormone replacement therapy on the quality of life of postmenopausal women. Hormone replacement therapy is defined as oral therapy comprising estrogen alone or combined with progestogen.

Methods

Criteria for considering studies for this review

Types of participants

Suitable participants were postmenopausal women recruited from any health care setting or a population-based sample.

Postmenopausal women were defined as women with surgical menopause or with spontaneous menopause or amenorrhea for more than 12 months.

Table 1. Summary of studies.

RCT	Participants	Intervention	Comparsions	Outcome
WHI 2003	16,608 postmenopausal women	CEE 0.625mg & MPA 2.5mg daily*	Placebo	RAND-36
Veerus 2008	1,823 postmenopausal women	CEE 0.625mg & MPA 2.5 or 5.0 mg daily	Placebo or no treatment	EuroQoL
Walton 2008	2,130 postmenopausal women	CEE 0.625mg & MPA 2.5mg daily	Placebo	EuroQoL

*CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate.

Types of interventions

All estrogens, alone or combined with progestogens, administered by oral route, and prescribed as postmenopausal therapy.

Types of comparisons

Placebo

Types of outcome measurements

Quality of life

Types of study design

Randomized controlled trials

Search methods for identifying studies

We obtained relevant publications that described randomized, controlled double-blinded trials of hormone replacement therapy by performing electronic searches of the Cochrane central Register of Controlled Trials on the Cochrane Library, PubMed, and Google Scholar. The research was restricted to articles in English published between 2003 and 2014 (Fig 1).

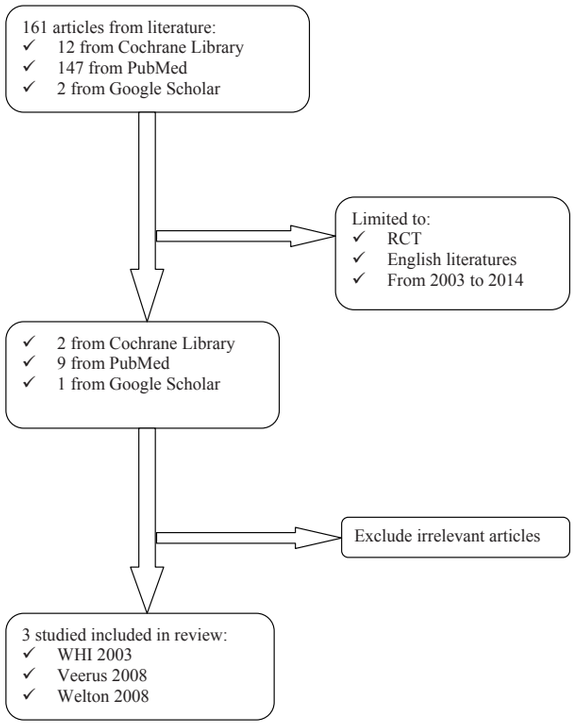

Fig. 1 Diagram of search strategy.

Data collection and analysis

Selection of trials

The following three studies met our inclusion criteria: Women's Health Initiative (WHI) 2003 [3], Verrus et al. 2008 [4], and Welton et al. 2008 [5] (Table 1).

Quality assessment

The Jadad score (Table 2).

Results

WHI trial published in 2003 reported no clinically meaningful effect of combined hormone replacement therapy on the quality of life, as assessed using the RAND 36-Item Health Survey (RAND-36) [3]. Verrus et al. (2008), using the European quality of life instrument (EuroQoL) [6], concluded that combined hormone replacement therapy decreased vasomotor symptoms and sleeping problems in the postmenopausal women but had no effect on their quality of life [4]. Welton et al. (2008), using the EuroQoL scores, found no significant differences in health-related quality of life by the visual analogue scale between the placebo and hormone therapy groups [5]. They concluded that combined hormone replacement

therapy does not improve overall generic measures of health-related quality of life after a 1-year treatment.

Discussion

The WHI study was a large scale randomized controlled trial that aimed to test the effects of hormone therapy on healthy postmenopausal women. The study enrolled 161,809 postmenopausal women aged 50–79 years. This study provided evidence indicating that combined estrogen plus progestin increased the risk of breast cancer. The RAND-36, assessed by the WHI study group showed that combined hormone replacement therapy does not have a significant effect on the quality of life among these women. However, the results were not applicable to perimenopausal women aged <50 years who were receiving hormone replacement therapy to treat vasomotor symptoms.

The Estonian postmenopausal hormone therapy (EPHT) trial reported by Verrus et al. (2008) was a long-term trial of combined hormone replacement therapy among 1,823 healthy postmenopausal women aged 50–64 years. Their quality of life was assessed using the EuroQoL scores. The data from the trial revealed that postmenopausal hormone therapy decreases episodes of hot flashes and sleep disorders but does not affect the health-related quality of life. Similar results were found in the EPHT and WHI studies, indicating that combined hormone replacement therapy does not significantly improve the quality of life of postmenopausal women.

Welton et al. (2008) studied 3,721 postmenopausal women aged 50–69 years, who were randomly assigned to combined hormone replacement therapy or placebo and measured their quality of life using the EuroQoL scores at 1-year follow-up. Importantly, fewer women in the combined hormone replacement therapy group reported hot flashes, night sweats, insomnia, and vaginal dryness, but no significant difference was noted in the overall quality of life at 1 year between groups. The beneficial effects of combined hormone replacement therapy on vasomotor symptoms were consistent with the results of previous trials, although there were no differences in the quality of life measurements. However, all participants were beyond their menopausal transition period, and the beneficial effect of hormone therapy may be underestimated for younger symptomatic women.

Conclusions

Implications for practice

With respect to the quality of life of postmenopausal women, none of the trials in the review showed significant differences between the combined hormone replacement therapy and placebo groups.

Implications for research

Further evidence is needed on the efficacy

Table 2. Quality assessments by the Jadad Scale .

Item	WHI 2003	Veerus 2008	Walton 2008
Was the study described as randomized (this includes such words as "randomly", "random", and "randomization")?	1	1	1
Was the method used to generate the sequence of randomization described and was it appropriate (e.g., table of random numbers, computer-generated)?	1	1	1
Was the study described as double-blind?	1	1	1
Was the method of double-blinding described and was it appropriate (e.g., identical placebo, active placebo, dummy)?	1	1	1
Was there a description of withdrawals and dropouts?	1	1	1
Deduct 1 point if the method used to generate the sequence of randomization was described but was inappropriate (e.g., patients were allocated alternately or according to date of birth or hospital number).	0	0	0
Deduct 1 point if the study was described as double-blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0	0	0
Total scores:	5	5	5

and safety of alternatives to hormone replacement therapy for treating menopausal symptoms in women.

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系統性回顧賀爾蒙補充療法是否影響停經婦女的生活品質

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受文日期：民國 104 年 04 月 30 日；接受刊載：民國 105 年 03 月 02 日

摘要

賀爾蒙補充療法被廣泛使用於改善停經後婦女的更年期症狀，賀爾蒙治療是否影響停經後女性的生活品質則是受到臨床醫師關注的議題。本文系統性回顧文獻資料庫中，臨床試驗採隨機對照研究，對於停經後女性使用口服雌激素加黃體素與使用安慰劑，兩組生活品質是否達統計學上的差異。目前的結論顯示賀爾蒙補充療法雖然有效改善更年期症狀，但並不能顯著改善停經後婦女的生活品質 。

關鍵詞：賀爾蒙補充療法、停經 、生活品質

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Tungs' Medical Journal 11 (2017) 10-19

Original Article

Decision-tree Algorithm Optimize Hematopoietic Progenitor Cell-based Prediction in Peripheral Blood Stem Cell Mobilization

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Received: Nov. 30, 2015; Accepted: Jan. 05, 2017

Abstract

Background and Objectives : Enumeration of hematopoietic progenitor cells (HPC) using an automated hematology analyzer provides rapid, inexpensive, and less technically dependent prediction of peripheral blood stem cell (PBSC) mobilization. This study aimed to incorporate HPC enumeration along with other predictors for optimizing a successful harvest.

Materials and Methods : Between 2007 and 2012, 189 consecutive patients who proceeded to PBSC harvesting with a preharvest HPC ≥ 20 × 10^6/L were recruited. A failed PBSC mobilization was defined as < 2 × 10^6 $CD34^+$ cells/kg. Variables predicting a successful harvest identified by multivariate logistic regression and correlation analysis were subjected to classification and regression tree (CART) analysis.

Results : A total of 154 (81.5%) patients successfully achieved mobilization of $CD34^+$ cells (median 8.18 × 10^6 $CD34^+$ cells/kg). Five independent host predictors including age ≥ 60, a diagnosis of solid tumor, prior chemotherapy cycles ≥ 5, prior radiotherapy, and mobilization with G-CSF alone or high-dose cyclophosphamide, as well as laboratory markers including HPC and mononuclear cell (MNC) counts, were used for CART analysis. The number of host predictors with a cutoff at two, HPC cutoff at 28 x 10^6/L and MNC cutoff at 3.5 x 10^9/L were best discriminative for successful prediction. In the decision tree algorithm, patients predicted as good mobilizers (0 to 2 risk factors) had a higher success rate (150/169, 88.8%) than that (4/20, 20.0%) of those predicted as poor mobilizers (3-5 risk factors). Moreover, patients predicted as good mobilizers and further with a HPC enumeration ≥ 28 x 10^6/L had a high probability of achieving successful mobilization (138/148, 93.2%).

Conclusion : Our CART algorithm incorporating host predictors, HPC enumeration and MNC count may improve prediction and thus increase the success of PBSC mobilization. Further prospective validation is necessary.

Key words: hematopoietic progenitor cell, mononuclear cell, peripheral blood stem cell harvest, autologous stem cell transplantation, classification and regression tree analysis

Introduction

High-dose chemotherapy followed by autologous peripheral blood stem cell (PBSC) transplantation is extensively used for the treatment of hematologic malignancies and solid tumors[1-4]. Successful transplantation requires the infusion of an adequate number of hematopoietic stem cells to achieve rapid and durable hematological recovery[5]. To mobilize stem cells from bone marrow to periphery, granulocyte-colony stimulating factor (G-CSF) alone or in combination with chemotherapy are commonly used. Patient responses to mobilization regimens vary, and the optimal window of PBSC harvesting with maximal collection while minimal leukapheresis procedures is

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narrow[6-8]. Therefore, both adequate mobilization and optimal strategy for PBSC collection are crucial for an efficient and cost-effective harvest.

In the literature, various factors have demonstrated the impact on mobilization, and different criteria have been proposed to define a poor mobilizer[5,9]. A working group promoted by Gruppo italianoTrapianto di Midollo Osseo GITMO (Italian Group for Stem Cell Transplantation) selected 3 major and 5 minor criteria to identify the "predicted poor mobilizer", including failed previous mobilization attempt, extensive radiotherapy and previous cytotoxic chemotherapy, among others. However, the use of baseline characteristics alone is inadequate to predict mobilization failure[9]. In a large cohort conducted by Costa et al., a predictive score derived from baseline characteristics could identify 80% of good mobilizers, but misidentify one half of poor mobilizers as good mobilizers, which would result in unnecessary harvests[10]. Thus, we need other laboratory markers to precisely predict mobilization as well as the initiation of PBSC collection.

The CD34 antigen, a surface protein presents on hematopoietic stem cells, has proven to be a reliable marker for identification of mobilized stem cells in blood products. The role of the infused $CD34^+$ cell count in predicting the engraftment potential of PBSC transplantation is well established, and a minimum infusion of 2×10^6 $CD34^+$ cells/kg is recommended to achieve prompt hematological recovery[5]. Plenty of studies have also demonstrated that the number of circulating $CD34^+$ cells, which is well-correlated with the $CD34^+$ cells yield in PBSC collections, presents as an important predictive marker for a successful harvest[11-13]. However, the enumeration of circulating $CD34^+$ cells by using flow cytometry is an expensive, time-consuming, and technically dependent method. At least one to two hours as well as an experienced technician on standby are required for daily CD34 monitoring, which frequently delay the harvest procedure and complicate patient management.

The Sysmex automated hematology analyzer (Sysmex Corporation, Kobe, Japan) can detect a specific population representing hematopoietic progenitor cells (HPCs) based on cell size, cell density and differential resistance to lysis[14]. The measurement requires less than three minutes and can be performed as part of a complete blood cell (CBC) count in the routine clinical laboratory. Moderate to strong correlation between the preharvest HPC counts and the collected $CD34^+$ cell counts has been reported in previous studies[15-17]. A prospective study conducted by Suh et al. demonstrated an excellent success rate of harvest guiding by HPC. An optimal harvest was achieved in 97% of patients with HPC $\geq 5 \times 10^6$/L[18]. Serial cutoff counts of HPC ranging from 5 to 80 $\times 10^6$/L have been examined, and the best cutoff has not yet been determined[19-22].

The recovery of white blood cells (WBCs) and peripheral mononuclear cell (MNC) counts after chemotherapy have been used to guide the timing of PBSC collection as well. Harvest could be initiated when WBC count recovers to 1×10^9/L, and a higher WBC cutoff of 2 to 10 $\times 10^9$/L may be advantageous[7,23,24]. A MNC cutoff of 1×10^9/L could also predict an adequate PBSC collection[17]. Although having a weaker correlation with the PBSC yield than did HPC and circulating $CD34^+$ cell counts[11,12,22], WBC and MNC counts are still alternative surrogate markers for successful harvests given the convenience and accessibility.

The ability to accurately predict the likelihood of a successful harvest could help avoid unnecessary harvests while minimize the risk of missing an adequate stem cell collection, which would achieve cost savings, decrease resource utilization and improve patient care. The consensus guidelines from American Society of Blood and Marrow Transplantation recommends each center develop its own algorithm to optimize mobilization and harvest [5]. By examining clinical host predictors and laboratory markers, the goal of the present study was to improve HPC-based prediction and to develop a more reliable model to guide the PBSC harvest.

Materials and Methods

Patients and mobilization

This single-center retrospective study included a total of 189 consecutive patients with hematologic or solid malignancies undergoing first PBSC harvests at Taipei Veterans General Hospital between January 2007 and January 2012. By reviewing the medical records, we collected the following variables: patient demographics at the time of PBSC collection, mobilization regimens, preharvest hemogram and HPC counts on the first day starting leukapheresis, and apheresis product data. The number of cycles of

chemotherapy administrated before mobilization regimens was calculated. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital.

PBSCs were mobilized with chemotherapy plus granulocyte colony-stimulating factor (G-CSF), G-CSF alone, or G-CSF plus plerixafor. Chemotherapy regimens used for mobilization included CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone)-based regimens, HDCy (high dose cyclophosphamide), ESHAP (etoposide, cytarabine, methylprednisolone, cisplatin), among others[25-27]. The choice of regimens was made on individual bases at the discretion of the attending physicians, depended on diagnosis, clinical protocols, and disease status of the patients. G-CSF at a dose of 5μg/kg per day was administrated when the WBC count dropped below 1×10^9/L after chemotherapy. A dose of 10 μg/kg per day was prescribed subsequently after the WBC count passed through its nadir. For patients receiving G-CSF alone for mobilization, the dose of G-CSF was 10μg/kg per day. The others received G-CSF 10μg/kg daily plus plerixafor, which was administrated subcutaneously either at a fixed dose of 20mg or a weight-based dose of 0.24 mg/kg in the fourth evening of G-CSF injection. All patients received G-CSF subcutaneously until the last leukapheresis.

PBSC Collection

Harvests initiated on the day the HPC count reached 20×10^6/L [22, 28]. Leukapheresis was performed using the COBE Spectra Apheresis System version 6.1 (COBE Laboratories, Lakewood, CO, USA) in accordance with standard protocol, processing 2-3 total blood volumes per apheresis. After each collection, the total collected $CD34^+$ cells were analyzed. A successful harvest was defined as a minimal number of 2×10^6 $CD34^+$ cells/kg patient weight [5]. Leukapheresis was continued daily in an attempt to achieve the goal or until a maximal 4 apheresis sessions occurred.

Enumeration of HPC, MNC and $CD34^+$ Cells

The number of HPCs and WBCs were determined using the Sysmex XE-2100 automated hematology analyzer. A special lysis reagent (Stromatolyser-IM) could lyse mature WBCs due to their high membrane lipid content, while leaving immature cells intact in the immature myeloid information channel. HPCs were further identified by direct current-radiofrequency biosensors according to cell size and density, and were reported as an absolute number of cells per microliter[28,29].

To enumerate MNCs, which was defined as lymphocytes, monocytes and immature myeloid progenitor cells, cell differentials were performed microscopically on Wright Giemsa-stained cell smear. MNC counts were calculated by multiplying the WBC count with the percentage of MNC.

The quantities of $CD34^+$ cells in apheresis products were determined by standard flow cytometry analysis based on ISHAGE guidelines [30] using a phycoerythrin-conjugated monoclonal anti-CD34 antibody (HPCA-2; Becton Dickinson) and a fluorescein-isothiocyanate-labeled CD45 monoclonal antibody (FITC; Becton Dickinson, New Jersey, USA). Following red cell lyses and a phosphate-buffered saline wash, a minimum of 60,000 nucleated cells were analyzed for each sample using a flow cytometer (FACSCalibur, Becton Dickinson, New Jersey, USA), and results were reported as a percentage of $CD34^+$ cells. The $CD34^+$ cell yield after each collection was calculated by multiplying the WBC count of the apheresis product with the percentage of $CD34^+$ cells.

Statistical Analysis

Continuous variables were compared using Mann-Whitney U test, whereas categorical variables were analyzed by Chi-square or Fisher's exact test. Potential host predictors and laboratory markers were examined separately. A logistic regression model was used to analyze the contribution of host factors on mobilization failure. Variables with *p* values of less than 0.10 in univariate analyses were entered into multivariate analyses. In addition, the relationship between the preharvest hemogram and total collected $CD34^+$ cells was investigated using the Spearman rank correlation coefficient. A two-sided *p* value of less than 0.05 was considered significant. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS, Chicago, USA). Variables predicting a successful harvest identified by multivariate logistic regression and correlation analysis were entered into a classification and regression tree (CART) model, which was performed with R version 3.1.0. (R Core Team, 2014, Vienna, Austria) and rpart() package.

Results

Patient Characteristics

Between January 2007 and January 2012, 189 patients who proceeded to autologous PBSC harvests with a preharvest HPC ≥ 20 × 10^6/L were recruited in our study. Each patient received a median of three apheresis sessions, and a total of 562 sessions were performed. The baseline characteristics, preharvest hemogram, and apheresis products were summarized in Table 1. Age ≥ 60 years, prior radiotherapy and prior chemotherapy cycles ≥ 5 were associated with poor mobilization, whereas mobilization regimens showed a trend toward significance.

Host Predictors for Poor Mobilization

Multivariate analysis revealed five independent factors for poor mobilization, including age ≥ 60 years

Table 1. Characteristics between patients with successful and poor harvest

	Total (n= 189)	Successful harvest (n= 154)	Poor harvest (n=35)	*P*
Baseline characteristics, number (%)				
Male	128 (67.7)	104 (67.5)	24 (68.6)	0.906
Age ≥ 60 years	32 (16.9)	21 (13.6)	11 (31.4)	0.011
Body weight ≥ 65 kg	93 (49.2)	75 (48.7)	18 (51.4)	0.771
Diseases				0.246
Acute leukemia	12 (6.3)	11 (7.1)	1 (2.9)	
Lymphoma	103 (54.5)	85 (55.2)	18 (51.4)	
Myeloma	36 (19.0)	31 (20.1)	5 (14.3)	
* Solid tumor	38 (20.1)	27 (17.5)	11 (31.4)	
Prior radiotherapy	32 (16.9)	17 (11.0)	15 (42.9)	< .001
Mobilization regimens				0.069
CHOP-based	46 (24.3)	39 (25.3)	7 (20.0)	
HDCy	31 (16.4)	22 (14.3)	9 (25.8)	
ESHAP	32 (16.9)	28 (18.2)	4 (14.3)	
ICE	15 (7.9)	13 (8.4)	2 (7.4)	
Cytarabine-based	14 (7.4)	13 (8.4)	1 (2.9)	
VAD	12 (6.3)	11 (7.1)	1 (2.9)	
G-CSF alone	5 (2.6)	2 (1.3)	3 (8.6)	
plerixafor	5 (2.6)	5 (3.2)	0 (0.0)	
Others	29 (15.3)	21 (13.6)	8 (22.9)	
Prior chemotherapy cycles ≥ 5	97 (51.3)	70 (45.5)	27 (77.1)	0.001
Preharvest hemogram, median (range)				
HPC, × 106/L	88 (20-1056)	108 (20-1056)	43 (20-270)	< .001
WBC, × 109/L	12.6 (3.3-73.7)	12.8 (3.3-73.7)	11.9 (4.5-35.4)	0.420
MNC, × 109/L	3.7 (0.2-30.9)	4.1 (0.2-30.9)	2.6 (0.4-8.0)	< .001
Apheresis products, median (range)				
apheresis sessions in each person	3 (1-4)	3 (1-4)	3 (1-4)	
Total CD34+ cells yield, x 106/kg	6.41 (0.02-90.82)	8.18 (2.07-90.82)	1.05 (0.02-1.98)	

Abbreviations: Kg, kilogram; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HDCy, high dose cyclophosphamide; ESHAP, etoposide, methylprednisolone, cytarabine, and cisplatin; ICE, ifosfamide, cisplatin/carboplatin, and etoposide; VAD, vincristine, doxorubicin, and dexamethasone; G-CSF, granulocyte colony-stimulating factor; HPC, hematopoietic progenitor cell; WBC, white blood cell; MNC, mononuclear cell

* All patients categorized as solid tumor group belonged to 3 groups of diagnosis: brain tumor (such as neuroblastoma, medulloblastoma, etc., n=16), sarcoma (such as synovial sarcoma, Ewing's sarcoma, etc., n=12), and germ cell tumor (n=10).

(odds [OR], 8.86; 95% confidence interval [CI], 2.96 to 26.53), a diagnosis of solid tumor (OR, 5.31; 95% CI, 1.63 to 17.34), prior radiotherapy (OR, 6.72; 95% CI, 2.36 to 19.10), prior chemotherapy cycles ≥ 5 (OR, 4.55; 95% CI, 1.71 to 12.11), and mobilization with G-CSF alone or HDCy (OR, 3.45; 95% CI, 1.26 to 9.66) (Table 2). There was no patient who had all five risk factors. In those with the number of host predictors ranging from 0 to 4, the harvest success rate dropped subsequently from 97%, 90.8%, 76.3%, 21.1% to 0% (Fig. 1).

Relationship between Preharvest Hemogram and CD34$^+$ cell yields

The median number of peripheral HPCs, WBCs, and MNCs on the first day of leukapheresis were 88 × 10^6/L (range, 20 - 1056 × 10^6/L), 12.6 × 10^9/L (range, 3.3 - 73.7 × 10^9/L), and 3.7 × 10^9/L (range, 0.2 - 30.9 × 10^9/L), respectively. Higher preharvest HPC and MNC counts were associated with a successful harvest (both p values < 0.001), whereas WBC counts yielded no significant association (Table 1).

The correlation between peripheral cell counts and total CD34$^+$ cell yields in apheresis products was illustrated in Fig. 2. Preharvest HPC counts had a stronger correlation (r = 0.446, p < 0.001) with collected CD34$^+$ cells than did preharvest MNC counts (r = 0.335, p < 0.001), whereas preharvest WBC counts was not significantly correlated with collected CD34$^+$ cells (r = 0.317, p = 0.073).

Decision-tree algorithm for predicting optimal timing of PBSC collection

The number of host predictors at baseline, preharvest HPC and MNC counts were subjected to CART analysis as continuous variables, and all three indicators were selected to be strong predictors (Fig. 3). The number of host predictors with a cutoff at two, HPC cutoff at 28 × 10^6/L and MNC cutoff at 3.5 x 10^9/L were best discriminative for successful prediction determined by CART analysis. The first splitting parameter is "risk factors ≤ 2". For patients who were predicted to be poor mobilizers with more than 3 risk factors at baseline, only 5 out of 20 patients (20%) achieved a successful harvest. In contrast, between those who were predicted to be good mobilizers with 0 to 2 risk factors, HPC ≥ 28 × 10^6/L indicated a high harvest success rate of 93.2% (138/148). For the others with 0 to 2 risk factors but preharvest HPC < 28 × 10^6/L, MNC ≥ 3.5 × 10^9/L further predicted a higher success rate (75.0%, 6/8) than did MNC < 3.5 × 10^9/L (46.2%, 6/13). If we regard a predicted success rate ≥ 75% as success while a predicted success rate < 50% as failure, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of this model are 93.5%, 65.7%, 92.3% and 70.0%, respectively.

Table 2. Univariate and multivariate analysis for poor harvest

	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Gender						
Male vs. female	1.05	0.48-2.31	0.906			
Age						
≥ 60 vs. < 60	2.90	1.24-6.79	0.014	8.86	2.96-26.53	< .001
Body weight						
≥ 65 vs. < 65	1.12	0.54-2.32	0.771			
Disease						
Solid tumor vs. not	2.16	0.94-4.92	0.068	5.31	1.63-17.34	0.006
Prior radiotherapy	6.04	2.62-13.97	< .001	6.72	2.36-19.10	< .001
Mobilization regimens						
G-CSF alone/HDCy vs. not	2.83	1.24-6.43	0.013	3.45	1.26-9.66	0.016
Prior chemotherapy cycles						
≥ 5 vs. < 5	4.05	1.73-9.48	0.001	4.55	1.71-12.11	0.002

Abbreviations: HDCy, high dose cyclophosphamide; G-CSF, granulocyte colony-stimulating factor

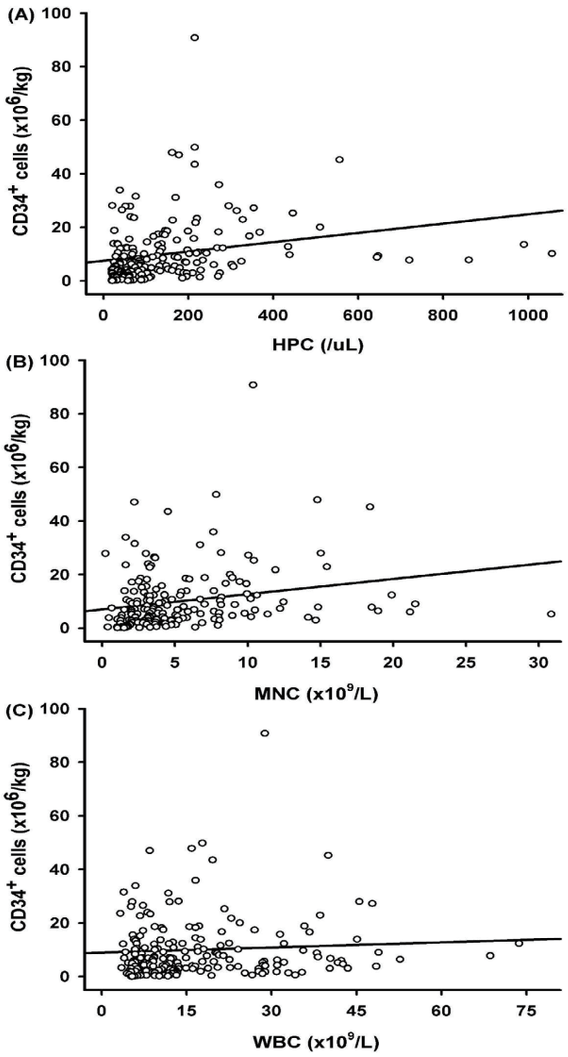

Fig. 1. Correlation between total $CD34^+$ cell yields and (A) preharvest HPC counts, (B) preharvest MNC counts, and (C) preharvest WBC counts

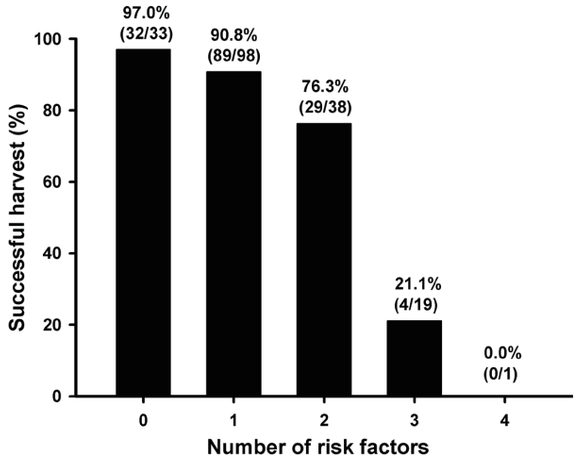

Fig. 2. Harvest success rates according to host predictors. The harvest success rate dropped subsequently from 97%, 90.8%, 76.3%, 21.1% to 0% in patients with the number of host predictors ranging from 0 to 4.

Discussion

Predicting good mobilization and determining the timing of PBSC collection, which are crucial for an efficient and cost-effective harvest for transplantation, remain a clinical challenge. Enumerating HPC by using an automated hematology analyzer, compared with enumerating peripheral blood $CD34^+$ cells, is a rapid, inexpensive, and less technically dependent method for predicting a successful harvest. However, the optimal HPC cutoff and the factors to be employed for improved predicting have not yet been determined. We reviewed our experience of autologous stem cell harvests in the last 5 years. Five baseline characteristics were identified as independent factors for poor mobilization, including age ≥ 60 years, a diagnosis of solid tumor, prior radiotherapy, prior chemotherapy cycles ≥ 5, and mobilization with G-CSF alone or high-dose cyclophosphamide. By incorporating host predictors and peripheral MNC counts, we propose a model to optimize HPC-based PBSC collection. To our knowledge, it is first time using CART analysis to construct a decision-tree algorithm to guide a PBSC harvest.

HPC has proven to be a surrogate marker for initiation of PBSC collection. The preharvest HPC counts correlated better with the collected $CD34^+$ cell counts than did MNC and WBC counts[17,22]. However, the relationship was not so strong. The correlation coefficient was 0.446 in our study, within the range previously reported (range, 0.32-0.78)[15-17,28]. Regarding the best cutoff values of HPC, a prospective study demonstrated that when the cutoff increased from 1 × 10^6/L to 50 × 10^6/L, the sensitivity decreased from 98% to 37% while the specificity improved from 35% to 90%[21]. By using a HPC threshold of 20 × 10^6/L to guide the PBSC harvesting in our institution, 35 out of 189 patients (18.5%) failed to achieve minimal requirement of $CD34^+$ cell yields. In our new model, a higher HPC threshold of 28 × 10^6/L was defined using CART analysis, and could identify 138 out of 150 successful harvests (92%) between those who were predicted to be good mobilizers.

Besides the different cutoff of HPC, several efforts have been made to optimize HPC-based prediction. Teng *et al*. proposed a formula based on circulating $CD34^+$ cells and HPC counts for predicting harvest potential[29]. MNC and WBC counts can also play an auxiliary role, as their predictive values when using alone are not satisfactory. Based on a relatively small cohort with 60 patients, Padmaabhan et al. proposed a strategy using HPC and WBC testing in tandem to determine the initiation of harvests. Those who reached the HPC threshold along with those who did not reach the HPC threshold but did reach the WBC threshold could proceed to PBSC collection, and 90% of adequately mobilized patients were identified[20]. In our study, a MNC count of 3.5×10^9/L aided in prediction. Patients with low HPC who reached the MNC threshold still had a 75% of incidence of achieving an adequate harvest.

Five baseline characteristics were identified as host 381 predictors for poor mobilization in our study, which were 382 consistent with the published data[5,9]. Over the past decades, different criteria for defining poor mobilizers have been proposed. Grounded evidence demonstrates that old age, prolonged chemotherapy, and previous extensive radiotherapy are strong predictors for poor mobilization; the Italian working group for stem cell transplantation has included these factors in criteria for predicting poor mobilization[9]. IIn addition, we determined that the cancer diagnosis and the mobilization regimen affected poor mobilization in this study. Most patients with solid tumors who proceeded to PBSC transplantation had a relatively advanced or refractory disease[3,4], which might have had a negative impact on stem cell mobilization. Regarding mobilization regimens, it is well described that chemotherapy with G-CSF results in a better harvest than does G-CSF alone[9]. In addition, Sorasio and coworkers and Lee and coworkers[36] have reported that the HDCy regimen was inferior to other chemotherapy for mobilizing PBSCs in patients with lymphoma. The results from patients receiving these two less-effective regimens demonstrated an independent association with poor harvests in our study (multivariate

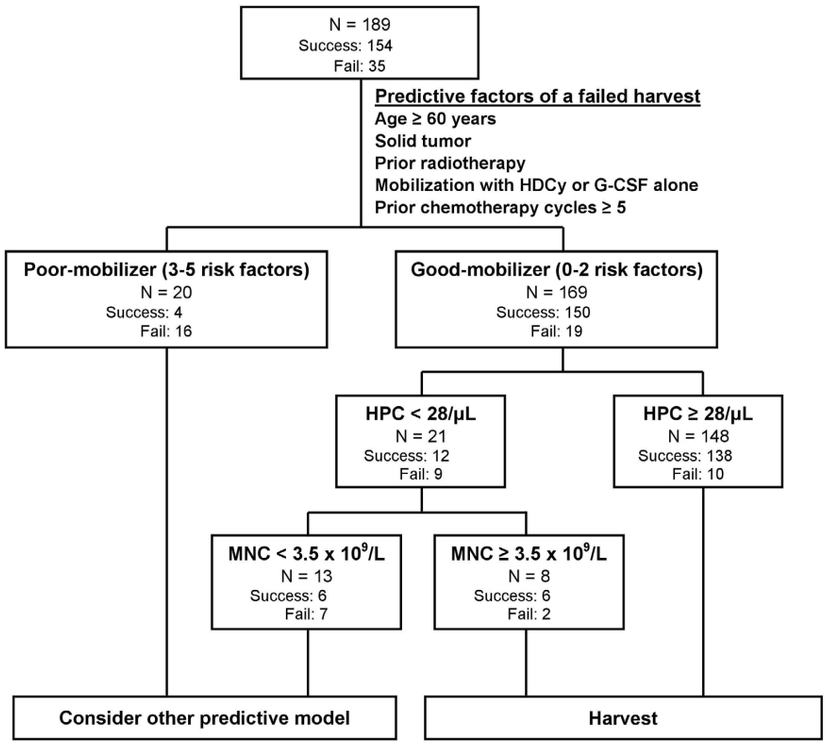

Fig. 3 Decision-tree algorithm to determine optimal timing of PBSC harvesting.

analysis OR, 3.45; 95% CI, 1.26-9.66; p 5 0.016).

We used CART analysis to develop a predictive model for successful harvests. The indicators that were chosen, the discriminative values of the indicators and the splitting order were all determined by recursive partitioning, and a decision tree with maximal predictive accuracy was constructed. In the first place, patients were stratified by host predictors. For those who were deemed to be good mobilizers, a higher HPC threshold of 28×10^6/L could help avoid unnecessary harvests. A MNC threshold of 3.5×10^9/L could further rescue patients with low HPC from missing an adequate PBSC collection. Patients with a probability of optimal mobilization higher than 75% could proceed to harvest without parallel examination of the peripheral $CD34^+$ cells. The sensitivity and the PPV were high (sensitivity, 93.5%; PPV, 92.3%).

In contrast, for the patients with more than 50% probability of harvest failure, applying other predictive marker with a low false-negative rate, such as preharvest $CD34^+$ cell counts, would minimize the risk of missing an adequate collection. By early identification of those with high failure rate in their first mobilization attempt, administration of plerixafor, a highly active mobilizing agent, might further rescue them from mobilization failure. Growing body of studies reported an "on-demand" administration of plerixafor to avoid both mobilization failure and dispensable use of this expensive drug[33,34]. Sorasio *et al*. set up an algorithm for early detection of poor-mobilizing patients based on the percentage of $CD34^+$ cells at the first and second day of hematological recovery to guide the use of plerixafor[31]. Milone *et al*. conducted a prospective study to evaluate another "on-demand" strategy based on the peripheral $CD34^+$ cell counts at the thirteenth day from DHAP (dexamethasone, cytarabine, cisplatin) or the fifteenth day from HDCy mobilization, respectively. It significantly improved mobilization of PBSC with no increase in overall cost comparing to conventional treatment in the historical controls group[35]. Without enumeration of preharvest $CD34^+$ cells, our simple strategy could identify 33 out of 189 patients (17.5%) who had more than 50% probability of harvest failure and hence might benefit from "on-demand" plerixafor rescue.

Our study has several limitations. First, we did not monitor the quantities of peripheral $CD34^+$ cells. Whether the preharvest $CD34^+$ cell counts could be incorporated into our decision-tree algorithm to improve predictive value is unknown. However, the CD34 analysis may not be favorable for intensive monitoring because it requires a competent technician on standby. Second, a potential selection bias was present because only patients with preharvest HPC $\geq 20 \times 10^6$/L were enrolled. Our results should be extended to those with low HPC counts with caution, and further prospective validation is necessary.

In conclusion, we provide a novel model to guide PBSC harvesting. Our CART algorithm incorporating host predictors, HPC enumeration and MNC count may improve prediction and thus increase the success of PBSC mobilization. In patients with a high probability of a successful harvest, it can help reduce the necessity of monitoring peripheral $CD34^+$ cells. In those with a high probability of harvest failure, the use of a $CD34^+$ cell count to aid in prediction and the administration of plerixafor on demand may help reduce unnecessary resource utilization and improve patient management.

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利用決定樹流程改良以造血前驅細胞為基礎對周邊血液幹細胞動員之預測

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受文日期：民國 104 年 11 月 30 日；接受刊載：民國 106 年 01 月 05 日

摘要

背景：以自動血液分析儀來計算造血前驅細胞（HPCs）的數目以預測周邊血液幹細胞（PBSCs）的動員程度是一個快速、較不昂貴、較不需技術導向的方式。本研究在探討如何整合 HPCs 及其他預測指標以成功的收集幹細胞。

方法：我們分析了自 2007 至 2012 年 189 位收集 PBSCs 的患者，患者在收集前 HPCs 均大於 $20x10^6$/L。收集失敗的定義是每公斤體重少於 $2x10^6$ 個 $CD34^+$ 的細胞。我們以多變數邏輯式回歸和相關性分析找出預測成功收集的變數，最後以分類和回歸樹（CART）分析。

結果：總共有 154 位患者成功收集到足量的 $CD34^+$ 細胞（中位數為 $8.18x10^6$/ 每公斤）。五個獨立的宿主因素包括年紀大於 60、固態腫瘤診斷、先前化學治療超過五次、先前曾經接受放射線治療及單獨使用白血球生長因子或高劑量 cyclophosphamide 作為動員處方，加上實驗室方面的 HPCs 及單核球數這兩個指標，進入最後的 CART 分析。兩個宿主危險因子、HPCs 數 $28x10^6$/L 及單核球數 $3.5x10^9$/L 是最能用以成功區別收集成不成功的分界值。在這個決定樹的流程中，有 0 至 2 個宿主危險因子的患者（預測其為良好動員者）其收集成功率遠高於 3 至 5 個危險因子的患者（88.8% vs. 20%）。在這些良好動員者中，若其 HPCs 數大於 $28x10^6$/L，則有更高的機會（93.2%）可以收集成功。

結論：這個 CART 流程整合了宿主因素、HPCs 及單核球數可望改善以往的預測模型而提高成功收集 PBSCs 的機會，未來仍需前瞻性的研究加以驗證。

關鍵詞：造血前驅細胞，單核細胞，周邊血液幹細胞收集，自體造血幹細胞移植，分類和回歸樹分析

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Tungs' Medical Journal 11 (2017) 20-25

Original Article

Ankle-brachial Index is Associated with the Initial Severity of Acute Ischemic Stroke

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Received: Dec. 04, 2015; Accepted: Feb. 02, 2016

Abstract

The ankle-brachial index (ABI) is an easy and reliable tool for identifying patients with subclinical peripheral arterial disease. Abnormal ABI (<0.9) is broadly used as an indicator of lower limb arterial disease and has been shown to predict all-cause mortality, vascular related deaths, and nonfatal cardiovascular events. Low ABI is an independent predictor of subsequent stroke, myocardial infarction, and death. However, data on the relationship between abnormal ABI and severity of acute ischemic stroke (AIS) is limited. The purpose of this study was to examine the relationship between ABI and severity of AIS. Consecutive patients with AIS were divided into three groups: low ABI (<0.9), borderline ABI (0.9–1.0), and normal ABI (1.0–1.4).

The results showed that among the 255 patients enrolled in this study, 18.8% had low ABI, 22.7% had borderline ABI, and 58.5% had normal ABI. Among patients with AIS, the initial National Institutes of Health Stroke Scale (NIHSS) scores were significantly different ($p < 0.001$). Age and plasma levels of triglyceride were also significantly different ($p = 0.034$ and $p = 0.018$, respectively). There were no significant differences in gender, history of hypertension, diabetes, or cigarette smoking among the ABI groups. Patients with low ABIs were older, had higher plasma levels of triglyceride, and higher initial NIHSS scores.

In conclusion, low ABI was associated with initial severity of AIS. Therefore, ABI may help to provide more effective care for these patients.

Key words: ankle-brachial index, acute ischemic stroke

Introduction

Stroke is still a leading cause of death in Taiwan[1]. Ischemic cerebral vascular accident generally refers to conditions that involve narrowed or blocked blood vessels that lead to stroke. Therefore, early detection of atherosclerosis with narrowed or blocked blood vessels is helpful in the prevention of cerebral vascular accident.

The ankle-brachial index (ABI) is an easy and reliable tool for identifying patients with subclinical peripheral arterial disease (PAD) and is used as an indicator of generalized atherosclerosis[2-4]. Abnormal ABI (<0.9) is broadly used as an indicator of lower limb PAD[5] and predicts all-cause mortality, vascular related death, and nonfatal cardiovascular events, even after adjusting for conventional vascular risk factors[2,4,6]. Recent studies have suggested a high prevalence of low ABI among patients with acute ischemic stroke (AIS) or transient ischemic attack, with prevalence estimates ranging from 24% to 51%[7-11]. In patients with AIS, low ABI is an independent predictor of subsequent stroke, myocardial infarction, and death[8,10,12]. Furthermore, low ABI may be a predictive factor of the initial severity and long-term functional outcomes of AIS[12-14]. However, no study has been conducted in Taiwan on the relationship between abnormal ABI and the severity of AIS. The purpose of this study was to examine the relationship between ABI and the severity of AIS.

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Study subjects and methods

We conducted a hospital-based retrospective study involving 255 consecutive patients with AIS hospitalized in the Department of Neurology at the Tungs' Taichung Metroharbor Hospital, Taiwan, between January 1, 2014 and December 31, 2014. The subjects were eligible if they were recruited within 1 week of the onset of stroke and had undergone ABI measurement during hospitalization. AIS was defined as the sudden onset of acute neurologic deficit with evidence of acute infarction on brain computed tomography or magnetic resonance imaging. The severity of the event was assessed according to National Institutes of Health Stroke Scale (NIHSS) score[15-18]. This scale is composed of 11 items, each of which scores a specific ability between 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, and a higher score is indicative of some level of impairment[15].

ABI measurement

ABI was measured using a noninvasive automatic pulse wave analyzer (OMRON HEALTHCARE Co., Ltd, Japan) after a 5-min rest in the supine position. According to the recommendations of the American Heart Association[19], ABI was calculated as the ratio of the systolic pressure in the posterior tibial artery and the highest systolic pressure in the two brachial arteries. After the individual calibration process, blood pressure was simultaneously measured using cuffs on upper (brachial arteries) and lower limbs (posterior tibial arteries). ABI was then automatically calculated and expressed as a ratio of the systolic blood pressure in the ankle to that in the arm. Abnormal ABI was defined as an ABI of 0.9 or less on either the right or left side[20].

Statistical analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS, Inc., Chicago, IL, USA). Categorical variables were reported as numbers and percentages. Variables of nominal or continuous data are presented as means and standard deviations. Category data were analyzed with the chi-square test, and for continuous data, one-way analysis of variance was used. A p value of less than 0.05 was considered as statistically significant.

Results

In total, 255 patients with AIS were recruited, and 174 of these (68.2%) were male. Previous histories included hypertension in 204 (80.0%) patients, diabetes in 119 (46.7%) patients, and cigarette smoking in 69 (27.1%) patients. Among the 255 patients enrolled in this study, 18.8% had low ABI (<0.9), 22.7% had borderline ABI (0.9–1.0), and 58.4% had normal ABI (1.0–1.4). Among the three ABI groups, a higher percentage of the patients were males (60.4%, 65.5%, and 71.8%, respectively). However, gender was not significantly correlated with the incidence of AIS (p = 0.297). Stroke was prevalent in patients with a history of hypertension (81.3%, 79.3%, and 79.9%, respectively for these three groups), diabetes (52.1%, 46.6%, and 45.0%, respectively), and less with cigarette smoking (22.9%, 25.9%, and 28.9%, respectively) (Table 1).

The severity of AIS was assessed using the NIHSS score. The NIHSS score was compared across the three ABI groups. The results showed that patients with low ABI had an NIHSS score of 7.98 ± 7.24, those with borderline ABI had a score of 6.10 ± 5.42, and those with normal ABI had a score of 5.39 ± 4.76 (p = 0.018). The severity of stroke was positively correlated with the NIHSS score (Table 1).

Among the three ABI groups, the mean age of patients with low ABI was 75.88 ± 11.93 years, those with borderline ABI were 69.52 ± 12.18 years of age, and those with normal ABI were 66.09 ± 11.58 years. Age was significantly associated with the severity of AIS (p < 0.001); older patients had more severe strokes (Table 1).

ABI was also associated with plasma levels of triglyceride (p = 0.034) (Table 1). The mean plasma levels of triglyceride among patients with low, borderline, and normal ABI were 198.44 ± 252.24, 126.36 ± 67.88, and 149.01 ± 116.46, respectively. The severity of AIS was correlated with plasma levels of triglyceride (p = 0.034); that is, these levels were higher in patients with low ABI. However, plasma levels of total cholesterol and low density lipoprotein (LDL) were not correlated with the severity of stroke or ABI. The mean plasma levels of total cholesterol of patients with low ABI was 183.98 ± 60.09, that of patients with borderline ABI was 176.86 ± 41.25, and that of patients with normal ABI was 173.54 ± 41.66 (p = 0.385). Similarly, plasma levels of LDL were 108.90 ± 49.12, 113.34 ±

Table 1. Comparison of clinical characteristics in stroke patients with different ABI values

	ABI				
	All patients N=255	ABI < 0.9 N=48 (%)	.9≤ABI≤1.0 N=58 (%)	1≤ABI≤1.4 N=149 (%)	p
Sex (M/F)	174/81	29/19	38/20	107/42	0.297
Hypertension(%)	204 (80%)	39 (81.3)	46 (79.3)	119 (79.9)	0.968
Diabetes (%)	119 (46.7%)	25 (52.1)	27 (46.6)	67 (45.0)	0.691
Smoking (%)	69 (27.1%)	11 (22.9)	15 (25.9)	43 (28.9)	0.946
Age (yrs)	68.7 ± 12.3	75.9 ± 11.9	69.5 ± 12.2	66.1 ± 11.6	<0.001
BMI	24.7 ± 3.9	23.8 ± 3.9	24.6 ± 3.3	25.0 ± 4.2	0.195
Triglyceride (mg/dl)	153 ± 145	198 ± 252	126 ± 68	149 ± 117	0.034
Total cholesterol (mg/dl)	176 ± 46	184 ± 60	177 ± 41	174 ± 42	0.385
LDL-Cholesterol (mg/dl)	108 ± 39	109 ± 49	113 ± 32	106 ± 38	0.435
NIHSS	6.04 ± 5.52	8.0 ± 7.2	6.1 ± 5.4	5.4 ± 4.8	0.018

ABI: ankle-brachial index; BMI: body mass index; LDL: Low-density lipoprotein; NIHSS: National Institute of Healthy Stroke Scale.

31.89, and 105.63 ± 37.72, respectively (p = 0.435).

Current smoking, body mass index, hypertension, and diabetes mellitus were not significantly different among the three groups of patients (Table 1).

Discussion

The results showed that ABIs of the three different groups (<0.9, 0.9–1.0, and 1.0–1.4, respectively) were significantly correlated with the NIHSS score. Since the severity of AIS can be assessed by the NIHSS score[15-18], abnormal ABI (<0.9) may predict the initial severity of AIS. ABI is an easy and reliable tool for identifying patients with subclinical PAD, and it has been used as an indicator of generalized atherosclerosis[2-4]. This is consistent with the notion that there is a high prevalence of low ABI among patients with AIS[7-11]. Patients with low ABI values presenting with more severe ischemic stroke have been reported in several large scale studies. In the international Reduction of Atherothrombosis for Continued Health (REACH) registry, the highest vascular mortality during 1- or 3-year follow-up periods occurred in patients with PAD[21]. In a cohort study in the primary care setting, in those with PAD, the incidence of stroke was doubled and that of fatal stroke was tripled[22,23]. In another study that included acute coronary syndromes and stroke, low ABI was associated with a two-fold increase in all-cause mortality during the 1-year follow-up period[7]. Furthermore, a recent Korean study showed that the initial presentation was more severe in patients with low ABI[13]. These findings suggest that poor outcomes in patients with PAD may be associated with initially severe strokes because initial severity of stroke is one of the most important surrogate markers for predicting long-term outcomes and mortality in stroke patients[24,25].

Poor clinical outcomes in patients with PAD may be partially explained by factors involved with severe stroke. We found that ABI was associated with NIHSS score (p = 0.018), age (p < 0.001), and plasma levels of triglyceride (p = 0.034), but there were no significant relationships between ABI and sex, hypertension, diabetes mellitus, current smoking, BMI, or total plasma levels of cholesterol and LDL. Our results are in agreement with several studies that have reported a strong relationship between ABI and age[13, 25, 26]. However, our results are different from studies that showed correlations between ABI and BMI[13,26], hypertension[25], diabetes mellitus[13,27], and current smoking[22,25].

The associations we found between ABI and NIHSS and plasma levels of triglyceride were similar to those observed in other reports that indicated ABI was positively associated with NIHSS score [13,26]. Although hypertension, diabetes, and cigarette smoking were prevalent in patients with AIS, they were not associated with ABI in our study and this agreed with other reports of no correlation of ABI with BMI[13,27], hypertension[26,27], diabetes mellitus[13,28], total cholesterol[26], or current smoking[26,28].

Our results showed that 18.8% of patients with AIS had low ABI (<0.9). PAD prevalence may be different in other ethnic groups. In the San Diego Population Study, a quarter of patients with AIS had PAD[29]. Other studies have shown that PAD prevalence is 10%–25% in Caucasians aged >55 years[30] and 30%–51% in patients with stroke in Germany[3133]. A history of stroke is associated with a 1.5–3-fold increase in PAD prevalence[34,35]. However, PAD prevalence in Asian populations is low[29,36,37]. Our result was consistent with a hospital-based study in Japan that showed a similar prevalence (21%) of PAD in stroke patients[38].

PAD in stroke patients is usually asymptomatic because these patients are more likely to have gait difficulty due to limb weakness, advanced age, compromised cardiopulmonary function, or orthopedic problems, rather than vasogenic claudication. Detecting PAD in (mostly asymptomatic) stroke patients may prompt physicians to intensify treatment strategies and to ensure patient compliance with treatment.

There were some limitations in this study, including the sample size and the clinical conditions of the patients. To minimize selection bias and enable researchers to identify the variables affecting ABI in patients with AIS, future studies should be conducted with larger sample sizes and a wider range of clinical conditions and should take into account all possible diet, behavior, and metabolic factors of patients with AIS.

In conclusion, the results of this study indicate that low ABI was associated with initially severe AIS. Therefore, ABI may be a useful prognostic factor for patients with AIS. In addition, ABI was correlated with plasma levels of triglyceride and age. Evaluation of effective interventions to reduce the risk of future events in patients with stroke and abnormal ABI (e.g., lowering plasma levels of LDL, optimizing antihypertensive treatment, and stronger antithrombotic treatment) is required.

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踝肱指數與急性缺血性腦中風病患之初期嚴重度之關係

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受文日期：民國 104 年 12 月 04 日；接受刊載：民國 105 年 02 月 02 日

摘要

踝肱指數（ankle-brachial index, ABI）是一個簡單的可靠的工具用來鑑定在臨床上無症狀的週邊動脈疾病患者。一個不正常的踝肱指數（ABI<0.9）是被廣泛用來作下肢週邊動脈疾病指標。研究顯示在急性缺血性腦中風患者或暫時性腦缺血患者中，低踝肱指數佔了很高的流行率。無論如何，目前少有資料提到有關於不正常的踝肱指數與急性缺血性腦中風的嚴重度之間的關連性。此研究的目的是去探討踝肱指數與急性缺血性腦中風的急性期的嚴重度關連性。急性缺血性腦中風患者依其踝肱指數分成：(1) 低踝肱指數（<0.9），(2) 邊緣踝肱指數（0.9-1.0) 以及 (3) 正常踝肱指數（1.0-1.4）三組進行分析比較。

結果顯示在所有 255 住院患者中，低踝肱指數佔 18.8%，邊緣踝肱指數佔 22.8% 以及正常踝肱指數佔 58.4%。在三組踝肱指數群中，NIHSS（p= 0.018）有顯著的意義。另外，年齡（p<0.001）及血清三酸甘油脂（p = 0.034）也有顯著的關連性。低踝肱指數病人有較高之年齡、三酸甘油脂與 NIHSS，而年齡、性別、高血壓、糖尿病及吸煙病史等則在三組病人間並無顯著差異。

結論：不正常的踝肱指數與急性缺血性腦中風的嚴重度有明顯的關連性，所以踝肱指數可以幫助醫師給予這些患者更有效的預防與照護。

關鍵詞：踝肱指數、急性缺血性腦中風、中風病患嚴重度

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Tungs' Medical Journal 11 (2017) 26-30

Case Report

Re-expansion Pulmonary Edema following Thoracoscopic Drainage of a Massive Pleural Effusion: A Case Report and Literature Review

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Received: Oct. 12, 2015; Accepted: Dec. 03, 2015

Abstract

Re-expansion pulmonary edema (RPE) is a rare complication of treatment for pleural effusion and pneumothorax. It typically manifests as edema within the lung that has recently been re-expanded. The condition generally occurs unexpectedly and dramatically, either immediately or within 24 h. Its clinical manifestations are varied, ranging from chest X-ray findings alone in asymptomatic patients to severe cardiorespiratory insufficiency. Here we present a case on unilateral RPE after draining a left-sided massive pleural effusion. In addition, several recent research articles on the pathophysiology and treatment of RPE are discussed.

Key words: re-expansion pulmonary edema, pleural effusion, pneumothorax, thoracoscopic surgery, thoracentesis

Introduction

A sudden evacuation of a pneumothorax, pleural effusion, or severe atelectasis may cause a rare and potentially lethal re-expansion pulmonary edema (RPE), which is associated with a 20% mortality rate [1]. Furthermore, some reports showed that an even more acute form of RPE may occur after lung expansion after only several hours of atelectasis. Here we present a case on unilateral RPE after draining a left-sided massive pleural effusion caused by malignant hemothorax. In addition, several recent research articles on the pathophysiology and treatment of RPE are discussed.

Case Report

A 48-year-old man presented with dyspnea on exertion and non-productive sputum but without chest pain, fever, or chills and reported worsening of symptoms in the early morning. After admission, a series of examinations were performed before operation. A chest X-ray (CXR) revealed massive pleural effusion in the left lung fields with a partial atelectasis of the left lung (Fig. 1). The arterial blood gas (ABG) analysis with oxygen nasal cannula flow of 3 l/min revealed a pH of 7.40, PaO_2 of 72 mmHg, $PaCO_2$ of 42 mmHg, and base excess (BE) of 1.8 mEq/l. Blood pressure was 149/87 mmHg, and heart rate was 94 beats/min. The results of other laboratory tests were unremarkable. Surgical intervention with thoracoscopy for the pleural effusion was scheduled.

General anesthesia was induced using 100-mg ketamine, 100-μg fentanyl, 100-mg xylocain, 90-mg citosol, and 100-mg succinylcholine. The trachea and left main bronchus were intubated with a 37-F, left-sided, double-lumen endobronchial tube. The appropriate placement of this tube was confirmed by chest auscultation of breath sounds and fiberoptic bronchoscopic examination. Anesthesia was maintained with sevoflurane. Rocuronium was used to maintain adequate muscle paralysis and facilitate controlled

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mechanical ventilation. Video-assisted thoracoscopic operation for the left pleural effusion was performed with the patient placed in a right lateral position. During operation, the left-side bronchial tube was disconnected and the dependent lung was ventilated.

During this period, an analysis of ABG (FiO_2: 100%) revealed a PaO_2 of 280 mmHg, $PaCO_2$ of 43 mmHg, pH of 7.389, and BE of −4.5 mEq/l. There were no specific findings except the bloody pleural effusion. The drainage of the left bloody pleural effusion was uneventfully completed 45 min later, and the total volume of pleural fluid drained was 2000 ml. The estimated blood loss was 200 ml during the procedure. The total volume of fluid given during the 90-min procedure was 1250 ml. Before thorax closure, the left lung was reinflated to examine any air leakage, and both lungs were expanded by manual positive-pressure ventilation with 25 cmH_2O of peak inspiratory pressure. The duration of one-lung ventilation was 40 min. A 24-F thoracostomy tube was placed and connected to a pleur-evac device and kept at −20 cm H_2O pressure. The operation was smoothly performed, and no remarkable changes in blood pressure and heart rate were detected during the surgery. At the end of the surgery, 1-mg intravenous atropine and 2-mg neostigmine were administered for the reversal of muscle relaxation. Finally, the endotracheal tube was removed when the patient started breathing spontaneously and adequately.

In the recovery room, the patient had progressive cardiopulmonary embarrassment. Shortness of breath, cough with frothy sputum, dyspnea, tachycardia, and restlessness were observed. Desaturation (SpO_2: 83%) developed even with 50% ventrimask. Unilateral crackles and rales were heard on the left lung. A repeat CXR (Fig. 2) demonstrated pulmonary edema in the left lung. The patient was re-intubated and supported by a mechanical ventilator with positive end-expiratory pressure (PEEP) due to worsening respiratory distress and admitted to the surgical intensive care unit for further management under the impression of acute pulmonary edema.

The patient dramatically improved within 24 h after the administration of diuretics and ventilation support with PEEP. A series of CXR also revealed progressive improvement. He was extubated the next day and transferred to the ordinary ward on the third hospital day. CXR (Fig. 3) taken on the sixth

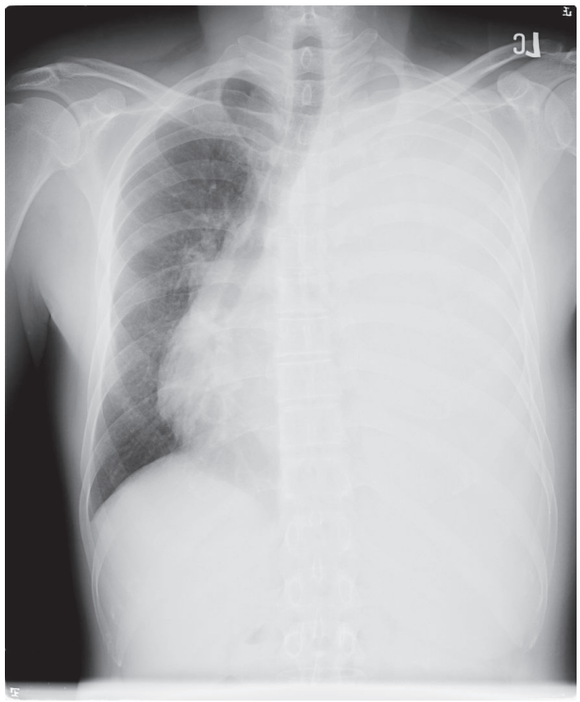

Fig. 1 Preoperation chest radiograph revealed massive pleural effusion in leftlung fields with partial atelectasis of the left lung.

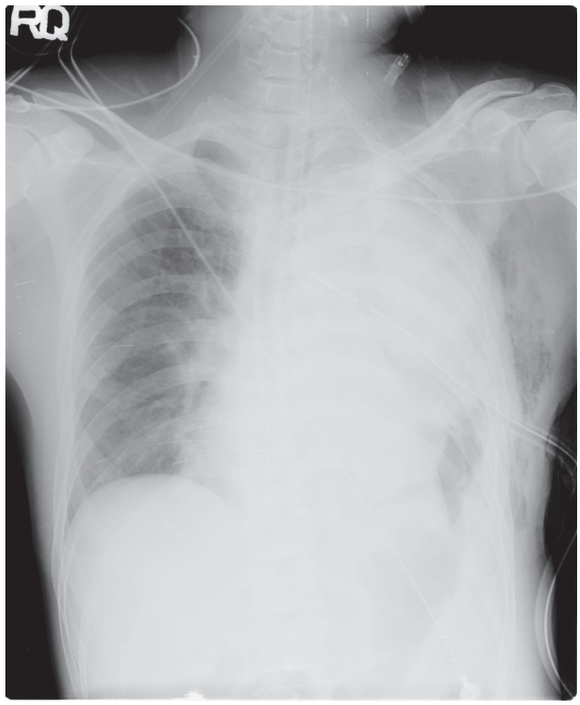

Fig. 2 Postoperative chest radiograph revealed fluffy infiltrates in left lung.

postoperative day revealed both lung fields to be clear. The final cytology report on the pleural effusion indicated small cell carcinoma.

Discussion

A sudden evacuation of a chronic collapsed lung may induce RPE. Symptoms may include cough with or without sputum, hypotension, tachycardia, and respiratory distress. Approximately 64% of patients exhibit symptoms within 1 h after the re-expansion of the collapsed lung, and all patients are symptomatic within 24 h [1]. RPE frequently occurs in the collapsed lung but occasionally occurs in the contralateral or bilateral lung field [2]. If the patients receive appropriate treatment, symptoms usually resolve within 24 to 72 h.

Since the initial description of RPE in the literature, the mortality associated with this complication is not well defined. A case series suggested that RPE may be more lethal than previously expected[1] .They reported its mortality to be 20% in the 53 reviewed cases. However, the estimated mortality rate with selection bias was higher in some reports[1,3,4].

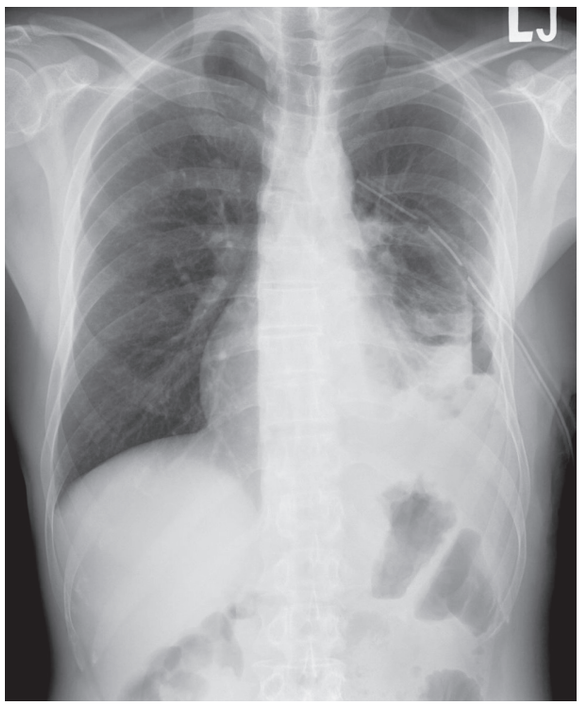

Fig. 3 Chest radiograph taken on the 6th postoperative day showed near-complete resolution of the lung infiltration.

Many authors have investigated possible risk factors for RPE. The duration and severity of lung collapse and the speed of re-expansion are the most important factors[1]. Furthermore, the severity of the collapse may be more predictive than its duration. In Matsuura's series, no patient with a pneumothorax smaller than 30% of the lung field versus 17% of patients with total collapse and 44% of patients with tension pneumothorax suffered this complication after re-expansion[5]. In another study, Ravin *et al.* found that when brief spontaneous pneumothorax was complicated with RPE, the pneumothorax was more severe[6].

The pathophysiology of RPE is complex and still not completely understood. Several potential mechanisms have been suggested, including an increased permeability of pulmonary capillaries or hemodynamic mechanisms[7-9]. RPE appears to be due to increased pulmonary capillary permeability rather than due to hemodynamic mechanisms. Sprung *et al.* recorded the colloid osmotic pressure and pulmonary wedge pressure of two patients who experienced RPE[10]. The colloid osmotic pressure and pulmonary wedge pressure of the pulmonary edema fluid was 73% and 81% of the serum value, respectively. The pulmonary arterial wedge pressure in one patient was within normal limits.

Another research reported an occurrence of inflammatory response when the lung re-expanded[11]. This response was secondary to expansion-related mechanical injury to the alveolar-capillary membrane and reperfusion injury of the collapsed lung tissue. In another report on five patients with large pleural effusion, Trachiotis *et al.* supported this point[12]. They found that the effusion did not completely fill the hemithorax, and part of or entire ipsilateral upper lobe remained aerated. RPE developed in the collapsed portion of the lung but not in the aerated portion of the lung. They suggested that hypoxic injury to the atelectatic lung, rather than mechanical stress, was a plausible explanation for RPE.

The evidence of an inflammatory response can be found in both animal and human studies. Recent studies in rabbits indicated that inflammatory mediators might play an important role in RPE development[13,14]. A unilateral re-expansion of the lung induces an inflammatory response not only in the re-expanded lung but also in the contralateral lung. This mechanism could explain the bilateral presence of

RPE in some cases. In human research, Nakamura *et al.* observed protein leakage and polymorphonuclear leukocyte (PMN) accumulation in the re-expanded lung[15]. Interleukin-8, PMN elastase, and leukotriene B4 in edema fluid increased during RPE. They speculated that some of these fluid mediators play important roles in the chemotaxis and activation of PMN during RPE development[15,16]. Thus, the pathophysiology of RPE is not only related to hemodynamic mechanism but the increased permeability of pulmonary capillaries induced by hypoxic injury might also play a more important role.

Although no randomized clinical trial has been performed to compare the different methods of drainage, many authors suggested that the rapidity of re-expansion might play a role in RPE development [17,18]. Even though Abunasser *et al.* concluded that a large-volume thoracentesis is safe to perform [19,20], many physicians advise to drain not more than 1 l of fluid or air at once, according to the conclusions of the American College of Chest Physicians.

The traditional management of RPE is supportive treatment including mechanical ventilation with PEEP, restriction of fluid, and diuretics. Hypotension and low cardiac output should be managed with volume replacement and inotropic agents. Some physicians recommend non-steroidal anti-inflammatory agents [12]; however, there are no further studies to support this recommendation. The authors also suggested positioning the patient in the lateral decubitus with the affected side up as this position can reduce intrapulmonary shunting and improve the global oxygenation.

In conclusion, our patient possessed the potential risk factors for RPE (duration and severity of lung collapse). For such patients, it is advisable to use water valves instead of vigorous suction and to drain small volumes of air or fluid. A careful and close monitoring of the patient is recommended during the first few hours after drainage. In cases wherein RPE occurs, timely and appropriate management should result in dramatic improvement.

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胸腔鏡施行大量肋膜積水引流併發術後擴張性肺水腫之病例報告與文獻回顧

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受文日期：民國 104 年 10 月 12 日；接受刊載：民國 104 年 12 月 03 日

摘要

在治療肋膜腔積水與氣胸時，再擴張型肺水腫是少見的併發症。典型上當肺再次擴張時反而引起肺積水。這情況的發生常常無法預期而且是戲劇性的。在 24 小時內臨床上的表現是輕重程度不同，從只有 X 光上的表徵而沒有症狀，到嚴重的心肺衰竭。再此我們報告一例病人，在做完左側大量的肋膜腔積水引流後發生再擴張型肺水腫，並對其形成原因與治療做相關文獻回顧討論。

關鍵詞：再擴張型肺水腫、肋膜腔積水、氣胸、胸腔鏡手術、胸腔引流

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Case Report

Fatal Pulmonary Embolism During Bipolar Hemiarthroplasty: A Case Report and Literature Review

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Received: Nov. 12, 2015; Accepted: Mar. 23, 2016

Abstract

Pulmonary embolism (PE) is a well-documented complication of orthopedic trauma. Multiple studies have provided data on the prevalence of PE, the probability of death from a PE, and the risk factors for PE development after lower extremity and pelvic trauma.

Venous thromboembolism (VTE) during hemiarthroplasty is considered a relatively rare phenomenon but can be a dangerous and life-threatening condition. Here we report a case of a 56-year-old woman who died from PE resulting from lower limb deep vein thrombosis during hemiarthroplasty under spinal anesthesia. This case raises awareness of the need for precautions against VTE following orthopedic surgery and shed light on the identification of high-risk patients. We also review the current literature and recommendations for prophylaxis against VTE.

Key words: Pulmonary embolism, venous thromboembolism, intraoperative complications, bipolar hemiarthroplasty

Introduction

Venous thromboembolism (VTE) is a condition that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Thrombi formation is associated with the Virchow's triad, i.e., circulatory stasis, vascular wall injury, and a hypercoagulable state. Most data on VTE in orthopedic surgeries are based on studies on patients who undergo hip or knee arthroplasty. The risk of VTE following lower limb surgery is considerably higher than that following upper-limb surgery. Here we describe and discuss a case in detail to reveal the possible contributing risk factors. This case aimed to increase awareness of this relatively rare but potentially serious complication.

Case Report

A 56-year-old woman, 158 cm in height and 62 kg in weight, was admitted to our hospital via the emergency room due to a left femur neck fracture. The patient had a 5-year history of hypertension, which was relatively well controlled with the medication regimen of an antihypertensive agent. She exhibited cardiomegaly on the preoperative chest X-ray, an ejection fraction of 68% on echocardiography and EKG, other blood studies, and her vital signs were within the normal limits. The preoperative PT/PTT was 12.5/23.4 s, INR was 1.12, and the arterial blood gas analysis revealed the following: pH of 7.376, PaO_2 of 80.2 mmHg, and $PaCO_2$ of 30.5 mmHg.

On the fifth hospital day, she was scheduled to undergo bipolar hemiarthroplasty. Upon her arrival at the operating room, standard monitoring devices were applied. Her blood pressure, heart rate, and O_2 saturation were 136/62 mmHg, 78 beats/min, and 99%, respectively; she was fitted with a simple facial mask with 4 L/min of oxygen. Spinal anesthesia was administered with the patient placed in the left lateral position using a 26-gauge Quincke spinal needle at the L3-4 interspace with 0.5% heavy bupivacaine (10 mg) under standard aseptic conditions.

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The patient was then placed in the supine position, and the pin-prick test was performed; the paresthesia level reached T10. The patient was hemodynamically stable with a systolic pressure of 120 mmHg, a heart rate of approximately 80 beats/min, and O_2 saturation approximately 99%, with 100% oxygen under a face mask. The patient was placed in the right lateral position after adequate anesthesia. Her general condition was satisfactory during the first 55 min of anesthesia, and systolic blood pressure remained above 110 mmHg. She was intravenously administered 5000ml normal saline, as the estimated blood loss was 200 ml in the first hour. After assembling the non-cemented prosthesis, she developed a sudden and progressive bradycardia of 40–50 beats/min and her blood pressure decreased to an undetectable level with non-invasive blood pressure monitoring. Injection of adrenaline 1 mg was given intravenously, but in vain. Emergency endotracheal intubation and ventilation with 100% oxygen and external cardiac massage was started. Rapid infusion of normal saline (total 1000 ml) and adrenaline (1 mg) were given intravenously and repeated every 3 min (total 10 mg). Central venous catheterization via the right internal jugular vein was performed to administer the drugs and for hemodynamic monitoring. The central venous pressure was 32 mmHg. The operation wound was closed immediately and the patient was transported to the intensive care unit. Echocardiography and a CT scan were performed when the patient's hemodynamic parameter became temporarily stable. Echocardiography revealed an enlargement of the right atrium and right ventricle, straightening of the interventricular septum, and hypokinesia, both of which were consistent with PE. The CT scan showed bilateral pulmonary embolism and bilateral kidney infarction (Figs. 1 and 2). Forty-five minutes later, her heart beat decreased to 30 beats/min and cardiopulmonary resuscitation was performed. During the following one hour resuscitation, ventricular fibrillation persisted even after defibrillation with 360 joules direct current and acidosis correction with bicarbonate. After five cycles of cardiopulmonary resuscitation, the patient developed pulseless electric activity and could not be revived after one hour of resuscitation. The patient was pronounced dead at the intensive care unit two hour later. The patient's relatives did not consent to autopsy.

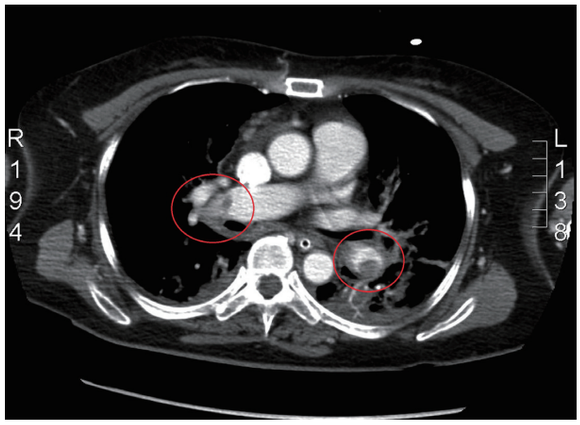

Fig. 1 Bilateral pulmonary embolism with thrombus noted in the right main pulmanary artery and left inferior pulmonary artery.

Discussion

PE would is a fatal disease unless a prompt treatment is taken. In particular, it is known to commonly occur following the onset of fracture of the lower extremities and surgery. Other risk factors include an age of 40 years or older, long-term bed rest, a malignant tumor, multiple trauma, a past history of PE, obesity, congestive heart failure, and a long-term use of estrogen [1]. PEs occurring during anesthesia

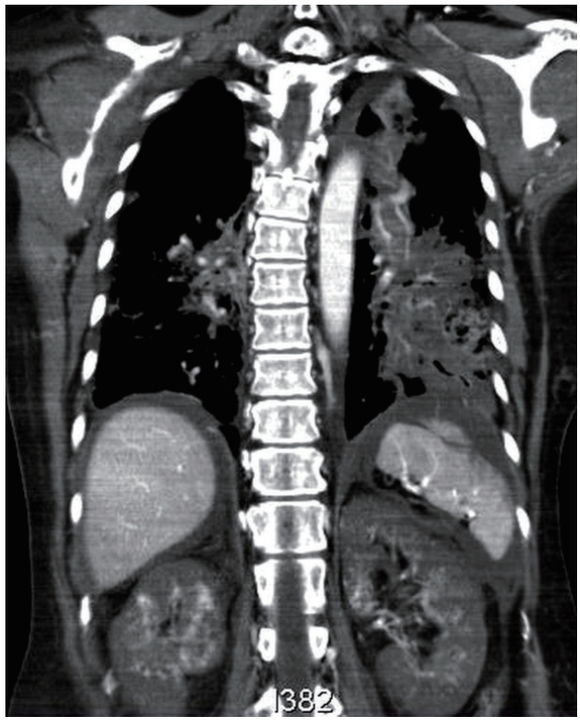

Fig. 2 Bilateral kidneys hypoperfusion, mainly involving renal cortex, suspect ischemic changes.

or surgery always bewilder anesthesiologists and surgeons. They are, however, also fatal diseases that raise mortality or morbidity. Lower limb surgery is a risk factor for VTE events. The prevalence of DVT in patients who undergo hip fracture surgery and hip or knee arthroplasty ranges from 40% to 60% [2,3]. Total hip arthroplasty (THA) is one of the most common surgeries associated with venous thrombosis [4,5] with DVT forming in up to 70% of patients with no prophylaxis [6]. The pathophysiology of thrombus formation after a THA is partially due to endothelial injury. This can occur via kinking of the femoral vein during manipulation of the leg or through direct vascular injury, which may release clotting factors from the endothelium [4]. In addition, venous stasis may occur as a result of immobilization after surgery or swelling in the affected leg, and coagulability may be increased by thromboplastin release from the femoral canal [4]. Prolonged surgery may involve prolonged immobilization and blood loss, which in turn increase the risk of VTE, based on Virchow's triad. It is possible that prophylaxis for VTE is necessary in lower limb surgery when the surgery is delayed and the patient is immobilized for several days.

The American College of Chest Physicians (ACCP) [7,8] recommends the use of VTE prophylaxis for a minimum of 10 to 14 days following major orthopedic surgery. In patients who undergo total joint replacement, the ACCP suggests the use of low-molecular-weight heparin (LMWH) in preference to other agents (such as fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin, adjusted-dose vitamin K antagonist or aspirin), irrespective of the concomitant use of an intermittent pneumatic compression device. For those patients who refuse injections, apixaban or dabigatran is recommended.

In addition to LMWH, the National Institute for Health and Care Excellence clinical guideline and the American College of Chest Physicians (ACCP) also mention the newer non–vitamin K antagonist oral anticoagulants (NOACs) [7,8]. This group of drugs is associated with a rapid onset of action and predictable pharmacokinetics and pharmacodynamics. There are also fewer interactions with food and other drugs. When prescribing VTE prophylaxis, it is important to balance the associated benefits and risks. Pharmacological prophylaxis should be considered for those who are at relatively high risk of developing VTE—for example, patients who have more than one risk factor, and those for whom there will be a delayed operation and immobilization for several days.

Respiratory difficulty, hypoxia, and tachycardia were the most common symptoms that led to the diagnosis. A fall in end-tidal CO_2 concentration can be the first sign of pulmonary embolism. In conscious patients, initial symptoms can include dyspnea and altered sensorium. Transesophageal echocardiography has been recommended as a diagnostic technique for rapidly confirming the diagnosis of PE. Secondary signs of acute pulmonary artery obstruction, such as the leftward bowing of the interatrial septum, or acute right ventricle dysfunction, may be helpful in supporting a clinical diagnosis of PE in conjunction with other clinical signs. We should maintain a high level of vigilance when these symptoms are identified during surgery.

In conclusion, meticulous monitoring of the clinical course, a prompt diagnosis and accurate treatment in an operating theater should be mandatory.

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雙極人工股骨頭置換術過程中發生致命的肺栓塞：病例報告及文獻回顧

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受文日期：民國 104 年 11 月 12 日；接受刊載：民國 105 年 03 月 23 日

摘要

肺栓塞是骨科手術中的一個已有充分證據的併發症。多個肺栓塞的研究已提供了關於肺栓塞的患病率，死亡率和下肢和骨盆創傷後危險因子的數據。

靜脈血栓栓塞發生在人工股骨頭置換術被認為是一種相對較少的現象，但可以是一個危險和威脅生命的併發症。我們報告一位 56 歲的女性在腰椎麻醉下進行人工股骨頭置換，過程中由於下肢深靜脈血栓引起致命的肺栓塞。這案例提高我們對骨科手術和辨別高風險患者對於靜脈血栓栓塞的防範意識。我們也檢討現行的文獻和建議對靜脈血栓栓塞的預防方法。

關鍵詞：肺栓塞、靜脈血栓栓塞、術中併發症、雙極人工股骨頭置換術

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Case Report

Delayed Hemorrhage from Puncture Site After Central Venous Catheter Misplacement

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Received: Nov. 12, 2015; Accepted: May. 03, 2016

Abstract

Central venous catheter (CVC) insertion is a common procedure in major operations and functions to provide fluid access and a parameter in hemodynamic monitoring. However, CVC insertion is risky, resulting in complications, such as arterial injury, stroke, and hematomas. Here we reveal a case on an incident that occurred during CVC insertion. The catheter misplacement resulted in the extravasation of the right common carotid artery. For this case, we concluded that surgical management would be the most effective to safely treat arterial puncture during jugular vein catheterization.

Key words: common carotid artery, extravasation, surgical ligation

Introduction

Central venous catheter (CVC) insertion is a common procedure in major operations that provides fluid access and the means to monitor hemodynamics. However, CVC insertion can be risky [1]. We describe a case on an incident that occurred during CVC insertion.

Case Report

A 73-year-old man with a thoracic spine compression fracture was scheduled for surgery. After the induction of general anesthesia, central venous catheterization and arterial line installation were planned for hemodynamic surveillance. The right internal jugular vein was the chosen site for insertion. At the beginning of this procedure, the landmarks at the puncture site were determined and sterilized. On palpating the right common carotid artery and at the first attempt on its lateral side using a small-gauge test needle, dark red venous blood was aspirated out. The point of catheter insertion was marked, and the Seldinger technique was followed [2,3] for CVC insertion. However, soon after the catheter was connected to the infusion line, dark, but not fresh, red blood pulsated out in the reverse direction. A puncture into the common carotid artery was recognized. CVC was immediately removed, and then compression was applied at the puncture site for 10 min. In the meantime, the patient's mean blood pressure was 85 mmHg. The remedy was to insert another CVC into his left internal jugular vein. This procedure was smooth, and the connected intravenous line drained well as the infusion bag was lowered below the patient. Subsequently, the surgery was completed uneventfully. When the patient was transferred to the post-anesthesia recovery room, he was awake, alert, and clear, and his right neck was supple and without hematoma. However, he contracted some irritable cough. After returning to the ward, his coughs became more strenuous. Approximately 2 h later, the right side of his neck had enlarged and become swollen. Breathing was compromised, which required endotracheal intubation. He was then transferred to the ICU for further

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investigation. Through CXR and CT scan examinations (Fig. 1-3), active extravasation from the anterior wall of the right common carotid artery at C6 level, with a huge hematoma approximately 7.7 × 6.4 × 10.9 cm along his right deep neck region, was revealed. The compression and deviation of the trachea were noted. Without delay and under general anesthesia, surgical exploration with the ligation of the injured site was performed. The bleeder was checked, and the wound was closed. The follow up CXR revealed that the swelling on the right side of his neck had diminished. However, he was diagnosed with pneumonia and remained intubated for 2 weeks before being discharged from our hospital.

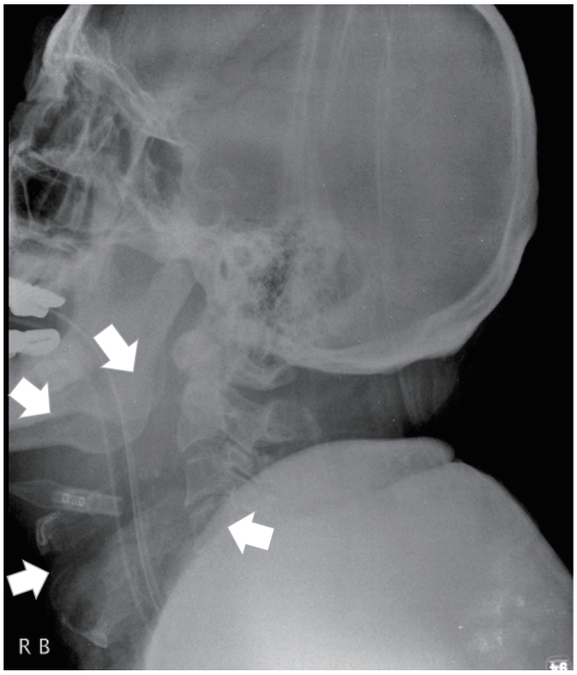

Fig. 1 Huge swelling of anterior neck region

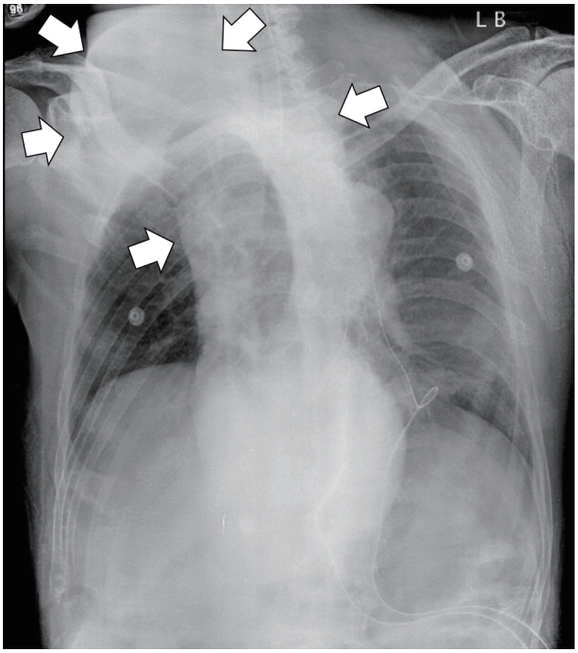

Fig. 2 Active extravasation of ruptured right common carotid artery with mediastinum widening.

Discussion

Serious complications, including hematomas, arterial injury, pneumothorax, stroke, and even death, can occur due to improper CVC insertion [4]. In our case, a huge hematoma was formed that compressed the trachea, compromised breathing, and occupied the mediastinal space. In future, we recommend the use of ultrasound probe guiding to decrease placement attempts, errors, and complications and increase successful insertion rates. In addition, central line associated bloodstream infection may also be minimized [5].

We speculated that the patient's vigorous movement of his neck while coughing may have caused the blood clot to detach from the puncture site of the arterial wound. Thus, it may have been necessary to compress at the puncture site for longer than 10 min.

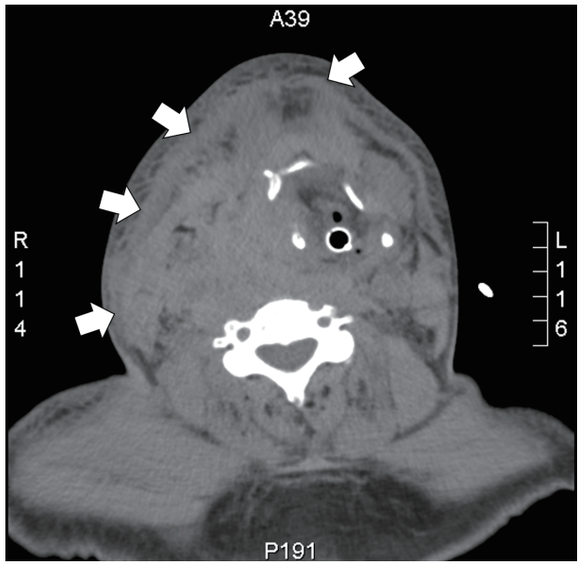

Fig. 3 Huge hematoma at C6 level with deviation of the trachea.

Increased vigilance for hematoma formation would also be necessary for future cases. Preoperatively, the patient was poorly nourished and had a history of chronic bronchitis. Such factors may have induced his vigorous coughing after post-anesthesia extubation [6,7]. Furthermore, before the operation, his coagulation profile data was within the normal range, but 4 months after this incident, he was diagnosed with multiple myeloma and received a chemotherapy course. Because of this oncohematologic disease, a retrospective consideration of the patient's increased potential of bleeding during operation is warranted.

Dark red blood aspirated through the small-gauge needle cannot be confirmed as being arterial or venous blood [8]. If the patient is at a low pressure state or has other respiratory problems, dark aspirated arterial blood may be obtained. Collecting arterial blood gas data would be necessary for proper identification. Moreover, connecting the inserted catheter to show waveforms would provide useful information to differentiate between arterial and venous blood [9]. Emergent and abrupt surgical ligation is the only option to find and mitigate an active extravasation of a pulsating artery [10].

Based on this case, we suggest that the most dependable method for CVC insertion is via ultrasound probe guidance. It might facilitate the differentiation between an artery and a vein. Site with collapsed internal jugular vein or no vessel should not be considered for CVC insertion [5]. Such guidance may minimize CVC misplacements and decrease patient complications. In other fields, such as radiology or cardiology, a guide wire for catheterization is simultaneously applied during fluoroscopic examination, which greatly minimizes the possibility of catheter misplacement. However, this is not a common practice in anesthesiology, but for better patient care, such techniques may need to be considered.

Conclusions

In our case, surgical management was the most effective to safely treat the ruptured common carotid artery with active extravasation. Further study is needed to determine the optimal management and prevention of CVC misplacement.

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中央靜脈導管錯位置入後引發穿刺部位延遲性出血

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受文日期：民國 104 年 11 月 12 日；接受刊載：民國 105 年 05 月 03 日

摘要

中央靜脈導管（CVC）之置入是具有調節流體容積的功能和監測血液動力學參數的通用方法，但它是有相當程度的危險性。我們將披露一宗 CVC 的事件。不幸的是，由於該導管錯位置入，導致總頸動脈的外滲。我們的結論指出於本病例中外科手術處理似乎是內頸靜脈導管錯位置入內頸動脈而後引致外滲之情況時，為最有效、最安全的處置。

關鍵詞：總頸動脈、血管外滲、外科結紮

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Case Report

Distraction Histiogenesis for the Treatment of Lichtman Stage II Kienböck's Disease: A Case Report

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Received: May. 09, 2016; Accepted: Aug. 02, 2016

Abstract

Kienböck's disease is a rare disorder of wrist which eventually shows osteonecrosis of the carpal lunate. Untreated, the disease usually results in fragmentation of the lunate, collapse with shortening of the carpus. However, there is no consensus regarding treatment, whether conservatively or surgically. Various surgical treatments have been described with varying outcome. Different stages of the disease also warrant different surgical treatment. Here we report our experience in the treatment of a patient with Lichtman stage II Kienböck's disease. Debridement of necrotic lunate bone was performed, followed by distraction with an external fixation device. Our result indicate favorable functional outcome with improvement in wrist strength and mobility. Further studies are necessary to understand the full potential of our treatment.

Key words: Kienböck's disease, distraction histiogenesis, osteonecrosis, lunatomalacia

Introduction

Kienböck's disease is a disorder of the lunate which occurs mainly among patients between 20 and 40. Various methods of treatment have been used since its description by Robert Kienböck in 1910. Patients complained of pain, loss of mobility, and prominence in the area of the wrist. Radiographic evaluation may show isolated changes in the proximal aspect of the lunate, with eventual collapse and fragmentation of the bone.

Various surgical procedures have been proposed, depending on the stage of pathological development and on anatomic variables such as ulnar variance and radial inclination[1]. Proposed procedures include radial shortening[2], ulnar lengthening[3], conventional or pedicled vascular bone graft[4], arthrodesis[5], proximal row carpectomy[6] and arthroplasty[7].

In the hope to simplify a surgical procedure that is easily accessible and familiar to general orthopedic surgeons, we applied the principle of distraction histiogenesis as used in Perthes disease in children[8, 9]. We hypothesized that debridement of necrotic bone will start the healing process, which when combined with distraction of the carpus will unload and relief the injured bone, increase vascularity of the region and help maintain the health of the lunate bone. In addition, lunate height is maintained while healing occurs.

Case report

A 32-year-old Asian man, who is a labor intensive worker, came in with the complaint of left wrist pain, decreased grip strength and limited range of motion, noted for 1 month. He is previously healthy with no traumatic accident to his left wrist. Roentgenogram revealed loss of radial-lunate joint space and mild

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sclerotic change over lunate bone (Fig 1a). His magnetic resonance imaging (MRI) demonstrated long T2 signal on the lunate with loss of normal short T1 signal (Fig 2a, b), suggesting osteonecrosis of lunate bone (Kienböck's disease). It is a Lichtman stage II disease, where the outline is normal, but definite density changes are present within the lunate.

Operative treatment with volar wrist approach was performed. Necrotic bone over lunate bone near the radial-lunate joint was carefully debrided with preservation of general structure of the bone. After wound closure, we applied external fixator device commonly used for operative reduction of distal radial fracture. Some distraction force was applied before tightening down the external fixation device.

The patient was discharged the next day. The external fixator device was removed 2 months post-operatively. Due to extended joint fixation, some loss of range of motion and disuse osteoporosis was noted on follow-up roentgenogram. However, improved contour of radial-lunate joint line is observed (Fig 1b). Rehabilitation program followed and on the third month follow-up, the patient revealed pain free wrist with good range of motion and grip strength.

Discussion

The goals of treating Kienböck's disease include prevention of further osteonecrosis and collapse and restoration of lunate to normal alignment and function [10].

Conservative treatment with wrist immobilization such as casting may be considered for early stage disease (Lichtman stage I or II). However, with unpredictable outcome and extended length of immobilization (may require 4 months or more), it is quite unacceptable for patients[11].

Joint leveling procedures include ulnar lengthening and radial shortening and usually are indicated for Lichtman stage I through IIIA Kienböck's disease, with a negative ulnar variance and without degenerative changes in the radiolunate or capitolunate joints [11]. However, as reported by Ryogo Nakamura [12], not all patients with Kienböck's disease have negative variance. Patients with ulnar-positive or ulnar-neutral variance cannot undergo a joint leveling procedure.

Sources of vascularized graft for lunate revascularization procedures include the distal radius based on the pronate quadratus, the pisiform as a pedicle

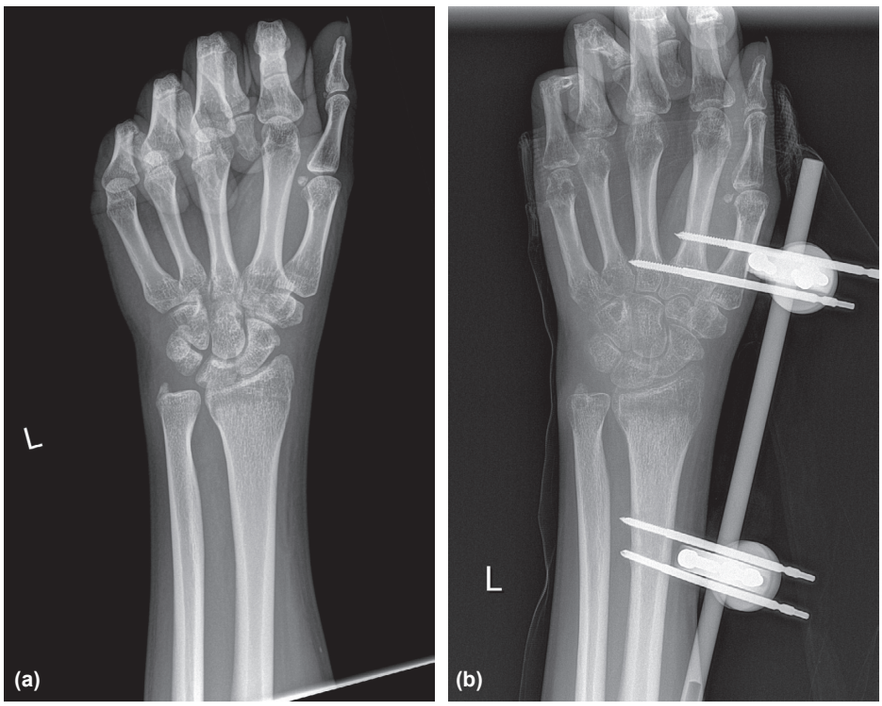

Fig. 1 (a) Initial presentation. Roentgenogram revealed loss of radial-lunate joint space and mild sclerotic change over lunate bone. (b) Two months post-operative, before external fixator removal. Disuse osteoporosis was noted on follow-up roentgenogram. However, improved contour of radial-lunate joint line is observed.

graft, and various other grafts from the distal radius, second metacarpal, and pisiform[11]. However, such procedures put a great demand on technical and surgical expertise[13], and cannot be reliably performed by surgeons with less experience. Moreover, most reports reflect that the promising early radiographic changes may not persist over time, and in many patients there is further deterioration in radiographic and clinical results[11].

Temporary internal fixation of the scaphotrapezio-trapezoidal (STT) joint for the treatment of Kienböck's disease is another viable option for early stage diseases[14,15]. This is slightly less effective in reducing the load across the lunate with progressive ulnar deviation of the wrist. This procedure aims to decompress the lunate by shifting the load transferred through the wrist via the capitoscaphoid and radioscaphoid joints. It also may prevent the radiocarpal arthrosis that is secondary to rotary subluxation of the scaphoid following lunate collapse [14]. Complications occurring during temporary fixation included K-wire loosening and breakage. However, without associated vascular procedure, the positive effect of STT is still uncertain.

Advanced stage Kienböck's disease leads to destruction of other carpal bones and severe loss of wrist function. In advanced stages, patient may require extensive procedure such as proximal row carpectomy. However, proximal row carpectomy may not be appropriate for Kienböck's disease since lunate collapse damages joint surfaces of the capitate and radius. Wrist arthrodesis is indicated in persons who use their hands for heavy labor, have severe degenerative changes, or fail to improve following other surgical procedures. Our aim is to hold the progression of Kienböck's disease and hopefully stop extensive destruction of the wrist joint.

In order to find a less technically demanding procedure for the treatment of Kienböck's disease and prevent associated complications, we applied the principle of distraction histiogenesis as used in Perthes disease in children[8,9]. Debridement of necrotic bone will start the healing process where osteocytes become viable. Distraction of the carpus will unload and relief the injured bone, increase vascularity of the region and help maintain the health of the lunate bone. The combination will provide a biologically viable bed for the surviving osteocytes. In addition, lunate height is maintained while healing occurs.

In our particular case, the patient's roentgenogram did not reveal ulnar-negative variance, thus the

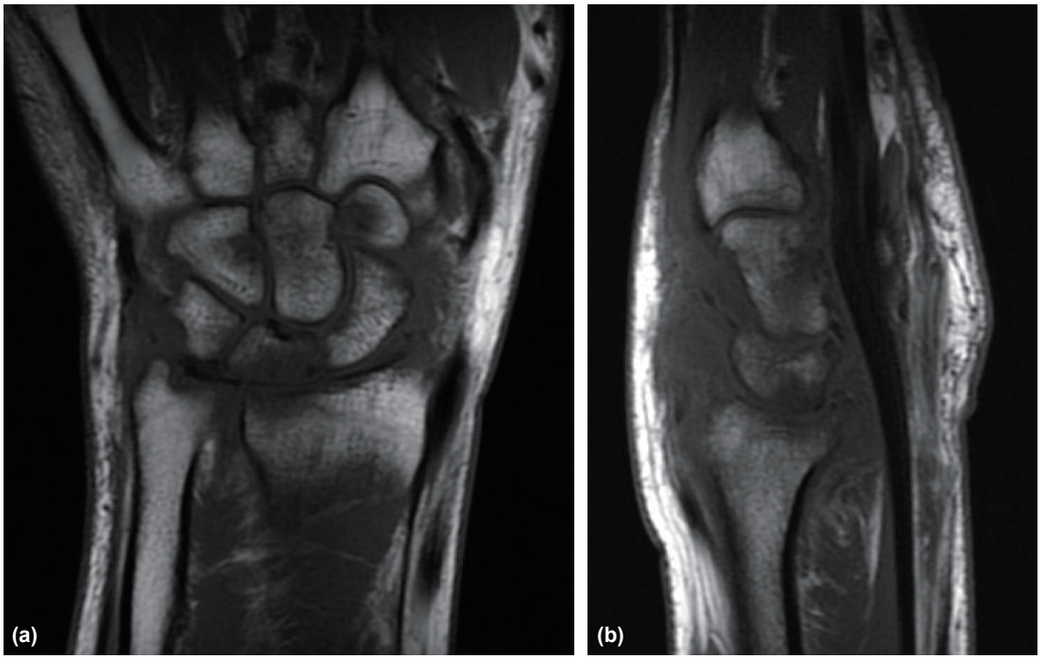

Fig. 2 (a) MRI of wrist demonstrated loss of normal short T1 signal on the lunate, suggesting osteonecrosis of lunate bone. (b) MRI of wrist demonstrated loss of normal short T1 signal on the lunate, suggesting osteonecrosis of lunate bone.

patient cannot undergo a joint leveling procedure. Due to the relatively early stage of the disease (Lichtman stage II), we decided to utilize a simple and familiar procedure that young orthopedic surgeon can comfortably perform instead of technically demanding procedures such as vascularized graft. The debridement procedure uses standard volar wrist approach, which is safe and familiar to general orthopedic surgeons. Distraction was done after wound closure with a simple external fixation device commonly used for treatment of distal radial fracture. The application of such external fixation device is familiar to most orthopedic surgeons.

This procedure is not without complications. The extended length of fixing a wrist with an external fixator device produces wrist joint stiffness with limited mobility. Although rehabilitation program should be followed afterwards, sometimes patient cannot regain his previous level of strength or mobility, resulting in loss of wrist function. Another common complication with using external fixator device is pin tract infection. With careful patient education and wound care, such complication still occurs from time to time. Oral antibiotics combined with local wound debridement should allow retaining of the external fixator device.

In conclusion, our method of treating Kienböck's disease resulted in good symptomatic relief, with return to normal activities. It is unfortunate that Kienböck's disease is a rare occurrence. Our method of treatment requires further experience and research. To our knowledge, there were only a few reports on the treatment of Kienböck's disease with distraction histiogenesis [10]. Using the distraction principle, osteonecrosis of other bones may also benefit from this method of treatment.

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病例報告：以牽引骨增生之方法治療第二期的月狀骨無菌性壞死

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受文日期：民國 105 年 05 月 09 日；接受刊載：民國 105 年 08 月 02 日

摘要

月狀骨無菌性壞死是手腕的一種罕見的疾病，最終會造成腕部月狀骨完全壞死。如不積極治療，這種疾病通常會導致月狀骨碎裂，塌陷與腕骨縮短。然而，現階段關於治療沒有達成共識，方法包括保守或手術治療。各種手術治療的方法已有多種嚐試，各種手術方法也有達成其不同的預後。在此疾病的不同階段手術治療的方法也不盡相同。在此篇文章，我們報告了一位月狀骨無菌性壞死第二期病患的手術治療經驗。我們手術進行月狀骨死骨清創，接著使用外固定支架來達到牽引骨增生的作用。我們的結果顯示，這位病患在手腕的力量和活動性都有不錯的改善，有利於功能的恢復。應行進一步研究來了解這種治療方法的全部潛力。

關鍵詞：月狀骨無菌性壞死、牽引成骨術、骨壞死

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Tungs' Medical Journal 11 (2017) 44-49

Case Report

Fentanyl-Induced Muscular Rigidity and Pulmonary Edema after Induction of General Anesthesia: A Case Report

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Received: Nov. 18, 2015; Accepted: Mar. 02, 2016

Abstract

We present and discuss a case of a 48-year-old woman who developed muscular rigidity and acute pulmonary edema after the administration of a lower dose of fentanyl as the primary agent during the induction of anesthesia. The patient experienced difficulty in breathing and could not be ventilated using an O_2 mask and was thus immediately administered a 1.5-mcg/kg bolus of fentanyl. Other clinical symptoms such as loss of consciousness, tight mouth closure, thoracoabdominal rigidity, and rapid peripheral capillary oxygen desaturation also developed in the present case. Airway compromise was treated by endotracheal tube intubation followed by an intravenous administration of thiamylal sodium (300 mg), rocuronium (50 mg), and propofol (100 mg). Acute pulmonary edema was diagnosed because there were observations such as high peak airway pressure, an ascending slope of graph on capnogram, chest auscultation with rales over bilateral lungs, and pink foamy secretions spilled over from the endotracheal tube. Postoperative plain chest X-ray confirmed the diagnosis of acute pulmonary edema. The patient had no history of asthma or any pulmonary or cardiac disease. The occurrence of pulmonary edema could only be explained as negative pressure pulmonary edema due to fentanyl-induced muscular rigidity that resulted in glottic closure with the involvement of all skeletal muscles.

Opioid-induced muscle rigidity, although uncommon, may result in life-threatening respiratory compromise and requires a high level of suspicion and prompt intervention.

Key words: Anesthesia, Opioids, Muscular Rigidity, Pulmonary Edema

Introduction

Direct laryngoscopy and tracheal intubation are noxious stimuli that can provoke adverse responses in the cardiovascular, respiratory, and other physiologic systems. These adverse responses can be attenuated by intravenous opioids that are widely used during the induction of anesthesia.[1-3] High-dose opioid administration may be accompanied by prolonged respiratory depression and intense muscle rigidity.[4]

Opioid-induced muscle rigidity was first described by Hamilton and Cullen in 1953.[5] Since the introduction of fentanyl in anesthetic practice (1981), fentanyl-induced muscle rigidity has been reported both in adults and children.[6,7] Thereafter, opioid-induced muscle rigidity became a well-documented side effect, most commonly observed with lipophilic synthetic opioids such as fentanyl, alfentanil, remifentanil, and sufentanil, although its pathophysiology is yet to be clarified.[8,9] However, muscle rigidity is not a common adverse effect, and its incidence remains unknown.

Although muscular rigidity has been exclusively reported in patients that have received large doses and rapid administration of opioids,[10] a number of reported cases have demonstrated a correlation between muscle rigidity and lower doses of opioids[11-14] Muscle rigidity involving the respira-

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tory muscles is a serious complication that must be immediately diagnosed and treated. Patients unable to breathe or be ventilated during anesthesia may develop hypoxemia and hypercarbia, leading to respiratory and cardiovascular complications and thereby increasing morbidity and mortality.

We report the case of a patient who developed both muscular rigidity and acute pulmonary edema after the administration of a dose of fentanyl. Acute pulmonary edema caused by fentanyl-induced muscle rigidity during the induction of anesthesia, as observed in the present case, has not previously been reported in the literature. These unusual reactions require prompt recognition and appropriate interventions to prevent poor outcomes.

Case Report

A previously healthy 48-year-old (height, 150 cm; weight, 70 kg; ASA, II) female was scheduled for laparoscopic operation owing to a right ovarian tumor. Her previous surgical history included three cesarean sections and laparoscopic cholecystectomy. She denied any drug allergies and had no history of pulmonary or cardiac events or adverse anesthetic reactions. Preoperative laboratory data, plain chest X-ray (CXR), and electrocardiography (EKG) were normal.

After setting up routine intraoperative monitors, including electrocardiogram, a non-invasive blood pressure device, a pulse oximeter, and capnogram, preoxygenation using face mask with 100% oxygen was performed, followed by the administration of general anesthesia using anesthetics. After rapid intravenous administration of fentanyl at a dose of 1.5 mcg/kg, the patient suddenly developed severe cough and became apneic. It was difficult to manually ventilate the patient with the O_2 mask and an oropharyngeal airway was impossible to place because it was not possible to open the patient's mouth. Despite the insertion of a nasopharyngeal airway, attempts to ventilate the patient with the O_2 mask remained unsuccessful. The patient demonstrated a paradoxical breathing pattern and rigid chest wall. Pulse oximetry (SpO2) values dropped to 40% after airway manipulation for a short duration. Subsequently, tracheal intubation was promptly performed as soon as thiamylal sodium (5 mg/kg), rocuronium (0.6 mg/kg), and propofol (1.5 mg/kg) were intravenously administered. Once the placement of endotracheal tube was confirmed, the patient was mechanically ventilated with 2% sevoflurane in 100% oxygen. The SpO2 increased to 100% after a few cycles of mechanical ventilation with a setting of the tidal volume at 700 ml and respiratory rate of 12 breaths/min. Peak airway pressure raised to approximately 43 cm H_2O. An ascending slope of graph on capnography and an end-tidal CO_2 ($ETCO_2$) value as high as 45 mmHg were observed. Chest auscultation revealed no wheezing but rales over bilateral lung fields. Despite administering two puffs of fenoterol (100 mcg/puff) via the endotracheal tube, the airway

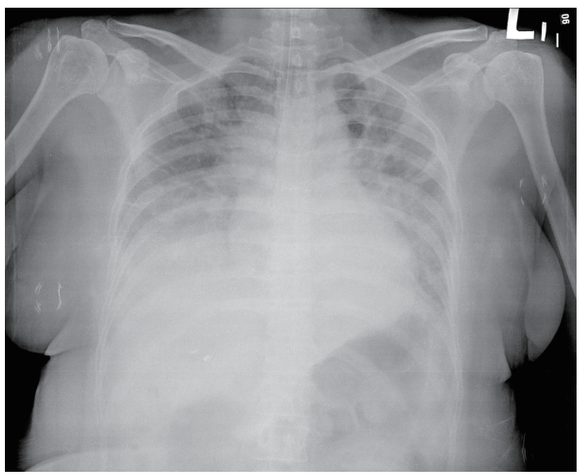

Fig. 1 Postoperative chest x-ray taken at the arrival of the intensive care unit reveals increased interstitial opacity throughout bilateral lung.

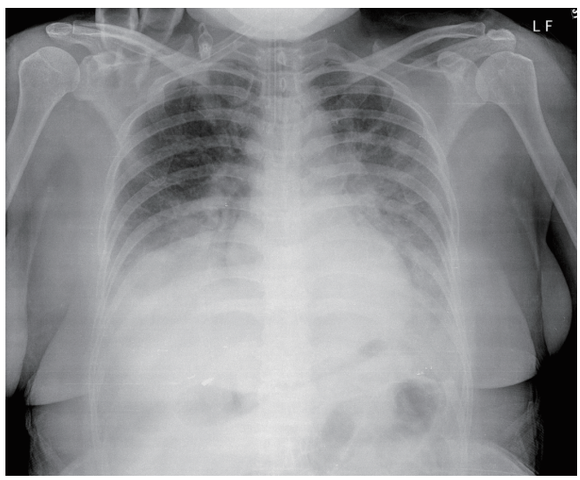

Fig. 2 Much improvement of the pulmonary condition on the next day after operation.

pressure persistently remained high. Accordingly, the surgeon was informed and the operation was converted to a laparotomy. The patient's blood pressure and heart rate were stable, except for the high airway pressure, throughout the operation. At 1 h into the operation, pink foamy secretions emerged from the endotracheal tube. Arterial blood gas analysis while receiving a FiO_2 of 100% demonstrated the following: PaO_2, 96.11 mmHg; pH, 7.31; $PaCO_2$, 52 mmHg; and bicarbonate, 25.5 mEq/L. Morphine sulfate (5 mg) and furosemide (30 mg) were intravenously administered and a positive end expiratory pressure (PEEP) of 5 cm H_2O was maintained. The operation lasted for 3 h with an estimated blood loss of 100 ml. The total input of fluid was 800 ml of lactated Ringer's solution, and the urine output was 550 ml. Owing to the compromised airway and poor pulmonary oxygenation, the patient was transferred to the intensive care unit for postoperative care.

Postoperative CXR demonstrated severe bilateral infiltration that confirmed the proposed diagnosis of acute pulmonary edema (Fig. 1). Treatment strategies such as mechanical ventilation with a PEEP of 10 cm H_2O, intravenous diuretics and morphine, and serial arterial blood gas examinations were planned. The patient's oxygenation gradually improved and the FiO_2 was adjusted to 40% over the next two days. The follow-up CXR demonstrated resolution of edema in bilateral lung fields (Fig. 2). The endotracheal tube was extubated on postoperative day 4. The patient was discharged on postoperative day 7 without any sequelae.

Discussion

Although fentanyl-induced muscular rigidity has been exclusively reported in patients when large fentanyl dosages (>30 mcg/kg) were administered,[6,15] a number of reported cases have been observed with the administration of lower doses of opioids.[12,16] This rigidity can primarily involve the chest and abdominal musculature, resulting in the "wooden chest syndrome." Chest wall rigidity decreases chest wall compliance and leads to ineffective spontaneous ventilation and may also make ventilation difficult.[8,17] The mechanism underlying opioid-induced rigidity remains poorly understood, but it appears that the origin of rigidity lies outside the stretch reflex arc and in some other area of the spinal cord or higher areas of the central nervous system.[18,19]

Here we report a case of muscle rigidity induced by an unusually low dose of fentanyl and complicated with acute pulmonary edema. Only 1.5 mcg/kg of fentanyl was intravenously administered as the sole agent during the induction of anesthesia. Instantaneously, the patient developed severe cough and experienced paradoxical breathing. It was difficult to ventilate the patient and the insertion of an oropharyngeal airway also failed due to the inability to open the patient's mouth because of masseter muscle spasm.[20] Glottic rigidity was suspected as the cause of the severe cough and paradoxical breathing pattern, which resulted in acute pulmonary edema due to glottic closure and negative pressure breathing.[21,22] Bennet *et al.*[22] and Abrams *et al.*[23] reported ventilatory difficulty induced by sequential vocal cord closure, jaw closure, and thoracoabdominal rigidity; however, they did not report acute pulmonary edema, as observed in the present case, despite endotracheal intubation and successful ventilation. Muscular rigidity typically develops within 1–2 min of opioid administration,[4] but it may develop as quickly as 40 s after a fentanyl injection,[13] with all skeletal muscles ultimately involved.[4] That was why the chest wall and abdomen became very rigid and successively ceased movement in our case.

To ventilate and oxygenate the patient, tracheal intubation was performed as soon as hypnotics and a muscle relaxant (rocuronium) were intravenously administered. Although the SpO2 increased to 100%, the peak airway pressure remained as high as 43 cm H_2O. Acute pulmonary edema was demonstrated by capnography changes, abnormally high $ETCO_2$ and $PaCO_2$ values, a high airway pressure, bilateral rales, and a pink foamy secretion from the endotracheal tube. Negative pressure pulmonary edema developed due to closure of the glottis as a part of the initial process of muscle rigidity.

Muscle rigidity is a less common adverse effect of lower doses of opioids. Although its incidence is unknown, muscle rigidity may develop in 50%–100% of patients administered large doses of opioids.[25] Chest wall rigidity is a serious complication that must be immediately treated. Respiratory and cardiovascular complications may develop from hypoxemia and hypercarbia, resulting in morbidity and mortality. Other complications, such as gastric insufflation, may be caused by persisting attempts to mask ventilate a

patient with muscular rigidity. To date, no objective methods or monitoring approaches have demonstrated utility in detecting the occurrence of opioid-induced rigidity. However, electromyographic studies have demonstrated that many narcotics increase the abdominal muscle tone, especially when supplemented with nitrous oxide.[26,27] Therefore, the diagnosis of opioid-induced rigidity must rely on clinical experience and vigilance of the anesthesiologist.

Muscular rigidity, difficult airway maintenance and ventilation, and acute pulmonary edema were the major problems in the present case and required appropriate and immediate management. Upon reviewing the literature, muscle relaxant or naloxone was found to be the most common drug used to successfully reverse the rigidity in previous case reports.[11-14] We administered a rapidly acting, nondepolarizing neuromuscular blocking agent at a usual intubating dose (rocuronium 0.5 mg/kg) for tracheal intubation to recover adequate ventilation and oxygenation and treat the pulmonary edema in our case.

A 7.6% incidence of delayed postoperative muscle rigidity has been reported and is probably related to the second peaks that can occur in plasma opioid concentrations.[4] Sung *et al.*[24] reported a case where 100 mcg of fentanyl was administered for induction of anesthesia, with muscular rigidity and pulmonary edema developing postoperatively at a postanesthetic care unit. Although opioid-induced rigidity is difficult to prevent, the risk can be reduced by slow injection of the opioid agent[28] and premedication with midazolam (0.1 mg/kg) or α_2-agonists such as clonidine and dexmedetomidine.[29,30]

In summary, the present case report describes an otherwise healthy woman who experienced fentanyl-induced muscular rigidity complicated with intraoperative acute pulmonary edema. The application of rapid muscular paralysis or naloxone reversion and airway control are imperative and should be immediately performed to prevent cerebral hypoxia. This side effect of fentanyl, although very rare, requires strict anesthesiologist vigilance and timely intervention to avoid potentially critical complications.

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病例報告：全身麻醉時 Fentanyl 引起的肌肉僵硬與肺水腫

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受文日期：民國 104 年 11 月 18 日；接受刊載：民國 105 年 03 月 02 日

摘要

一個 48 歲女性病人在全身麻醉誘導時注射 Fentanyl 引起肌肉僵硬與肺水腫。術後的胸部 X 光片證實了肺水腫的診斷。依據過去病史，病人並無氣喘或其他肺部疾病。唯一可能的解釋是麻醉誘導時注射的 Fentanyl 所致。Fentanyl 引起肌肉僵硬與肺水腫雖然罕見，但需靠麻醉醫師的高度警覺性，早期發現和及時處理，才能避免不良的後遺症。

關鍵詞：麻醉、鴉片類藥物、肌肉僵硬、肺水腫

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Tungs' Medical Journal 11 (2017) 50-53

Case Report

Emphysematous Pyelonephritis Patient Presenting with Hematuria: a Case Report

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Received: Nov. 19, 2015; Accepted: Apr. 07, 2016

Abstract

Emphysematous pyelonephritis (EPN) is a rare, severe, gas-forming necrotizing infection of the renal parenchyma and its surrounding areas. This report examines the case of a patient with EPN that initiated only with gross hematuria. After receiving a radical nephrectomy for impending septic shock, the patient was discharged in a stable condition after 1 month. The risk factors of EPN include alcoholism, malnourishment, renal calculi, and diabetic ketoacidosis. Patients with EPN should be treated using aggressive medical management and prompt surgical intervention, if necessary.

Key words: emphysematous pyelonephritis, hematuria, thrombocytopenia

Introduction

Emphysematous pyelonephritis (EPN) is a severe necrotizing infection of the renal parenchyma that causes the accumulation of gas in the skin tissue. EPN is common in patients with diabetes; it often has a fulminating course and can be fatal if not promptly recognized and treated.

Case Report

A 48-year-old female presented to the emergency department with gross hematuria without dysuria for 1 week. She had a past history of diabetes and hypertension but had not visited another doctor before presenting to our emergency department. A physical examination revealed clear breathing sounds and a soft abdomen without flank-knocking tenderness. She had a body temperature of 36.2℃, a pulse of 98 beats/min, and a blood pressure of 125/85 mmHg.

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Based on her past history and clinical examination, the patient was initially diagnosed with hematuria; therefore, an examination was arranged. Urine analysis (U/A) revealed >100 red blood cells (RBC) per high-power field (HPF) (normal range, 0–2 per HPF) and 61–80 white blood cells (WBC) per HPF (normal range, 0–5 per HPF). Both counts were well above the normal range. In addition, imaging of the kidneys, ureter, and bladder (KUB) displayed a streaky gas pattern over the entire right kidney (Fig. 1). Based on the U/A and imaging findings, blood tests were performed. The complete blood count (CBC) revealed leukocytosis (WBC count, 18 420) and thrombocytopenia (platelet count, 56 000/μL). Further laboratory data also showed elevated blood glucose (434 mg/dL), elevated creatinine (Cr, 4.43 mg/dL), and a high C-reactive protein (CRP) (CRP > 38.0 mg/dL) levels. Urinary tract infection with acute renal failure was the differential diagnosis.

Based on the abnormal laboratory results, an abdominal computed tomography (CT) scan without contrast was soon conducted, showing right renal and perinephric gas (Fig. 2). Therefore, right emphysematous pyelonephritis was highly suspected. Unfortunately, the patient's general condition worsened at

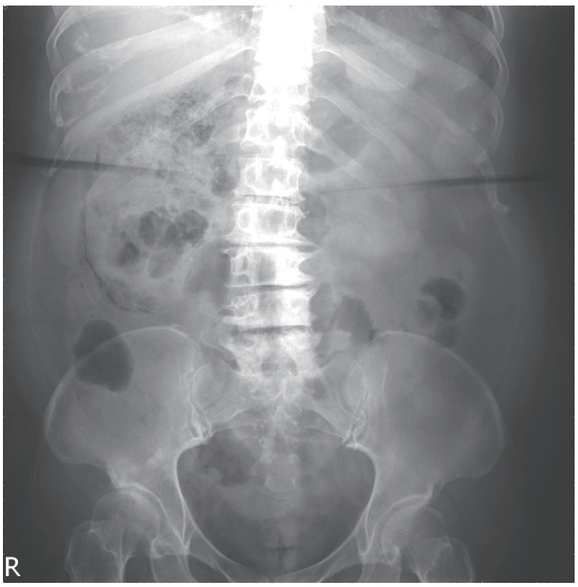

Fig. 1 KUB reveals gas distribution over the region of the right kidney.

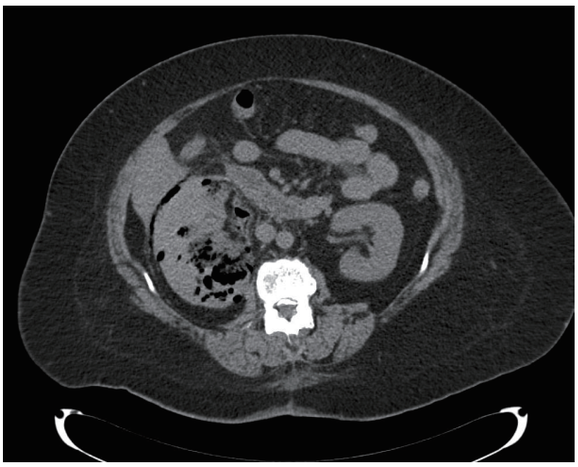

Fig. 2 CT reveals crescent-shaped gas accumulation in the right perinephric area.

the emergency department, including the onset of a fever and a drop in the blood pressure. A urologist was consulted, and an immediate radical nephrectomy was recommended and arranged because of impending septic shock.

The finding from the surgery was the same as that from the CT scan: right emphysematous pyelonephritis. The patient was admitted to the intensive care unit to control the infection using antibiotics postoperatively. Although the blood, urine, and kidney tissue cultures grew *Escherichia coli* (*E. coli*) with senstivity to cefazolin, flomoxef, and ciprofloxacin, the patient's condition remained unstable postoperatively and after 5 days of flomoxef treatment. The antibiotic was changed to ciprofloxacin according to the recommendation of the infection specialist, and the infection was gradually brought under control. The patient was discharged 1 month later with no postoperative complications.

Discussion

EPN is a severe infection of the renal parenchyma that causes accumulation of gas in the tissues. EPN is common in patients with diabetes; it often has a fulminating course and can be fatal if not promptly recognized and treated.

Patients typically have fever (79%), abdominal or flank pain (71%), nausea and vomiting (17%), dyspnea (13%), acute renal impairment (35%), altered sensorium (19%), shock (29%), and thrombocytopenia (46%)[1]. It is not uncommon for a patient to present only with gross hematuria. Comorbidities include alcoholism, malnourishment, renal calculi, and diabetic ketoacidosis. The laboratory findings include leukocytosis, pyuria, thrombocytopenia, elevated creatinine level, and positive blood culture results. Therefore, *E. coli* has been found to be the most common causative pathogen.

In the present case, KUB revealed gas distribution over the region of the right kidney, as depicted in the images below. CT scanning is the definitive imaging test for EPN. Several patterns have been described on CT images, including streaky, streaky and mottled, and streaky and bubbly. The appearance of the gas on the images can be rim-like or crescent-shaped in the perinephric area. Perinephric abscess can also lead to significant gas accumulation in the perinephric space.

Several different staging systems for EPN have been suggested. In 2000, Huang and Tseng modified the staging proposed by Michaeli et al. as follows [2]: Class 1, gas is confined to the collecting system; Class 2, gas is confined to the parenchyma alone; Class 3A, perinephric extension of gas or abscess; Class 3B, extension of gas beyond the Gerota fascia; and Class 4, bilateral EPN or EPN in a solitary kidney. The present case falls into the Class 3A category because the patient showed right renal and perinephric gas.

Patients with EPN should be treated using aggressive medical management and prompt surgical

intervention, if necessary. Conservative treatment using percutaneous drainage with antibiotics is advised when patients have localized areas of gas and functioning renal tissue. In more severe cases, nephrectomy may be required. Huang and Tseng reported a 66% success rate with percutaneous drainage and antibiotics in patients with EPN, whereas Aswathaman et al. achieved an 80% success rate [3]. Huang and Tseng also reported a 90% success rate with surgical treatment for patients who underwent nephrectomy.

Conclusion

EPN is a potentially serious, fulminant bacterial infection of the kidneys that is characterized by the accumulation of gas in the collecting system, renal parenchyma, and perinephric tissues. Prompt diagnosis of EPN is imperative and should be followed by aggressive medical management with antibiotics and possible surgical intervention to minimize life-threatening complications.

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一個以血尿為表現的氣腫性腎盂腎炎病人的病例報告

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受文日期：民國 104 年 11 月 19 日；接受刊載：民國 105 年 04 月 07 日

摘要

氣腫性腎盂腎炎為一少見且嚴重的產氣性腎臟壞死性感染，本案例病人臨床上僅以血尿為表現症狀，病人隨後因為休克而接受了腎臟切除手術並在一個月後康復出院。發生氣腫性腎盂腎炎的危險因子包括酒癮、營養不良、腎結石及糖尿病等，如發生氣腫性腎盂腎炎不但需積極治療且常需要外科手術方式介入。

關鍵詞：氣腫性腎盂腎炎、血尿、血小板低下

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Tungs' Medical Journal 11 (2017) 54-61

Case Report

Lumbar Intervertebral Disc Herniation and Work: A Case Report

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Received: Jun. 24, 2015; Accepted: Mar. 14, 2016

Abstract

It is known that ergonomic hazards usually contribute to the occurrence of musculoskeletal Cumulative Trauma Disorders (CTDs). Especially, lumbar intervertebral disc herniation (LIDH) is a common CTD. Here, we describe a 38-year-old worker with heavy loads at a steel plant for 8–11 hours per day. He began this work since May 2004, and a year consisted of approximately 260 workdays. He was mainly responsible for loading heavy metal materials weighing 20 to 50 kg. Further, the loads on his L4–L5 (4th and 5th lumbar vertebrae) were exceeded than 3200 N (Newton), and the cumulative exposure loads on the lumbar also reached proximally to 43 × 10^6Nh (Newton hour) over the criteria at 25 × 10^6 Nh, which according to the diagnostic criteria for the recognition of occupational LIDH established by our government, the above results exceeded the exposure threshold. A review of medical history revealed that the patient developed LIDH after work exposure, corresponding to the temporality in the diagnostic criteria. Also, medical literature indicates that prolonged loading of heavy materials with bending can increase the risk of LIDH. The patient has no personal history of major trauma, rheumatoid arthritis, or genetic or immunological diseases; hence, another general causes were also ruled out. After the occupational identification report was completed, the results were transferred to an appraisal review unit, and the patient received reasonable compensation. Currently, the patient is assigned a non-weight-loading task and receives regular rehabilitation.

Key words: ergonomic hazard, lumbar intervertebral disc herniation (LIDH), evidence of exposure, evidence of disease, appropriate temporality

Introduction

In recent years, both laborers and employers have realized that numerous diseases are related to occupations since our Occupational Safety and Health Administration (OSHA) promotes the safe and health services. Therefore, occupational diseases have gradually received more attention. The identification for occupational diseases differs from that of other medical conditions. Critically, occupational exposure data should be checked and evaluated by consulting with laborers and employers.

However, data on workplace environments may not be available; thus, complete exposure data may be difficult to obtain. It is also difficult to establish appropriate temporality for the relationship of occupational exposure and disease. Even, formulating a complete identification report for an occupational disease usually requires several weeks. In July 2013, an amendment was passed to rename the Labor Safety and Health Act as the Occupational Safety and Health Act[1] in response to the domestic industrial transformation and changes in the characteristics of jobs. Article 6 of this act lists musculoskeletal disorders that are induced by repetitive operations and related tasks. OSHA also developed prevention program

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guidelines for ergonomic hazards [2] to prevent musculoskeletal cumulative trauma disorder caused by repetitive operations. Occupational LIDH is common in individuals who often carry heavy loads or excessively bend over, such as porters, delivery workers, and construction workers. According to the principles in "Conjunctures and Refutations" proposed by Karl Popper[3], occupational diseases are identified using the following steps: considering evidence of occupational exposure, evidence of disease, temporality, epidemiological evidence (evidence in the medical literature), and other disease factors (differential diagnosis). In this report, the evaluation of occupational LIDH was conducted using the diagnostic criteria for the recognition of occupational LIDH[4] , which was set up by the Taiwan OSHA.

Case Report

A 38-year-old man (height, 183 cm; weight, 94 kg) was employed in the formation processing department at Management Consultants Corporation Limited from July 2000 to April 2004. He has been an engineer at the steel plant since May 2004 and is covered by Labor Insurance. He has been working mainly on replacing machines, moving and trimming cast steel materials (Figs. 1 and 2) 8–11 hours per day, 5–6 days per week, for 10 years.

His major heavy loads are listed in Table 1. He has experienced lower back pain since April 2007, and he underwent acupuncture and alternative treatment at a traditional Chinese medicine clinic.

However, the symptom did not relieved, even the pain extended to the left leg with soreness, numbness, and loss of muscle strength. Therefore, he visited the neurosurgery department of a hospital

Fig. 1 Replacing machines and moving cast steel materials (provided by the patient).

and was diagnosed as LIDH in July 2014. Four months later, he underwent lumbar spine magnetic resonance imaging (L-spine MRI), and the result revealed LIDH at the disc level between the fourth and fifth lumbar vertebral bodies (L4–L5) and between the fifth lumbar vertebral body and the first sacrum (L5–S1) with compression at the fifth lumbar and the first sacral nerves (Figs. 4 and 5). LIDH with nerve compression was determined to be job-related. Therefore, he further visited our department of occupational medicine, where positive results for several left-leg straight-leg-raising tests (SLRTs) were obtained. He underwent intervertebral disc discectomy and fusion on November 12, 2014 and L-spine radiography on June 29, 2015 (Fig. 6).

Occupational LIDH was revealed according to the Taiwan OSHA diagnostic criteria[4], including (1) evidence of disease, (2) evidence of exposure, (3) appropriate temporality, (4) differential diagnosis, and (5) epidemiological evidence (evidence in the medical literature). Regarding the evidence of disease, he has experienced lower back pain that extended to the left leg with soreness, numbness, and muscle weakness for a period of at least four months. The subsequent examination from L-spine MRI also revealed LIDH at the disc levels L4–L5 and L5–S1 with compression at the fifth lumbar and first sacral nerves (Figs. 3 and 4). Moreover, on November 10, 2014, several left-leg SLRTs were performed at our department of occupational medicine, The positive results from several left-leg SLRTs were also obtained. Further, the patient underwent inter vertebral disc discectomy and fusion. Taken together, the aforementioned disease findings corresponded to the evidence of disease in the diagnostic criteria. Regarding the evidence of exposure, he works 5-6 days per week and approximately 260 days annually. Table 1 shows that he has carried heavy loads for ten and a half years,

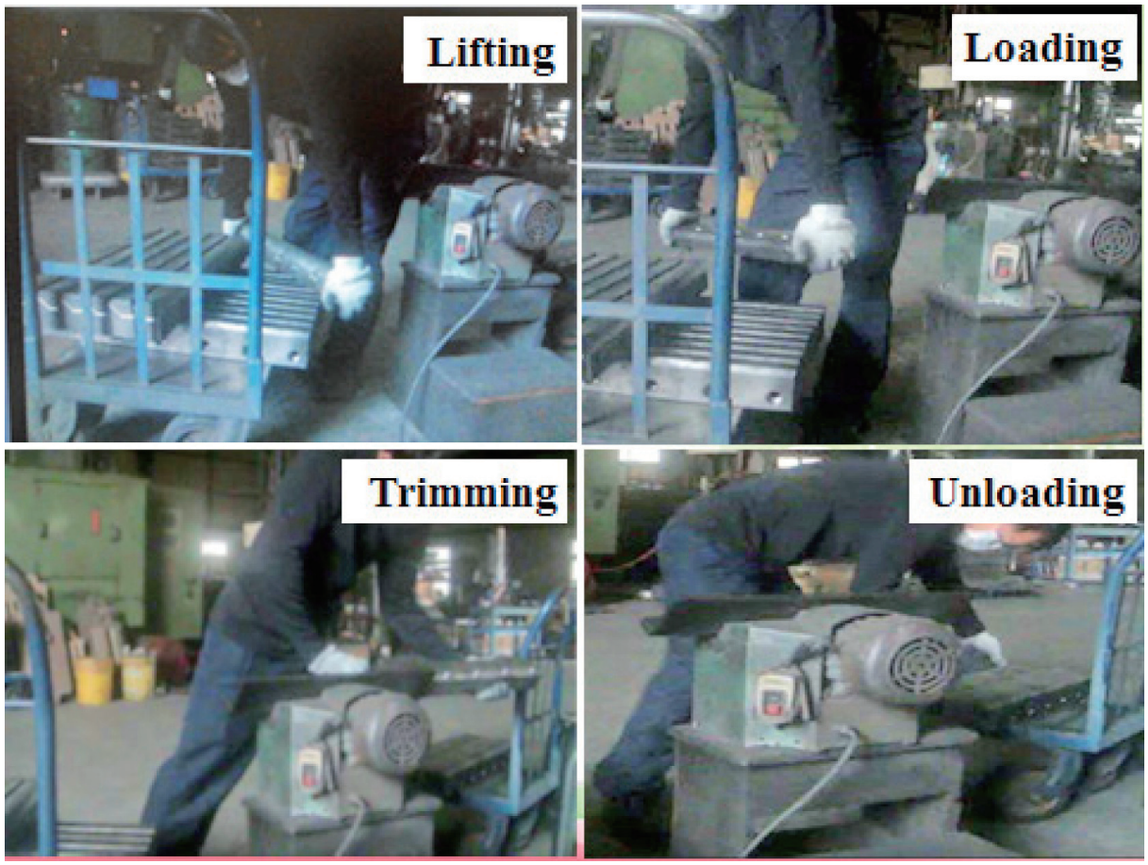

Fig. 2 Trimming of cast steel materials (provided by the patient).

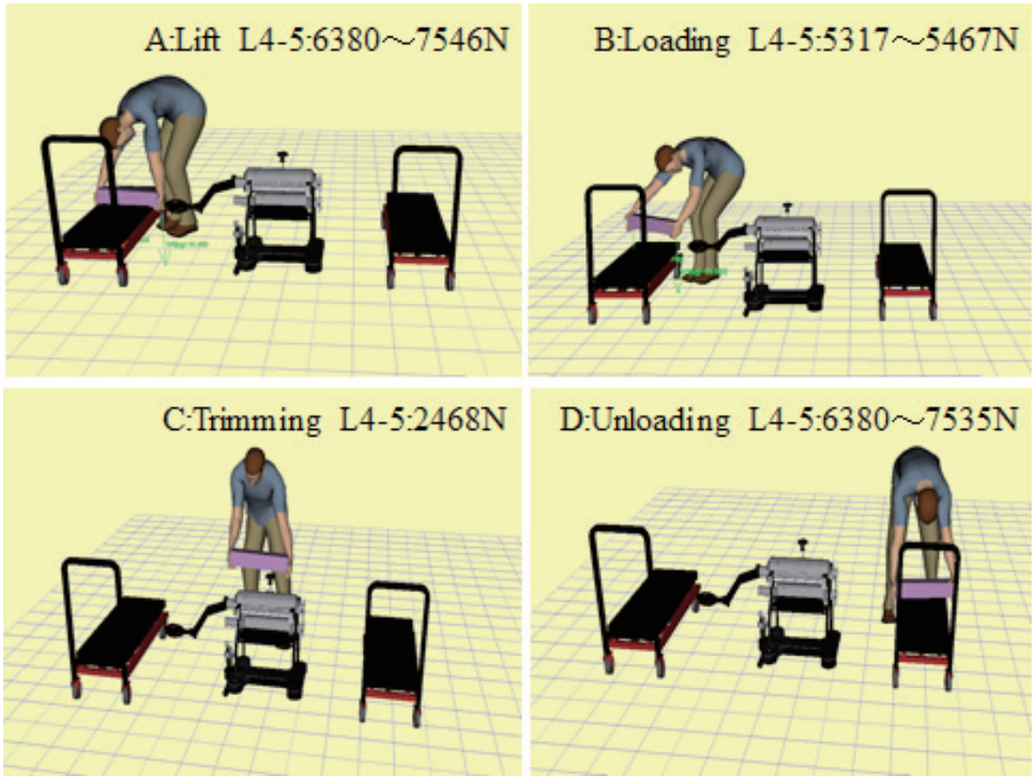

Fig. 3 Simulation and ergonomic analysis of the task were performed using the ergonomic software JACK. The assumed weight and height were equal to those of the worker (183 cm and 94 kg, respectively). The L4–L5 force (Newton; N) was analyzed for the average work-loading weight of 35 kg. The force was similar between machine replacement and trimming task (Fig 2), except for the trimming process in C. The average L4-L5 force was analyzed during the trimming process. The average force in A and D was 6963 [(6380 + 7546)/2], and the force in B was 5392 [(5317 + 5467)/2]; the total average force was 6439 N [(6963 + 5392 +6963)/3]. Heavy loads were moved every day for 6 hours during the 260 work days per year (Table 1), and the cumulative exposure was 43 × 10^6 Nh.

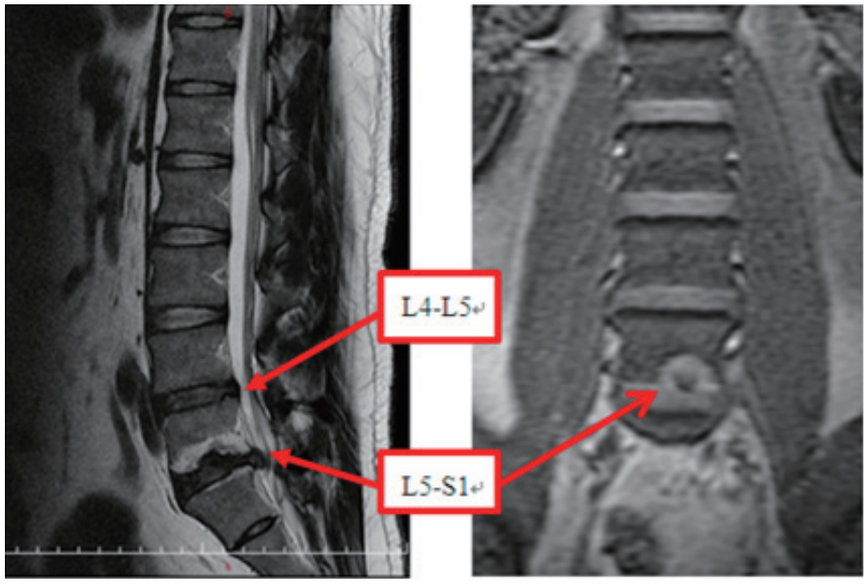

Fig. 4 L-spine MRI sagittal (right) and coronal (left) views: red arrows indicate lumbar LIDH at the disc level between the fourth and fifth lumbar vertebral bodies (L4–L5) and between the fifth lumbar vertebral body and the first sacrum (L5–S1) with compression at the fifth lumbar and first sacral nerves.

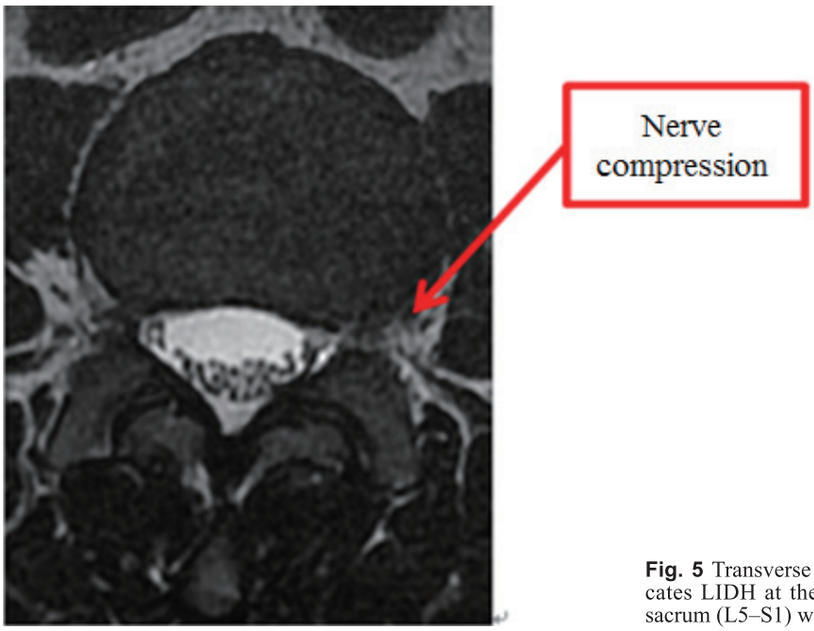

Fig. 5 Transverse view of L-spine MRI: The red arrow indicates LIDH at the fifth lumbar vertebral body and the first sacrum (L5–S1) with compression at the first sacral nerve.

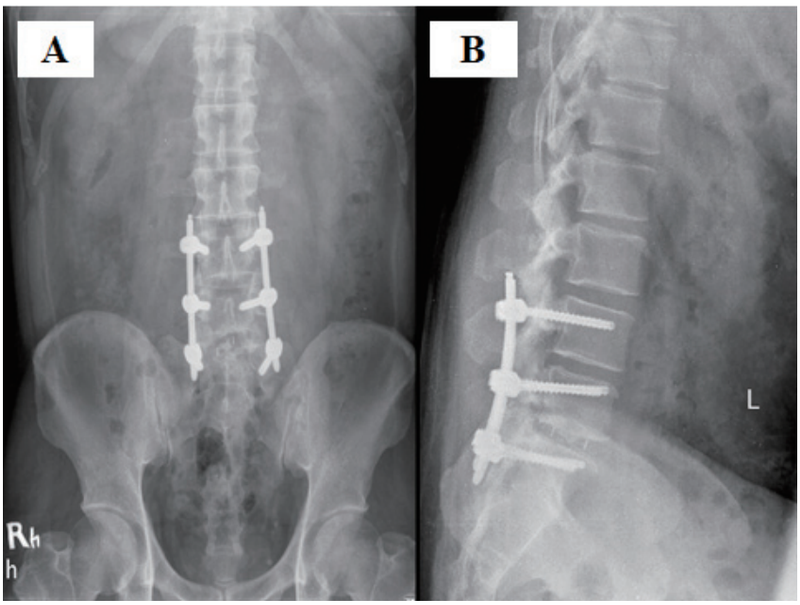

Fig. 6. Intervertebral disc discectomy and fusion at L4, L5, and S1. (A) Anteroposterior view. (B) Lateral view.

and the daily weight loading period was 6–10 hours; each steel material was between 20 and 50 kg, and the total daily load was approxi-mately 6 tons. Moreover, the cumulative exposure loads on the lumbar reached proximally to 43×10^6 Nh (Fig. 3). Therefore, his work conditions corresponded to the evidence of exposure in the diagnostic criteria. Regarding appropriate temporality, his weight-bearing work period was from May 2004 to November 2014 (Table 1). He was diagnosed with LIDH with nerve compression in November 2014. Therefore, LIDH was related to work exposure, corresponding to the appropriate temporality in the diagnostic criteria. He had no personal history of major trauma, rheumatoid arthritis, or genetic or immunological diseases (Table 2). Hence, aother general causes were ruled out.

Table 1. List of major heavy loads. The total daily heavy load was approximately 6 tons.

Heavy load period	duration: May 2004 to November 2014 (more than10 years) annually work about 260 days
Heavy load items	(1) replacing machines of cast steel materials (2) trimming of steel materials
Each steel weight (Kilogram)	(1) 20-50 kg (2) 20-50 kg
Daily frequency (times)	(1) 72-150 times (lifting: 36 × 2, putting down: 75 × 2) (2) 20-50 times [(20 to 50 times every other day) / 2] × 2 (lifting and putting down)
Daily weight weight × frequency	(1) 1,440-7,500 kg (2) 400-2,500 kg
total daily load [(1) and (2)]	1,840-10,000 kg (average 5,920 kg, approximately 6 tones)
Daily load hours	6-10 hours (average 8 hours)

Table 2. Laboratory data. All data were normal except for mildly elevated ALT.

Test item	Report	Reference Value	Result
Alk-P	71	35~129 IU/L	Normal
Bence Jones protein	Negative	Negative	Negative
ANA (IFA)	<40X(-)	< 40X(-)	Normal
RA	1.3	< 20 IU/ml	Normal
HLA-B27	Negative	Negative	Negative
IgE	40	<80	Normal
ESR	2mm/hr	0-15mm/hr (male)	Normal
CRP	0.2	<0.8 mg/dl	Normal
UA	5.8	3.6~8.0 mg/dl	Normal
BUN (blood)	16.00	8~20 mg/dl	Normal
Creatinine (blood)	0.89	0.7~1.2 mg/dl	Normal
ALT	68.0	10~40 IU/L	Elavated
AST	41.0	15~41 IU/L	Elevated

Alk-P: alkaline phosphatase, ANA: antinuclear antibodies, IFA: immunofluorescence assay, RA: rheumatoid factor, HLA-B27: human leukocyte antigen B27, IgE: immunoglobulin E, ESR: erythrocyte sedimentation rate, CRP: c-reactive protein, UA: uric acid, BUN: blood urea nitrogen, ALT: alanine transaminase, AST: aspartate transaminase.

Discussion

In our current report, a case of occupational LIDH was confirmed according to the OSHA diagnostic criteria in Taiwan [4]. Based on this criteria, the clinical manifestations should be reasonably consistent, and the manifestations or findings of 1, 2, and 3 are mainly required (ie, 1+2.1 or 2.2+3) as follows; 1. represents lower back pain accompanied by acute leg pain and numbness; 2. com- prises 2.1 or 2.2; 2.1 indicates positive SLRT results at 30–70 degrees at least twice, and 2.2 represents nerve conduction velocity (NCV) or lumbar radicu- lopathy on electromyography (EMG); finally, 3. indi- cates unilateral lumbar HIVD on myelography, MRI, or computed tomography (CT). Evidence of exposure corresponds to the findings of 1 or 2 as follows: 1. long-term heavy loading (annual work period of at least 220 days and working for at least 8–10 years) should include the loading of heavy weights of at least 20 kg for at least half of each work shift, with a total daily loading weight of at least 2 tons. 2. according to ergonomic simulation software, the working posture on the waist produces a load of at least 3200 N and lifetime cumulative exposure of at least 25×10^6 Nh. The formula of cumulative dose as follows: Sum dose for year = Days × $(8\ h \times [\Sigma F_i^2 \times t_i])^{1/2}$

Days: workdays in a year, F: loads on the lumbar (tons), t: time of the task (hours), cumulative exposure= work-years × sum dose per year. Another general causes, such as lumbar spondylolisthesis, lumbar spinal stenosis, or ankylosing spondylitis, should be ruled out.

Johanning[5] as well as Burdorf and Sorock[6] reviewed the medical literature to determine the risk factors for lower back pain and found that work load increases the risk of lower back pain inappropriate work load (awkward body postures), such as excessive forward postures, excessive scoliosis, and repeated stooped postures, increases the risk of lower back pain positions. Bigos and Battie[7] also indicated occupational LIDH was associated with the following job characteristics: prolonged sitting, frequent bending and twisting, bending to engage in heavy lifting, driving vehicles, or heavy whole-body vertical vibration. Further, Castorina and Deyo[8] determined that the relative risk of LIDH resulting from the following factors: an unnatural posture often be used when carrying heavy loads, 2.5–6.1; prolonged static posture, 1.6; whole-body vibration, 2.4; driving a car, 2.8; and driving a truck, 4.7. In the current case, the load lifted by the worker reached 50 kg, and his trunk was flexed excessively forward. These factors caused the lumbar loads to exceed the threshold of 3200 N and the cumulative exposure loads to exceed 25×10^6 Nh.

In general, the evidence of occupational exposure is difficult to collect. However, the biochemical data from the current case clearly revealed the abnormalities when compared with the reference value. In this report, the heavy loading of the case was calculated as a ratio between the total weight of the materials or products divided by the average individual weight. We also used the ergonomic software to estimate the lumbar force. Especially, the worker provided us with work data and images, which were attested by the signatures of his employer as the evidence of exposure.

After the occupational identification report was completed, the results were transferred to an appraisal review unit, and the patient received reasonable compensation. Currently, the case still receives regular rehabilitation. However, he gets recovery well and is assigned to a non-weight-loading task.

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職業性腰椎椎間盤突出：案例報告

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受文日期：民國 104 年 06 月 24 日；接受刊載：民國 105 年 03 月 14 日

摘要

眾所皆知，人因性危害通常引發肌肉骨骼累積性傷病。尤其腰椎椎間盤突出是常見肌肉骨骼累積性傷病。在此，我們敘述一位 38 歲在鋼鐵工廠從事負重員工，每天工作 8-11 小時。他從 2004 年五月開始，每年工作天約 260 日。他主要負責搬抬鋼鐵材料重 20 到 50 公斤。進一步，根據我們政府制定職業性腰椎椎間盤突出認定診斷標準，第四腰椎、第五腰椎受力超過 3200N（牛頓），累積劑量為 43×10^6 Nh（牛頓．小時）超過診斷標準 25×10^6 Nh，結果工作暴露超過標準閾值。醫學史回顧顯示負重工作會產生腰椎椎間盤突出，符合診斷標準適當的時序性。醫學文獻也指出長時間彎腰搬運重物，有增加罹患腰椎間盤突出的風險。個案病史過去無重大外傷、風濕性關節炎或其他遺傳和免疫關節疾病，因此大致排除其他原因。個案職業病鑑定報告完成後，轉送鑑定審查單位並且獲得理賠。現在個案配工到非負重作業區與接受定期復健治療。

關鍵詞：人因性危害、腰椎椎間盤突出、暴露的證據、疾病的證據、適當的時序性

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Pathology Page

Aspergillus Pericarditis Presenting As Anterior Mediastinal Malignancy

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Received: Feb. 13, 2015; Accepted: Dec. 03, 2016

Abstract

A 60-year-old woman had history of kidney transplantation 1 year ago and had received immunosuppressive drugs. She presented with fever, bilateral shoulder pain, lower abdominal pain, and poor appetite for 3 days. Whole-body positron emission tomography showed increase uptake in anterior mediastinum, pericardium, and lymph nodes, with the clinical impression of anterior mediastinal malignancy with lymph node and pericardium metastases. She received pericardiectomy and was diagnosed as having aspergillus pericarditis with abscess formation. Despite intensive antifungal treatment, she died of septic shock and multiple organ failure 3 weeks later. Aspergillus pericarditis occurs in immunocompromised patients and is always the result of contiguous dissemination of aspergillus from the lung or myocardium, with a high mortality rate. Only few cases have been successfully treated with intensive antifungal treatment and aggressive surgical pericardiectomy.

Key words: immunocompromised patients, kidney transplantation, septic shock, pericardiectomy

Pathology Page

A 60-year-old woman with a history of end-stage renal disease underwent post-status kidney transplantation 1 year ago and received treatment with immunosuppressive drugs. She also had hypertension and a history of cerebrovascular accident. She presented with a 3-day history of fever, bilateral shoulder pain, lower abdominal pain, and poor appetite. Laboratory data showed increased WBC count (13,000/μl) and B-type natriuretic peptide (3,110 pg/ml), but normal troponin I and ECG findings. Blood culture yielded *Pseudomonas aeruginosa* infection and serologic examination revealed cytomegalovirus infection. Chest X-ray showed progressive pneumonia in the right lung with extensive patchy areas of opacity, infiltration, and consolidation in the right lung. Computed tomography (CT) of chest (Fig. 1, upper panel) showed three lobulated pericardial lesions with fluid collection (up to 6.2 cm in size), and whole-body positron emission tomography (PET, Fig. 1, lower panel) showed increased uptake in the anterior mediastinum, pericardium, and lymph nodes, with the clinical impression of anterior mediastinal malignancy with lymph node and pericardium metastases. The patient received pericardiectomy for drainage of fluid, and the specimen was sent for pathology examination.

Microscopically, the lesion showed fungal hyphae with a necrotic background and septation and branching at acute angles (Fig. 2, upper panel), and the fungal hyphae were positive to Grocott's methenamine silver stain (Fig. 2, lower panel) and periodic acid Schiff. Pericardial fluid culture revealed *Aspergillus fumigatus*. The patient was diagnosed as having aspergillus pericarditis with abscess formation. Despite intensive antifungal treatment, she died of septic shock and multiple organ failure 3 weeks later.

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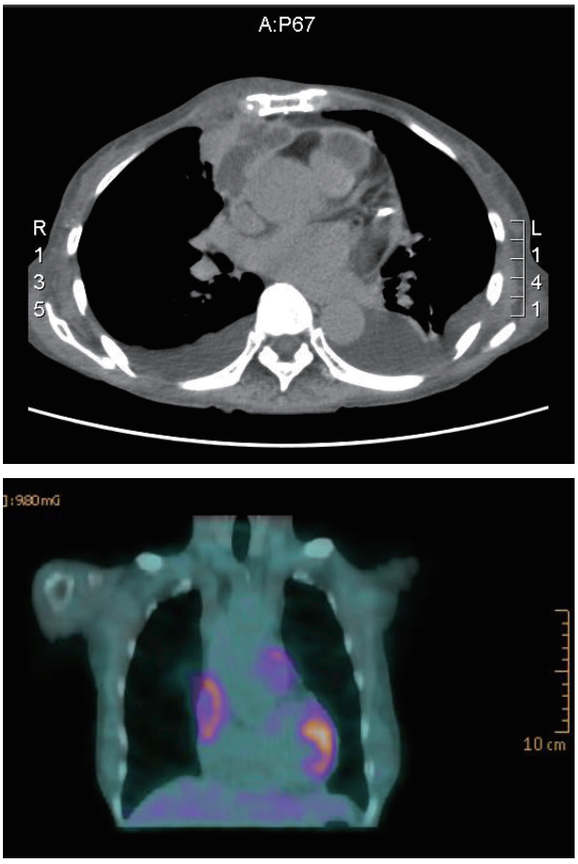

Fig. 1 The CT of chest (upper panel) showed 3 lobular lesions over pericardial area; and the PET scan (lower panel) showed enhance uptake in anterior mediastinum and pericardium area.

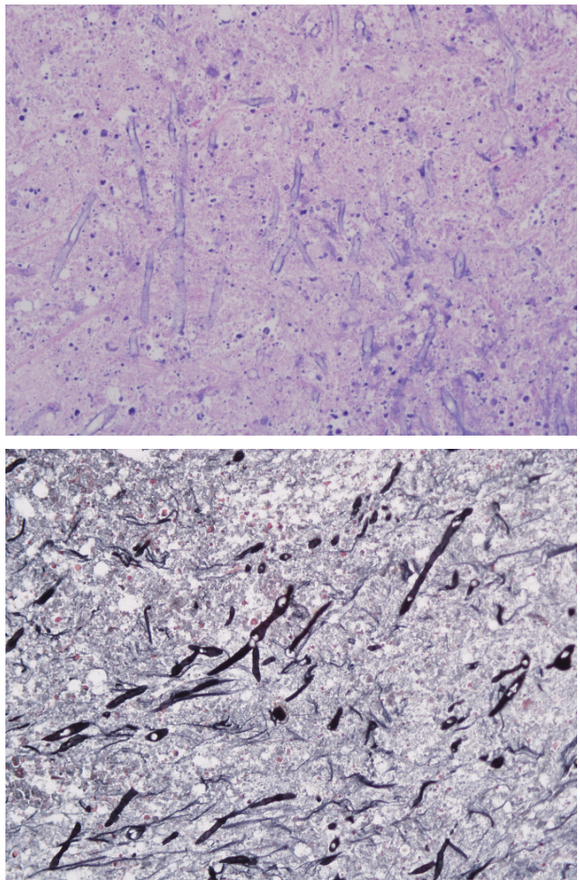

Fig. 2 Histopathology demonstrated fungal hyphae in necrotic background (upper panel, hematoxylin-eosin stain, 400x), and GMS stain highlighted the fungal hyphae (lower panel, 400x).

Aspergillus pericarditis occurs in severely immunocompromised patients and is due to contiguous dissemination of aspergillus from the lung or myocardium; it has a high mortality rate (85%). Less than 50% of cases are diagnosed before death, and 59% cases are associated with disseminated disease. *A. fumigatus* is the leading strain out of nearly 250 aspergillus species. Cardiac tamponade is present in 28% of cases. Only a few cases, who receive intensive antifungal treatment and aggressive surgical pericardiectomy, survive; these treatment regimens might thus lower the high mortality associated with aspergillus pericarditis.

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麴黴菌心包膜炎：臨床表現似前縱隔腔惡性腫瘤：病例報告

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受文日期：民國 104 年 02 月 13 日；接受刊載：民國 104 年 12 月 03 日

摘要

一位 60 歲女性一年前接受腎臟移植並接受免疫抑制性藥物治療，最近三天因發燒、雙側肩關節痛、下腹痛及食慾差求診。全身正子檢查顯示前縱隔腔、心包膜及淋巴結有異常顯影，因而懷疑前縱隔腔惡性腫瘤伴隨心包膜及淋巴結轉移。病患接受心包膜切除術後病理診斷為麴黴菌心包膜炎伴膿瘍。雖然積極用抗黴菌藥物治療，病患仍於術後三個星期死於敗血性休克及多重器官衰竭。麴黴菌心包膜炎好犯於免疫差的病患，通常是因為肺臟或心臟麴黴菌感染而擴散至心包膜，病患有很高的死亡率。只有少數病患接受積極抗黴菌藥物及心包膜切除術後可治癒。

關鍵詞：免疫缺乏病人、腎移植、敗血性休克、心包切除術

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Image

Tenosynovial Giant Cell Tumor of the Thigh: Pathological and Positron Emission Tomography Findings

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Received: Oct. 02, 2015; Accepted: Jan. 27, 2016

Abstract

Here we present an unusual case of a localized-type tenosynovial giant cell tumor (TGCT) in the left thigh of a 31-year-old woman with a history of colon adenocarcinoma. A restaging whole-body FDG PET/CT revealed a new, intensely FDG-avid soft-tissue mass in the left thigh (SUV = 11.4). Subsequently, magnetic resonance imaging (MRI) also revealed a well-circumscribed soft-tissue tumor (2.1 × 1.8 cm) in the left thigh. Clinically, a metastatic adenocarcinoma was considered. The final pathological diagnosis was a localized-type TGCT, which was confirmed by CT-guided biopsy. Increased FDG uptake in TGCTs can be explained by their high monocyte/macrophage content. In this case, to avoid a false-positive interpretation, radiologists and nuclear medicine physicians must be aware that both metastatic carcinoma and TGCTs can be intensely FDG avid.

Key words: tenosynovial giant cell tumor

Pathology Page

A 31-year-old female had a history of adenocarcinoma of the sigmoid colon (T3N2aM0) and had undergone a left hemicolectomy in another hospital on June 1, 2015. Subsequently, she visited our outpatient department for chemotherapy for colon cancer. She was admitted to our ward for a PET scan for restaging and port-A implantation. PET scan revealed an increased FDG uptake (SUVmax early: 9.5, delayed: 11.4) in the left hip, and nuclear medicine physicians suspected a left hip metastasis (Fig 1). Subsequently, an MRI also revealed a mild irregular well-circumscribed soft-tissue tumor (2.1 × 1.8 cm) between the left femoral neck and left quadratus femoris (Fig 2). This tumor was isointense on T1WI and mildly hyperintense onT2WI. No obvious invasion to the adjacent femoral neck was noted. Because of the patient's history of colon cancer, a metastatic tumor could not be ruled out. Thus, a CT-guided biopsy was performed.

Histopathologic examination revealed a proliferation of rounded to ovoid and slightly spindled cells growing in sheets. The cytoplasm was relatively abundant, pale, amphophilic, focally vacuolated, and foamy. The nuclei were vesicular with indistinct to small nucleoli, and a subset of nuclei exhibited membrane indentation. Scattered multinucleate giant cells were present, which were revealed to be diffusely positive for CD68 (Figs 3, 4). Mitosis was absent in this needle biopsy specimen. This confirmed a localized-type tenosynovial giant cell tumor (TGCT) in the left thigh. After consulting and discussing with the orthopedist, the patient decided to get discharged and seek a second opinion.

TGCTs, originally described by Jaffe and colleagues in 1941, are pigmented villonodular proliferative lesions originating from the synovium, bursa, or joint.[1] They tend to be locally aggressive and may have multiple occurrences, frequently leading to the impairment of joint function.[1] They mostly occur in women and in patients during 30–50 years of age.

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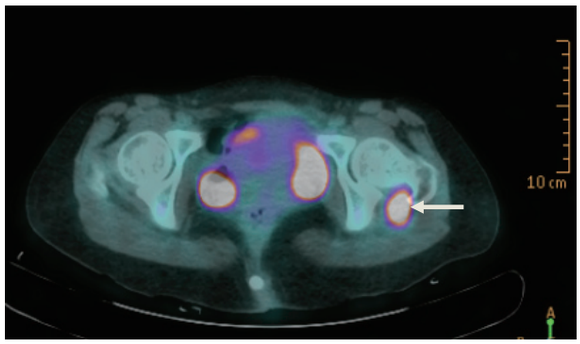

Fig. 1 PET/CT showed a high FDG uptake nodule adjacent to left femoral neck (SUV max early: 9.5, delay: 11.4) (arrow).

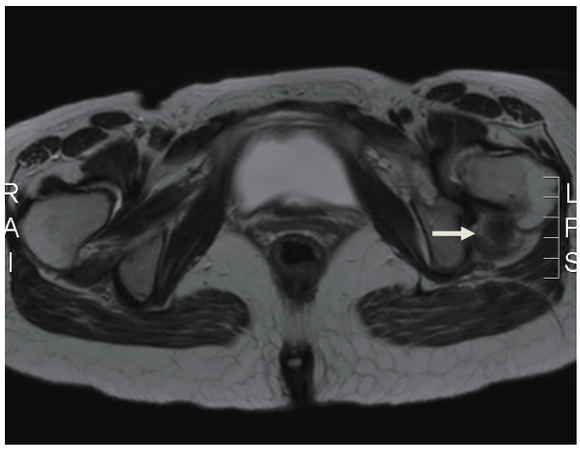

Fig. 2 T2-weighted MR image showed a 2.1 x 1.8 cm, irregular signal intensity soft tissue nodule adjacent to or overlapping a tendon of the quadratus femoris (arrow). Signal intensity over periphery zone of the nodule is lower than that muscle. Apparent irregular lower signal intensity is seen at central zone of nodule suggesting hemosiderin collection.

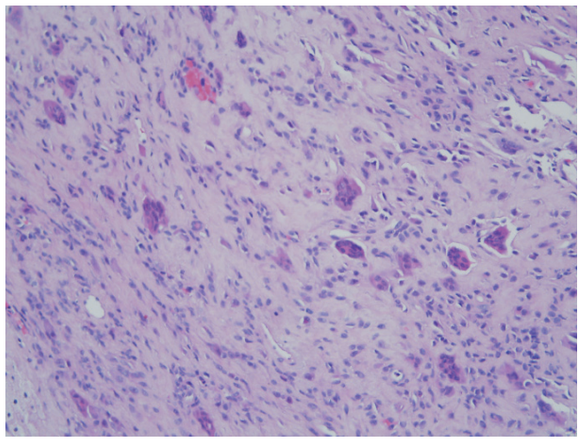

Fig. 3 The tumor cells showed oval to spindle nuclei with fibrotic stroma tissue and mixed scattered multinucleated giant cells (H & E stain, x 100).

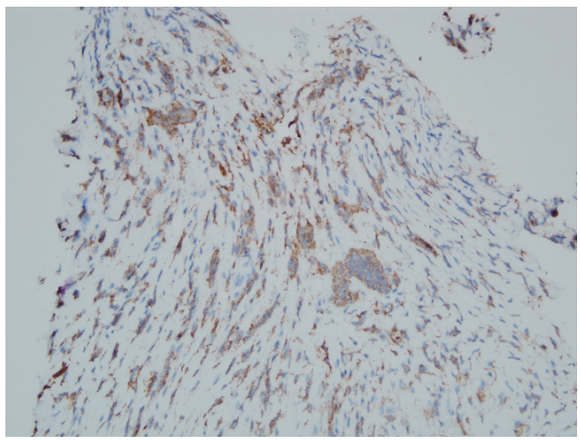

Fig. 4 The stromal spindle cells and multinucleated giant cells are diffuse positive for CD68 (IHC stain x 200).

[1, 2] Based on growth characteristics, two forms of TGCTs have been recognized: the diffuse form predominantly occurring in the periarticular soft tissue around the large joints, and the localized form predominantly occurring in the synovium of the tendon sheaths or interphalangeal joints.[3]

The localized TGTCs are also known as giant cell tumors of the tendon sheath (GCTTS). TGCTs also occur in extra-articular locations. GCTTS have a chromosomal translocation, t(1:2)(p13;q37), which results in the overexpression of CSF1, a chemoattractant for macrophages.[5] Current literature specifically addressing FDG avidity in TGCTs is sparse. Aoki et al. in a series of 114 soft-tissue masses, reported five cases on GCTTSs with SUVmax = 5.06 +/− 1.63.[4] Alex reported one case on GCTTS with SUVmax = 25. [5] Several investigators have previously demonstrated GLUT-1 upregulation in human monocyte-derived macrophages.[6] From such studies, we inferred that FDG avidity in TGCTs may be explained by their high monocyte/macrophage content. Notably, granulomatous lesions containing active macrophages are widely recognized as responsible for false-positive FDG PET interpretations in oncology. [6,7]

In conclusion, TGCT in our present case showed a high monocyte/macrophage content, with false-positive PET interpretations. Thus, radiologists and nuclear medicine physicians should be aware that metastatic tumors, recurrent malignant tumors, and TGCTs can be intensely FDG avid and that TGCTs

should be included in the differential diagnosis of intensely FDG-avid neoplasms located within synovial joints, tendon sheaths, or bursae.

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肌腱滑液膜巨細胞瘤：病理及正子掃描特徵

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受文日期：民國 104 年 10 月 02 日；接受刊載：民國 105 年 01 月 27 日

摘要

我們報告一位 31 歲女性有大腸癌病史。在 PET 分期檢查時發現在左大腿髖部旁有一 SUV=11.4 的腫塊，核磁共振檢查也發現在左大腿髖部旁有一 2.1 x 1.8 cm 的腫塊，臨床診斷為轉移性病灶，最後病理切片診斷為局部性肌腱滑液膜巨細胞瘤。肌腱滑液膜巨細胞瘤在氟 -18- 去氧葡萄糖正子攝影有高吸收值，是因為腫瘤內含有大量單核球及巨噬細胞。針對此病例，轉移癌及肌腱滑液膜巨細胞瘤對氟 -18- 去氧葡萄糖正子攝影都有高吸收值，因此放射科及核醫科師要小心不要做出假陽性的誤診。

關鍵詞：肌腱滑液膜巨細胞瘤

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1. Editorials are limited to 2000 words, with 150 words of abstract and 7 references.
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3. Original articles should be presented in the following order: Abstract, Introduction, Materials and Methods, Results, Discussion and Conclusion, Acknowledgements, References, Attachments, Tables, Legends for illustration, and Figures (photographs). This should be limited to 3000 words, with 300 words of abstract and 40 references.
4. Case reports should be arranged by the following sequence: Abstract, Introduction, the Clinical case, Discussion, References, Attachments, Table, Legends for illustration, and Figures. Patients' eyes should be covered for privacy. Diagnosis information or the chart of clinical process should be within 6 months. This should be limited to 1500 words, with 150 words of abstract and 10 references.
5. Brief communications should be concise presentations of preliminary clinical results and technological improvements. This should be exceeded 750 words, 150 words of abstract and 7

references.

6. Images and Pathology page should be limited to 500 words, with 150 words of abstract and 3 references.
7. For other details, please refer to International Steering Committee, for Uniform Requirements for Manuscripts Submitted to Biomedical Journals, please refer to The New England Journal of Medicine 336:309-315,1997.

Specifications for the different article categories

Article Category	Word count limit		No. of references allowed	No. of tables/ figures allowed
	Abstract	Min text*		
Original Articles	≦300	≦3000	≦40	≦5
Case Reports	≦150	≦1500	≦10	≦3
Review Articles	≦300	≦3500	≦60	≦6
Brief Communications	≦150	≦750	≦7	≦1
Images, Pathology Page	≦150	≦500	≦3	≦2
Editorials	≦150	≦2000	≦7	≦1

*Refers to the main body of text only, i.e., does not include article title, abstract, table headings/tables, figure legends and references.

Manuscript preparation:

Manuscript should be double-spaced and numbered pages, and comply with the "uniform requirements for manuscripts submitted to biomedical journals". The first page is the title page, which include title, name of author(s), organization and unit, contact name, phone number, e-mail address and mail address (in both Chinese and English). The second and the third page is for abstract (Chinese content needs to consist with English content) and key words (please include 3 to 5 keywords or phrases in Chinese and English), and should be written in paragraphs following by background and purpose, methods, results and discussion.

Co-corresponding author should mention the contributions on manuscript, such as initiation of research topics, the study design, statistical analysis, interpretation of findings, chapters writing involved, et al.

Please attach two original copies including attachments, charts and legends. Chart should be professional, with only one figure or one table per page, and is arranged in consecutive orders and numbered in Arabic characters. Table should have a title and appropriate interpretation. Picture should be 5" x 7" in size, black and white, glossy and numbered in consecutive orders of appearance.

Reference:

Unpublished articles or abstracts cannot be listed as references, but could be noted as "unpublished observations". Doctoral dissertation or master thesis can be used. Any articles being accepted by magazines but not published yet, please note the name of magazine, year and note "in press".

Original researches, case reports, review articles, communications (includes brief communications), images in clinical medicine, editorial follows the following format:

1. Abbreviations used should follow the format of Index Medicus for all journal titles. When authors are less than 6 people, list all author(s), when more than 6, only list the first 6 followed by "et al." for the rest.
2. References in the text should be placed where relevant. When a reference article is cited, only the primary author is cited; however, if only two authors are present, both should be listed.
3. Example of references:

Examples of Reference:

1. Periodicals:

   Yang KTA, Chen HD: A semi-automated method for edge detection in the evaluation of left ventricular function using ECG-gated single-photon emission tomography. Eur J Nucl Med 1994;21:1206-11.

2. Monographs:

   Plum F, Posner JB: Diagnosis of Stupor and Coma. 3rd ed. Philadelphia: Davis, 1980:132-3.

3. Monographs with multiple authors:

   Levinsky NG: Fluid and electrolytes. In: Thorn GW, Adams RD, Braunwald E, Isselbacher K, Petersdprf RG eds. Harrison's Principles of Internal Medicine, 8th ed. New York: Mcgraw-Hill, 1977:364-75.

4. References from website

   please indicate the title, source, and the retrieving date

   (Accessed Month day, 2016, at http://www.house.gov/xxxx/min/inves_xxx/index_accord.htm.)

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童綜合醫學雜誌投稿相關規則

95.9.01 製訂
99.08.17 修訂
100.07.11 修訂
102.07.08 修訂
102.12.27 修訂
103.07.14 修訂
103.12.12 修訂
104.03.13 修訂
104.11.19 修訂

本雜誌刊載與醫學有關之論述，包括原著論文（Original Articles）、病例報告（Case Reports）、綜論（Review Articles）、短論（Communications 、包括 Brief Communications）、影像判讀（Images）、臨床病理討論（Pathology Page）、編著的話（Editorials）等。惠稿請送 43503 臺中市梧棲區臺灣大道八段 699 號童綜合醫學雜誌編審委員會。（E-mail:Tungs_Journal@ms.sltung.com.tw）

壹、投稿前注意事項

1. 惠稿請以英文撰寫，本雜誌接受電子檔投稿或紙本投稿，電子檔投稿請直接將稿件 WORD 檔寄至編審委員會信箱 Tungs_Journal@ms.sltung.com.tw)，紙本投稿需檢附紙本稿件三份及電子檔一份寄至編審委員會（43503 臺中市梧棲區臺灣大道八段 699 號童綜合醫學雜誌編審委員會）。
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. 投稿同時請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，將致贈稿酬並贈送 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（Original Articles）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）。每篇字數 3000 字以內，摘要 300 字以內，參考文獻 40 篇以內。
2. 病例報告（Case Reports）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。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。每篇字數 1500 字以內，摘要 150 字以內，參考文獻 10 篇以內。
3. 綜論（Review Articles）不必按原著論文格式撰寫，但每篇字數 3500 字以內，摘要 300 字以內，參考文獻 60 篇以內。
4. 短論（Brief Communications），臨床上、技術上的精簡論著，每篇字數 750 字以內，摘要 150 字以內，參考文獻 7 篇以內。
5. 影像判讀（Images）、臨床病理討論（Pathology Page）圖例說明每篇字數 500 字以內，

摘要 150 字以內，參考文獻 3 篇以內。

6. 編者的話（Editorials），每篇字數 2000 字以內，摘要 150 字以內，參考文獻 7 篇以內。
7. 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）。
8. 將可接受投稿之稿件種類之摘要字數、字數、參考文獻及圖表相關上限規定，整理於下表：

稿件種類	字數限制		參考文獻	圖 / 表
	摘　　要	內文字數		
原著論文 (Original Article)	≦ 300	≦ 3000	≦ 40	≦ 5
病例報告 (Case Report)	≦ 150	≦ 1500	≦ 10	≦ 3
綜論 (Review Article)	≦ 300	≦ 3500	≦ 60	≦ 6
短論 (Brief Communication)	≦ 150	≦ 750	≦ 7	≦ 1
影像判讀 (Images)、 臨床病理討論 (Pathology Page)	≦ 150	≦ 500	≦ 3	≦ 2
編者的話 (Editorial)	≦ 150	≦ 2000	≦ 7	≦ 1

參、投稿須知

1. 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，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。
2. 第一頁爲標題頁，須列出中文及英文之論文題目、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。
3. 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，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）。
4. 相同貢獻作者請加註說明，如研究主題的設定、參與決定研究設計、進行統計分析、詮釋研究結果、以及各章節撰稿等貢獻。
5. 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且不可以照片形式。圖片或照片電子檔（.jpg）必須清晰、分明。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、病例報告、綜論、短論、影像判讀、臨床病理討論、編著的話按下列格式撰寫：

A. 雜誌及期刊

中文例〔作者姓名：題目。雜誌簡稱 年號；卷數：起訖頁數〕

薛玉梅、陳建仁：皮膚砷癌之流行性病學特徵與危險因子。中華衛誌 1996; 15: 1-26。

英文例〔英文原稿中引用的參考文獻，其雜誌或期刊之簡稱應參照 Index Medicus 型式〕

1. Feely J, Wilkinson GR, Wood AJ. Reduction of liver blood flow and propranonol metabolism by cimetidine. N Engl J Med 1981;304:691-6.
2. Kaplan NM. Coronary heart disease risk factors and antihypertensive drug selection. J cardiovasc Pharmacol 1982; 4(suppl 2): 186-365.（引用雜誌附冊時）
3. Tada A, Hisada K, Suzuki T, Kadoya S. Volume measurement of intracranial hematoma by computedtomography. Neurol surg (Tokyo) 1981; 9: 251-6.〔In Japanese: English abstract〕（引用文獻之作者之本文爲非英文，但有英文摘要）。
4. Bhasin S, Storer TW, Berman N, Callegari C, Clecenger B, Phillips J, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996; 335: 1-7.（作者超過 6 位時，只須列出前 6 位，其它以「等」(et al) 代替）

＊期刊若有「數位物件識別碼 (digital object identifier, DOI)」，則於文獻末。

B. 單行本：

中文例 [作者姓名：書名，版數（卷數）。發行地；出版公司，年代：引用部份頁數]。

楊志良：生物統計學新論，一版。台北；巨流圖書公司，1984：33-8.

英文例 [英文單行本的書名，除介系詞及連接詞外，第一字母需大寫]

(1) Plum F, Posner JB. Diagnosis of Stupor and Coma. 3rd ed., Philadelphia: Davis, 1980:132-3.

C. 多重作者之單行本：

中文例 [有關文章作者姓名：題目。編輯者姓名：書名。版數（卷數）。發行地：出版公司，年代；引用部份頁數]。

蔣欣欣：護理與健康。顧乃平：護理專業導論。一版。台北：匯華出版公司，1991：83-121。

英文例 Levinsky NG: Fluid and electrolytes. In: Thorn GW, Adams RD, Braunwald E, lsselbacher K, Petersdprf RG eds. Harrison’s Principles of Internal Medicine. 8th ed. New York: Mcgraw-Hill, 1977;364-75.

D. 參考文獻引用時，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].

E. 參考文獻引用網路資料請列出文獻名稱及出處以及引用時間

(Accessed Month day, 2016, at http://www.house.gov/xxxx/min/inves_xxx/index_accord.htm.)

伍、著作權

若著作人投稿於本刊經收錄後，同意授權本刊得再授權國家圖書館或其他資料庫業者，進行重製、透過網路提供服務、授權用户下載、列印、瀏覽等行爲。並得爲符合各資料庫之需求，酌作格式之修改。若爲摘譯、譯稿或改寫稿，需附原作者之正本同意書，並附原文影本一份；來稿如涉及版權，概由作者自負文責。

第十一卷　第一期　　民國 106 年 01-06 月

童綜合醫學雜誌

編著的話

綜　論

原　著

病例報告

臨床病理討論

影像判讀

ERRATA 勘誤表

Vol. (No.) 卷期	Page 頁數	Line 位置	Error 錯誤	Correction 更正
10(2)	38	關鍵詞後方多出不必要的文章	下方	下方

Error 錯誤

關鍵詞：博卡病毒、皮肌炎、肺炎 1. Allander T, Tammi MT, Eriksson M, Bjerkner A, Tiveljung-Lindell A, Andersson B. Cloning of a human parvovirus by molecular screening of respiratory tract samples. Proceedings of the National Academy of Sciences of the United States of America 2005;102: 12891-12896.

2. Chuang CY, Kao CL, Huang LM, Huang LM, Lu CY, Shao PL, et al. Human bocavirus as an important cause of respiratory tract infection in Taiwanese children. J Microbial Immunol Infection 2011;44: 323-327.
3. Allander T, Jartti T, Gupta S, Niesters H. G. M, Lehtinen P, et al. Human bocavirus and acute wheezing in children. Clin Infect Dis 2007;44: 904-910.

Correction 更正

關鍵詞：博卡病毒、皮肌炎、肺炎