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CONTENTS IN BRIEF

IMAGE

Editorial

Pandemic, Low Birth Rate and Increasing Cancer Rates

Hueng-Chuen Fan[1,2], Yu-Kang Chang[1], Yen-Chuan Ou[1,3,*]

[1]Department of Medical Research, [2]Department of Pediatrics, [3]Department of Urology, Tungs' Taichung MetroHarbor Hospital, Taichung, Taiwan

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Abstract

Trending topics in Taiwan includethe Pandemic Coronavirus Disease 2019 (COVID-19), low birth rate, and increment in thecancer rates. The problems underlying these topics are far simpler than we thought.Therefore, the key objectives of this study are to highlight the recent studies that addressed the key elements associated with these trending and hot topics and to provide a broader perspective of the diagnosis, therapeutic, prognosis, and educational aspects of these issues.

Key words: Pandemic, low birth rate, increasing cancer rates

The 21st century is far from being safe. A Pandemic disease that surreptitiously emergedatthe end of 2019, namely Coronavirus Disease 2019 (COVID-19),has alreadyaffected ~90 million people, killing>2,000,000 worldwide so far, according to the World Health Organization (WHO)[1]. Globally, people are experiencing a rapid and potentially more loss of collective innocence than ever before, and no one can be an exception. Similar to a scene in the movie "Titanic," we are likely to be sailing on a tremendous cruise ship and dancing in the ballroom with an orchestrawhile the ship is going to sink and water is gushing in below the decks, drowning the crew. Everyone is suddenly terrified, going from partying to panicking.All medical doctors in Taiwan, standing on the brink of the 21st century, have a strong obligation to take action to guard the health of the 26 million people on this island. In this context, Tsai et al[2] conducted a meta-analysis focusing on the 28-day mortality of patients with COVID-19 by using a comprehensive Meta-Analysis 3.0 analyzing web-available data, and concluded that the non-antiviral agent dexamethasone may be as an adjunctive therapy for more severe patients. Another different and unusual conditionthat was mistakenly impressed as a lung infection,eventually was caused by the microorganism migrating to the lung through bloodstream, leading to aseptic pulmonary embolism[3].

As more and more women in Taiwan voluntarily embrace degrees and jobs, the idea of having a family and children is no more their priority, which is an important causeofthe low birth rate observed in Taiwan. Moreover, the use of contraceptive pills is common in Taiwan. In this context, Liu et al[4] reported a life-threatening condition, namely a case of cerebral venous thrombosisin a female using oral contraceptive pills for 2 years. The female patient's conditioncompletely recovered with anticoagulant, direct catheter thrombolysis, mannitol, and hyperbaric oxygen therapy.Because low birth rate is common in Taiwan, it is precious for a girl to be willing to conceive. Problems, such as dehiscent uterine scar should be early detected and timely repaired during pregnancy because devastating complications of this uterine defectinclude preterm delivery, massive maternal blood loss, and potential death of both mother and baby. Law et al[5] reported a successful early surgical repair in a woman with this condition and whohad a safely and uneventfully Cesarean delivery with a healthy baby. Moreover, it is laborious to properly look after children because they do not

*Correspondence to: Yen-Chuan Ou, MD, PhD, Department of Urology, Tungs' Taichung MetroHarbor Hospital, No.699, Sec.8, Taiwan Blvd., Wuqi, Dist., Taichung City 43503, Taiwan (R.O.C.)

always follow their parent's instructions and are not aware of potential environmental dangers. Lee et al[6] reported a girl showing bizarre behaviors due to taking excessive amount of cyproheptadine, which is a syrup for common cold. The authors concluded that a high index of suspicion, careful historytaking, and appropriate physical examination conducted by the first-line doctors enabled the prompt diagnosis and adequate treatment.

The word "cancer" reflects more fear than death. It has become a huge threat to the world, irrespective of factors, such as physical fitness, gender, social status, and age. The debilitating disease tortures not only one's health, but also finance, time, and emotions. Hsu et al[7] reported an extremely rare tumor, namely extrarenal Wilms' tumor, which occursprimarily in childhood, in a 41-year-old female. The patient made a full recovery after a whole course of chemotherapy.Although more and more people are getting cancers, the clinical evidence shows that cancer is preventable. Chen et al[8]summarized the advanced knowledge regarding the risks of developing a cancer and the advantages of increasing physical activity in fighting cancer.The authors emphasized that doing more exercise can not only decrease cancer risks, but can help people live longer and better.In contrast, good nursing care is a critical facet of health care. In this context, to improve the quality of nursing cares and deliver safe and high quality health care to patients in all clinical settings, Huang et al[9]conducted a study where they shared their experience from course learning objectives, team composition, precourse reading, and an assigned homework, team-based learning activity design through a flipped classroom with team-based learning model to teach literature appraisal skill in evidence-based nursing.

Finally, thanks to the ventilator as advanced maintaining life devices, the human lifespan has dramatically extended, leading to an increased number of patients that require prolonged mechanical ventilation (PMV) with or without their wishes. Arguably, it is a debate regarding the patient dignity, that is, to impersonally live with machine support or to die with a complete body and soul. Yue et al[10]investigated patients with PMV and concluded that those patients were indeed worse on admission and exhibited a higher mortality. The authors concluded that these patients required longer hospital stays and higher life and medical expenditure. Therefore, they suggested that the authorities should promote palliative care to these patients to improve their quality of life, reducing their financial burden on the expenditure of the public health.

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疫情，少子化，以及癌症的增加

范洪春[1,2]　張祐剛[1]　歐宴泉[1,3,*]

童綜合醫療社團法人童綜合醫院　醫學研究部[1]　小兒部[2]　泌尿科[3]

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摘要

新冠肺炎，少子化和癌症的增加是目前台灣炙手可熱的議題。潛藏於這些議題下的根源是千絲萬縷，難以釐清，因此，本輯所要介紹不光只與這些議題有關之關鍵因素，還有與這些議題有關的疾病的診斷、治療、預後以及教育等很豐富的內容以饗讀者。

關鍵詞：疫情、少子化、癌症的增加

* 通訊作者：歐宴泉醫師　童綜合醫療社團法人童綜合醫院　泌尿科　43503 臺中市梧棲區台灣大道八段 699 號

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Review Article

The Effect of Physical Activity on Preventing Cancer

Chieh Chen[1,2,*]

[1]*Division of Family Department of Medicine, Hualien Armed Forces General Hospital*
[2]*Institute of Medical Sciences, Tzu Chi University*

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Abstract

By 2030, patients over the age of 65 will account for 70% of all cancer patients. In terms of cancer mortality, the elderly have a much higher incidence of death by cancer than do the younger populations. Some types of cancer, such as breast, colon, and prostate cancer, may result from hormone imbalances in the human body. Scientific evidence has confirmed that about one-third of cancers are caused by lifestyle behaviors, such as body mass index, a diet low in fruit and vegetables, smoking, alcohol use, and a lack of physical activity. A vast body of analyses and studies of the strategizing of cancer prevention, research, and public health have concluded that the risks of cancer death can be divided into internal and external factors. The internal factors include inherited genetic variations, whereas the external factors are UV radiation, ionizing radiation, and carcinogens. Those factors may maliciously interplay with each other, leading to the rapid growth of cancer and death. This review summarizes the advancement in the knowledge of the risks of cancer and the advantages of increasing physical activity in fighting cancer. As exercise medicine is a substantial benefit against cancer, rather than a cliché, increasing the level of exercise may not only decrease cancer risk, but also help individuals live a longer and better life. Therefore, it has been shown that more and regular exercise can reduce the incidence rates of cancer via the secretion of myokines by skeletal muscle cells during exercise. In other words, the health benefits associated with exercise may occur through different types of physiological mechanisms, which may result in a lower incidence of cancer among individuals who engage in regular exercise.

Key words: cancer prevention, exercise prescription, cytokine, elderly population, endocrine

Introduction

By 2030, patients over the age of 65 will account for 70% of all cancer patients. In terms of cancer mortality, the elderly have a much higher incidence of death by cancer than do the younger populations. In fact, nearly 65% of patients who die from cancer are over 65 years of age. The Economic Development Council estimates that elderly people over the age of 65 represented more than 14% of the population in Taiwan in the year 2018; thus, Taiwan became an "aged society." In the year 2025, the elderly will exceed 20% of the general population, and Taiwan will be called a super-aged society[2,40]. Therefore, in addition to the changes in the social-demographic structure and the increased burden on young people that result from an aging population, "exercise medicine for the elderly," especially "medicine for cancer among the elderly," will become an increasingly urgent and problematic subject. According to research findings, some types of cancer, such as breast[3], colon, and prostate cancer, may result from hormone imbalances in the human body. Scientific evidence has confirmed that about one-third of cancers are caused by lifestyle behaviors, such as body mass index, a diet low in fruit and vegetables, smoking, alcohol use, and a lack of physical activity[4]. Therefore, it has been shown that more and regular exercise can reduce the incidence rates of cancer via the secretion of myokines by skeletal muscle cells

*Correspondence to: Chieh Chen, MD, Division of Family Department Of Medicine, Hualien Armed Forces General Hospital, No.163, Jiali Rd., Xincheng Township, Hualien County 97144, Taiwan (R.O.C.)

during exercise. In other words, the health benefits associated with exercise may occur through different types of physiological mechanisms, which may result in a lower incidence of cancer among individuals who engage in regular exercise. Moreover, patients with cancer may have compromised immunity compared with healthy subjects. Cancer became one of the top 10 causes of death in Taiwan in 1982, and has remained a leading cause of death for almost 40 years. In 2018, cancer accounted for approximately 28.2% of all causes of death[1,2]. In 2020, patients over 65 years of age accounted for 60% of all cancer cases, and, in 2030, patients over the age of 65 will account for 70% of all cancer cases. In terms of cancer mortality, the elderly also have a much higher incidence of death by cancer than do the younger populations. Nearly 65% of patients who die from cancer are over 65 years of age[5,7]. The incidence of developing tumors such as lung, colorectal, breast, and prostate cancer gradually increases with age. The possible causes of this phenomenon are long-term exposure to carcinogens, DNA instability (which increases the chance of cell mutation), immune regulation disorders, or decreased antioxidant capacity. However, the true underlying mechanisms remain unclear[5].

Risk of cancer death: internal and external factors

Cancer can brutally invade any tissue or organ, causing dysfunction and even death. The growth and development of a cancer cell is determined by both internal and external factors. Inherited genetic variations are internal factors. Tomasetti and Vogelstein et al. analyzed the relationship between dry-splitting replication and cancer prevalence, and found that random errors in human normal stem cell DNA replication are among the leading causes of subsequent cancer[6]. Specifically, if the tissue stem cells are renewed and replicated at a faster rate, the chance of occurrence of random replication errors is high. However, approximately 65% of cancers are strongly related to the maintenance of tissue constants, as well as to self-renewal and splitting time. Only 35% of cancers in tissues and organs are caused by factors such as the external environment and lifestyle. Traditionally, genetic inheritance seems to be the origin of one or more cancers in a given individual. However, a vast body of analyses and studies regarding the strategizing for cancer prevention, research, and public health indicates that cancer risk is heavily influenced by external factors, such as UV radiation, ionizing radiation, and carcinogens, which directly or indirectly affect the mutagenesis rates[7]. However, in contrast with the conclusions of Tomasetti and Vogelstein and colleagues, Wu et al. subsequently published their findings in *Nature* using a similar data analysis[7].

In addition, in the past, some scholars believed that 5%–10% of cancers were caused by the environment and by gene interactions that change the metabolism and mutation of cells, whereas the remaining 90%–95% of cancers were caused by lifestyle parameters[8]. Therefore, it would seem that genetically derived parental mutant genes, random mutations in stem cell replication, and environmental or lifestyle factors are all potential causes of cancer. If internal factors, which are like optic arts deceiving our eyes, are not a main factor in determining cancer development, and extrinsic factors, which result in deleterious mutations, are an unavoidable cancer risk, the only approach to avoid cancer is to improve our lifestyle parameters. Not surprisingly, increasing evidence confirms that regular exercise and physical activity can truly reduce the risk of cancer death[9,10].

Evidence of the reduction of cancer risk by physical activity

An integrated meta-analysis of 12 forward-looking generational studies from the United States and Europe provided insight into the importance of physical activity in reducing the incidence of cancer. Those researchers analyzed the risks of cancer in a population of 14.4 million people aged from 19 to 98 years (mean, 59 years)[11] and found that people who engaged in a greater amount of daily physical activity had a lower risk of esophageal cancer, liver cancer, lung cancer, kidney cancer, gastric cancer, endometrial cancer, myeloid leukemia, myeloma, colon cancer, head and neck cancer, rectal cancer, bladder cancer, and breast cancer[12] compared with people with lower daily physical activity[10]. Another integrated meta-analysis study covering a total number of 149,184,285 person-years included 174 studies, among which 35 focused on breast cancer, 19 targeted colon cancer, 55 concerned diabetes, 43 addressed ischemic heart disease, and 26 explored ischemic

stroke. That study discovered that, compared with individuals who engaged in insufficient exercise (total physical activity below 600 MET-min/week), breast cancer prevalence decreased by 14% and colon cancer prevalence decreased by 21% in subjects with sufficient daily physical activity[11]. Another study investigated 3,985,164 subjects, including 69,011 cancer survivors, and found that, compared with infrequent physical activity, the risk of cancer death was reduced by 17% when the average person's physical activity during leisure was 5, 10, 15, 20, and 25 MET-h/week; the mortality rates were reduced by 12%, 14%, 14%, 15%, and 16% for each of these physical activity levels, respectively. Among individuals with physical activity below 7.5 MET-h/week, for every MET-h/week increase in physical activity, the risk of cancer death was reduced by approximately 2%. This meta-analysis included 69,011 patients with cancer, and the results showed that the patients with the highest physical activity had a 22% reduction in cancer death rate compared with inactive patients[12]. Friedenreich et al. analyzed 26 studies and concluded that, compared with people who did not engage in regular exercise, young people with regular exercise habits had a 37% lower mortality rate. According to a small number of studies, the risk of recurrence and deterioration of breast cancer, prostate cancer, and colorectal cancer was reduced by 38%, 23%, and 40%, respectively, in patients who engaged in the highest level of physical activity[13]. Overall, based on the systematic reviews and integration analyses mentioned above, we can infer that a higher level of physical activity leads to a lower risk of cancer death. Although whether physical activity benefits patients with cancer has not been determined, according to Friedenreich et al., a physical activity level of 3600 MET-min/week may reduce the risk of cancer death[13].

Cardiorespiratory fitness (CRF) as an indicator of physical activity

Increasing physical activity can improve CRF. In addition to the studies of physical activity and cancer described above, which showed that high physical activity can reduce cancer risk and mortality, scientific studies focusing on CRF have also confirmed that a better CRF reduces the risk of death from cancer. As CRF can be classified as low, middle, or high, it can be used as an indicator to quantify the level of physical activity of a given subject in short- or long-term physical activity. In one report, the CRF of 13,949 males was graded by measuring oxygen uptake using treadmills. The individuals with the lowest oxygen uptake capacity (of up to 20%) were classified as belonging to the low CRF group, whereas the middle 40% made up the middle CRF group, and those with the highest 40% formed the high CRF group. The results of that study demonstrated that a high CRF in midlife was associated with an adjusted 32% risk reduction in all-cancer-related deaths and a 68% reduction in cardiovascular disease mortality after a cancer diagnosis compared with a low CRF in midlife[14]. The findings of this investigation were also corroborated by a generational follow-up study performed in Norway in 2017. Another study tracked 1997 men aged 40–59 years for 26.2 years. CRF was measured based on the maximum amount of exercise performed on a bicycle. The lowest cardiopulmonary fitness level (CRF level 1) was <118.9, whereas the second level (CRF level 2) was 119–161.4 and the third level (CRF level 3) was >161.5, before the CRF level and risk of cancer were compared, respectively. Compared with those with CRF level 1, individuals with CRF level 2 had a significantly reduced risk of proximal colon cancer (70%), lung cancer (61%), and pancreatic cancer (68%), whereas those with CRF level 3 had a reduced risk of bladder cancer (60%). A similar study that enrolled 5,876 retired men aged 60.5 ± 11 years and had an average follow-up of 9.9 years (range, 0.11–26.8 years) suggested that a higher CRF was correlated with a lower cancer mortality. At one MET, the risk of cancer death was reduced by 5%[15]. Compared with subjects with a CRF of less than five METs, individuals with moderate and optimal CRF exhibited a 26% and 46% reduction in cancer death risk, respectively, whereas the low CRF population attributable risk accounted for a 6.6% reduction[16]. Body mass index was used to classify individuals into overweight (24.0–26.9 kg/m^2) and obesity (>27.0 kg/m^2) groups, and subjects with a CRF of less than five METs were considered overweight with a CRF that was moderate or high. Among these subjects, the risk of cancer death was reduced by 48% and 79%, respectively, whereas individuals with moderate or optimal CRF who were overweight or obese had a reduced risk of cancer death, by 55% and 83%, respectively[17]. Schmid and Leitzmann used a systematic review and integrated analysis to analyze six previous prospective studies, which

included 71,654 subjects and 2002 cancer deaths[18]. The median follow-up time was 16.4 years. Those authors found that CRF exhibited a strong negative correlation with the risk of cancer death; moreover, the results remained similar after the study corrected them for the body fat interference factor. Therefore, it would seem that the overall CRF is an important risk factor for, and index indicator of the risk of, cancer death; furthermore, a higher implies a lower risk of cancer death. Several studies noted that various substances that are present in the blood after exercise inhibited the development of human cancer cells or induced apoptosis in cancer cells[19]. For example, an animal study assessed the serum collected after swimming for 1 h and compared it with the serum levels recorded before swimming. The serum collected after exercise was cultured with human breast cancer cells. The results showed that the proliferation of breast cancer cells was inhibited by 52% and that the activity of apoptosis proteins in cancer cells was increased by 54%[20]. Another study enrolled 10 adult male subjects to ride a bicycle for 1 h with 50%–65% $VO_{2\ m}$ax intensity. After exercise, the serum collected from these subjects was cultured for 96 h with human prostate cancer cells. The results of this experiment showed that the serum collected after exercise inhibited the growth of prostate cancer cells by 31%[21]. An in *vivo* study showed that the serum levels of breast tumor cells in patients with breast cancer were ultimately reduced at 6 months after the completion of treatment, with serum levels measured after 2 h of exercise (30 min warm-up, 60 min resistance training, and 30 min HIIT spinning). Compared with the control group, in which serum measurements were performed at rest, the serum collected immediately after exercise in the experimental group was cultured with breast cancer cells and improved the survival rate by 9.2%–9.4%[22]. In a study performed at Brock University in Canada, the researchers implanted lung cancer in a culture medium containing 10% post-exercise serum from six young men after 1 min of high-intensity interval training exercise, and found that this reduced lung cancer, with a cell survival rate of 59.1%–78.5%[23].

Proposed mechanisms via which increased physical activity can fight cancer

In addition, researchers studied patients who had recovered from colon cancer. These patients had undergone at least 1 year of medical treatment, including surgery, chemotherapy, or radiation therapy. The subjects were divided into immediate exercise and long-term exercise groups. The immediate exercise group performed high-intensity intermittent exercise (4 × 4 min at 85%–95% peak heart rate) and then provided a blood sample that was used to examine serum tumor markers, such as CEA, CA125, CA199, and CA153, or for cell culture aimed at identifying whether there had been an increase or decrease in cancer cells. In addition, the long-term exercise group performed the same high-intensity interval training. Training was carried out three times a week for 4 weeks, and serum was collected before and after training. The results showed that the serum collected immediately after exercise had a significantly reduced number of colon cancer cells. The serum collected at 120 min after exercise and in the absence of exercise did not have a reduced number of colon cancer cells. Therefore, these results suggest that the serum collected immediately after exercise contains a substance that can effectively inhibit the proliferation of cancer cells, whereas no such effect was observed in the serum collected in the resting time after long-term exercise training[24].

Molecular biology studies have also found that more than 9,000–10,000 different proteins and other substances are produced in muscles and blood after exercise[25]. Muscle is an endocrine organ that can secrete myokines, just as adipose tissue secretes adipokines. Exercise hormones may be proteins, peptides, and nucleic acids, which are collectively known as exerkines. Exercise hormones may be responsible for regulating the transmission of signals, physiological functional responses, and physiological functions and organizational structures after exercise in various cells, tissues, organs, and even physiological systems in the body[26]. Among them are calprotectin, osteonectin (or protein acidic, which is rich in cysteine), oncostatin M, and irisin (Fig. 1). These four muscle hormones may play an important role in inhibiting cancer cell development or inducing apoptosis in cancer cells after exercise[27]. In addition, micro ribonucleic acids (miRNAs or miRs), such as miR-133, miR-221/22, and miR1[28], and tumor suppressor factors produced in or released from muscles contracted by exercise and other organs and release into the blood, as well as pro-apoptotic miRNA, let-7, etc., may be

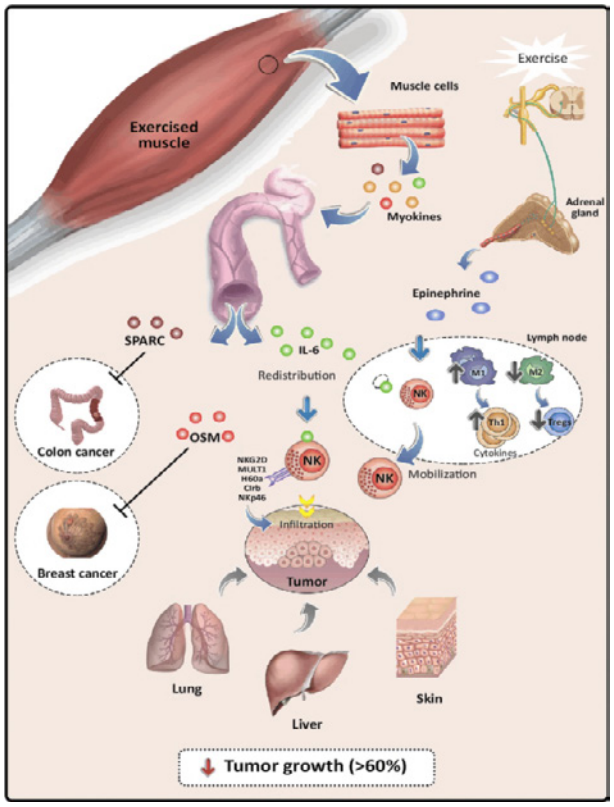

Fig. 1 Exercise, myokines, and antitumor immune responses. Working muscles produce myokines, such as IL-6, oncostatin M, and SPARC, which have potential antitumorigenic effects. Exercise also stimulates the mobilization of natural killer (NK) cells and promotes a polarized immunological response. The coupled effect of the IL-6 released from working muscles and the adrenal glands, respectively, might stimulate the mobilization and subsequent infiltration of IL-6 sensitive NK cells into tumors (reference 38).

important substances in the blood that inhibit the development or induce the apoptosis of cancer cells after exercise[29]. For example, based on a series of animal experiments, Idorn and Hojman found that immune cells, such as natural killer cells, were subjected to β-adrenergic signaling and β-adrenergic signaling during exercise[30].

Catecholamines are mobilized into the blood circulation, and increased blood perfusion occurs through the secretion of the muscle hormones IL-6, IL-7, and IL-5; a high body temperature caused by exercise; and other changes in the vascular structure in tumor tissues (Fig. 2). This is also an important mechanism for distributing natural killer (NK) cells into tumor tissues, to destroy cancer cells. Thomas et al. integrated past research findings regarding cell growth regulators, DNA damage repair proteins, androgen receptor coactivators, apoptosis, and the cell cycle after exercise in humans[31]. They found that direct biochemical changes, such as stagnation regulators, hormonal systems, immune system members, inflammation, oxidative stress, and antioxidant pathways, as well as indirect physiological beneficial parameters, such as sun exposure, weight loss, mood changes, etc., may also act as a preventative mechanisms against cancers. Focusing on the micro-environmental changes of the tumor tissue itself, including changes in tumor cell metabolism; reduction of PI3K signals, lactic acid, and monocarboxylate transporter 1 (regulation); regulation of the immune system; an increase of T cells and NK cells; and a reduction of tumor-associated macrophages, Koelwyn et al. proposed that angiogenesis, increased oxygen delivery, normal vascular maturation, and coverage of peripheral cells, among other factors, are also considered to be important exercise-related mechanisms in the prevention of cancer[32]. Hojman et al. believe that immediate responses to human physiology after exercise, resulting in physiological changes such as increased blood flow, shear stress, sympathetic activation, endocrine regulation of catecholamines and exercise hormones, and secretion of muscle hormones, contribute to increased blood perfusion in tumor tissues, the transport of oxygen, metabolic stress in tumor tissues, cell destruction, free radical production, and the creation of signaling pathways between cells to prevent metastasis[33]. The implementation of long-term exercise training, resulting in physiological changes that include improved immune system function, reduced systemic inflammation, improved metabolic function, increased normalization of tumor tissue vascular structure, increased tumor blood perfusion, improved overall immune function, and improved infiltration of immune cells, is the primary mechanism via which the risk of the development of cancer can be reduced[34]. Therefore, the mechanism of prevention of cancer can be divided as follows: (a) an immediate increase in exercise factors in the blood during exercise, which immediately inhibits the proliferation and development of cancer cells or induces apoptosis; and (b) a reduction of the risk factors for cancer caused by long-term regular exercise, as a result of benefits such as reduced inflammation, lower obesity rates, and reduced insulin resistance[29,35].

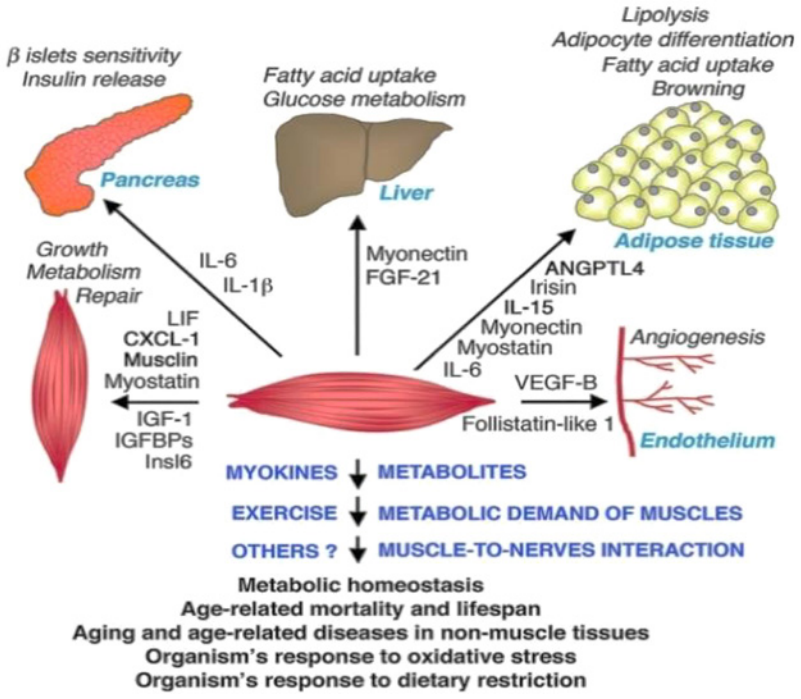

Fig. 2 Systemic regulation of metabolism by skeletal muscle. Studies performed in mammals highlight the important role of skeletal muscle in influencing metabolic homeostasis and the progression of age-related diseases. Muscle is also important in the response to dietary restriction and oxidative stress. Muscle may crosstalk with other tissues via cytokine interactions, the release of metabolites, systemic adaptations deriving from the energy demand of contracting muscles (exercise), and muscle-derived cytokines and growth factors (myokines). Myokines modulate several metabolic processes in the adipose tissue, endothelium, liver, pancreas, and other tissues (reference 39).

Conclusion

Increased physical activity, such as exercise, to improve cardiopulmonary fitness can reduce the risk of cancer death. Simply, the effects of increased physical activity in patients with various types of cancer can be roughly divided into short- and long-term ones: in the short term, exercise results in the immediate inhibition of cancer cell proliferation and the induction of apoptosis, whereas in the long-term, cancer risk can be drastically reduced through regular exercise over an extended period. Scientific evidence confirms that the causes of cancer are related to factors such as body mass index, a diet low in fruit and vegetables, smoking, alcohol use, hormone imbalance, and a lack of physical activity. Importantly, because increasing regular exercise can enhance the secretion of myokines by skeletal muscle cells and boost immune cell activity via cytokine stimulation, to decrease the risk of cancers, it will be beneficial to increase the levels of exercise, as it can promote a better life and reduce cancer risks[36,37].

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運動預防癌症的效果

陳 杰[1,2,*]

[1]國軍花蓮總醫院　家庭醫學科
[2]慈濟大學醫科所

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摘要

2030 年，65 歲以上人口將佔所有癌症患者的 70%。就癌症死亡率而言，老年人比年輕人的死亡率高得多；某些癌症可能是由於人體荷爾蒙所致，例如：乳癌，結直腸癌和前列腺癌。科學家證實約三分之一的癌症，是由不良生活型態所引起，例如 BMI 過高，蔬果攝取不足，吸菸，酗酒和缺乏身體活動。關於預防癌症，許多研究結果與公共衛生的大數據分析的結論：癌症死亡風險可以分為內在與外部因素；內部因素包含遺傳基因；外部因素則有紫外線照射、日常生活的輻射暴露和接觸致癌物質等；這些因素可能相互作用，而導致癌症死亡率增加。本文獻回顧關於罹患癌症風險的因子，及增加身體活動對於降低癌症發生的好處；運動醫學對於癌症預防不僅具有臨床證據效益；而且增加身體活動量還可以降低部分癌症的發生風險，並可以提升人類的生活品質；結論已經證實，增加規律的運動，可以促進運動期間肌肉分泌的細胞激素，降低癌症的發生率，透過不同的生理機制進行鍛煉，可能會對健康帶來益處。

關鍵詞：癌症預防、運動處方、細胞激素、老年族群、內分泌

* 通訊作者：陳杰醫師　國軍花蓮總醫院　家庭醫學科　97144 花蓮縣新城鄉嘉里村嘉里路 163 號

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Brief Communication

Re-purposed Anti-viral Agents On Patients' Mortality of COVID-19

Chung-Huang Tsai[1,2], Jen-Hsien Wang[3], Cheng-Chieh Lin[4], Su-Yun Huang[5], Che-Han Hsu[6,*]

[1]Division of Family Medicine, 6Division of Infection Diseases, Chung-Kang Branch, Cheng Ching Hospital
[2]Tunghai University Sports Recreation and Health Management Continuing Studies-Bachelor's Degree Completion Program
[3]Division of Family Medicine, [4]Division of Infection Diseases, China Medical University Hospital
[5]Department of Family Medicine, Tungs' Taichung MetroHarbor Hospital

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Abstract

According to Western media reports, the former U.S. President Donald Trump tested positive for SARS-CoV-2 infection leading to coronavirus disease 2019 (COVID-19); however, after a short period of treatment with a combination of antiviral drugs (antivirals), he then quickly recovered, suggesting great hope internationally for treatment success with the current antivirals. Unfortunately, the interim results of the SOLIDARITY trial by the World Health Organization (WHO) showed that all the promising antivirals had little effect on mortality. The present study reviewed large-scale trials for the current antivirals by using the drug name as the keyword to search published findings. These data were analyzed for 28-day mortality using Comprehensive Meta-Analysis 3.0 software and an integrated forest plot with Microsoft Excel 2019. The results showed that except for the ordinal score 5 (receiving O_2) patients had the benefit result in the Remdesivir trial, there was no significant benefit on mortality for all other antivirals. However, non-antiviral agent Dexamethasone was suggested to use, yet just as adjunctive therapy for more severe patients rather than mild patients.

Key words: Dexamethasone, Remdesivir, SARS-CoV-2, SOLIDARITY, WHO

On October 1, 2020, Western media announced that former U.S. President Donald Trump, First Lady Melania Trump, and other White House officials had tested positive for SARS-CoV-2 infection leading to coronavirus disease 2019 (COVID-19). Trump's symptoms then worsened, and on the next day he was admitted to Walter Reed National Military Medical Center in Bethesda, Maryland. After a short period of treatment with Remdesivir, Dexamethasone, and a high-dose (8-g) experimental cocktail of two monoclonal antibodies from Regeneron Pharmaceuticals, he recovered very quickly. Based on these results, the world held great hope for the current repurposed antiviral treatment for COVID-19. Nevertheless, notably absent from Trump's treatment plan was Hydroxychloroquine, an antimalarial agent that he had touted as a promising treatment throughout the COVID-19 pandemic, even after it was shown to be ineffective and potentially harmful. Indeed, Trump was still tweeting about the drug in late July 2020, long after its emergency use authorization had been rescinded. (https://www.the-scientist.com/news-opinion/what-we-know-about-donald-trumps-covid-19-treatment-plan-68023)

The World Health Organization (WHO) has launched a global megatrial called SOLIDARITY, with a pragmatic trial design that randomizes confirmed patients into either the standard of care or one of four active arms receiving a repurposed antiviral: Remdesivir, Hydroxychloroquine, Lopinavir-Ritonavir, or Lopinavir-Ritonavir plus Interferon-β (https://www.sciencemag.org/news/2020/03/who-launches-global-megatrial-four-most-promising-coronavirus-

*Correspondence to: Che-Han Hsu, MD, Division of Infection Diseases, Chung-Kang Branch, Cheng Ching Hospital, No.966, Sec. 4, Taiwan Blvd., Xitun Dist., Taichung City 407, Taiwan (R.O.C.)

treatments). Moreover, warranting special mention in this trial were three promising adjunctive therapies: corticosteroids, anticytokine or immunomodulatory agents, and immunoglobulin therapy.[1] Unfortunately, the interim results of the SOLIDARITY trial showed that all of these promising agents had little effect on COVID-19 mortality, which strikes a blow to the hopes of the world for a successful treatment (https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1).

The analysis of the Adaptive COVID-19 Treatment Trial (ACTT-1, Remdesivir) from the U.S. National Institutes of Health study of 1062 patients showed a decrease in hospital stays of about 5 days (from 15 to 10 days); however, no significant survival benefit was observed for mortality over 28 days (HR 0.73; 95% CI 0.52-1.03; P = 0.071). Only the patients who were hospitalized and required any supplemental oxygen at baseline had the best results, with 70% reduced mortality (HR 0.30; 95% CI 0.14-0.64; P = 0.002); the other groups showed no significant benefit as categorized in the following groups:[2] 1) not hospitalized and no limitations of activities; 2) not hospitalized, with limitation of activities, home oxygen requirement, or both; 3) hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection control or other nonmedical reasons); 4) hospitalized, not requiring supplemental oxygen but require ongoing medical care (related to COVID-19 or to

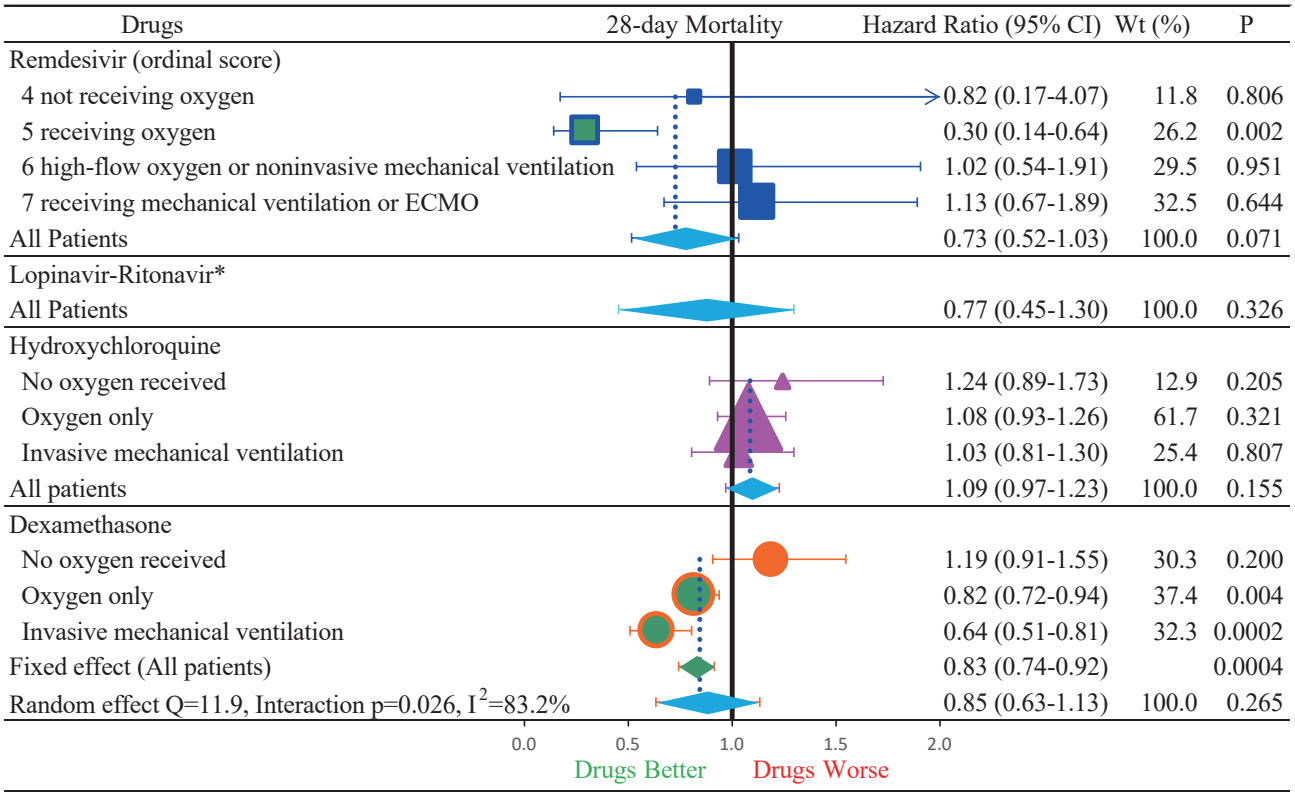

Fig. 1 The 28-day mortality of Remdesivir, Lopinavir-Ritonavir, Hydroxychloroquine, and Dexamethasone for patients with coronavirus disease 2019.
ECMO = extracorporeal membrane oxygenation; Wt = weight.
*The hazard ratio 0.77 (95% CI 0.45-1.30) of the Lopinavir-Ritonavir trial was transformed from the rate differences -5.8 (95% CI-17.3 to 5.7) using Comprehensive Meta-Analysis 3.0 software.
The categories of ordinal scores are as follows: 1) not hospitalized and no limitations of activities; 2) not hospitalized, with limitation of activities, home oxygen requirement, or both; 3) hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection control or other nonmedical reasons); 4) hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related to COVID-19 or to other medical conditions); 5) hospitalized, requiring any supplemental oxygen; 6) hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7) hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; and 8) death.[2]
The P value denotes a probability for overall effect and the p probability for interaction between subgroups was considered.

other medical conditions); 5) hospitalized, requiring any supplemental oxygen; 6) hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7) hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; and 8) mortality.[2]

The Lopinavir-Ritonavir trial showed differences in the 28-day mortality rate of-5.8 (-17.3 to 5.7) transformed to HR 0.77 (95% CI 0.45-1.30) using Comprehensive Meta-Analysis 3.0 software. Both of the Lopinavir-Ritonavir trial[3] and the RECOVERY trial (Hydroxychloroquine, HR 1.09; 95% CI 0.97-1.23; P = 0.155)[4] showed no significant benefit for 28-day mortality.

The Dexamethasone trial showed a significant reduced mortality by 17% (HR 0.83; 95% CI 0.74-0.92; P = 0.0004) with substantial heterogeneity (Q = 11.9, interaction p = 0.026; I^2 = 83.2%). Because of the high heterogeneity, the random effect result was suggested and no significant benefit was noted herein (HR 0.85; 95% CI 0.63-1.13; P = 0.265). Dexamethasone was suggested as an adjunctive use for patients with more severe disease and requiring oxygen support (HR 0.82; 95% CI 0.72-0.94, P = 0.004) and mechanical ventilation (HR 0.64; 95% CI 0.51-0.81; P = 0.0002). This drug had no benefit for patients who were not receiving oxygen (HR 1.19; 95% CI 0.91-1.55; P = 0.200).[5]

In conclusion, except for the patients who were receiving oxygen support and experienced a mortality benefit from Remdesivir, no significant benefit for 28-day mortality has been shown for any of the repurposed antivirals to date. However, Dexamethasone was suggested for use as adjunctive therapy for patients with severe disease, such as those receiving oxygen support or mechanical ventilation.

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重新用途抗病毒藥對 COVID-19 患者死亡率的影響

蔡崇煌[1,2] 王任賢[3] 林正介[4] 黃素雲[5] 許哲翰[6,*]

澄清綜合醫院中港分院 [1]家庭醫學科 [6]感染醫學科
[2]東海大學運動休閒與健康管理進修學士班學位學程
中國醫藥大學附設醫院 [3]感染科 [4]家庭醫學科
[5]童綜合醫療社團法人童綜合醫院 家庭醫學科

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摘要

根據西方媒體的報導，美國總統川普（Trump，特朗普）對新冠肺炎（SARS-CoV-2，COVID-19）的檢測呈現陽性後，即接受短期混合抗病毒藥物治療，之後很快就康復，因此，世人對當前作為重新用途的抗病毒藥寄予厚望。可惜的是，世界衛生組織（WHO）進行的 SOLIDARITY 試驗的期中分析結果顯示，所有目前有希望的抗病毒藥物對死亡率幾乎沒影響。我們根據抗病毒藥的名稱作為關鍵詞，選取已發表的大規模試驗，使用 Comprehensive Meta-Analysis 3.0 分析抗病毒藥對 28 天死亡率的影響，並使用 Microsoft-Excel 2019 繪製森林圖。結果在四種藥物的研究結果顯示，除了序數得分為 5（接受 O2 治療）的患者在瑞德西韋（Remdesivir）試驗中具有獲益的結果外，其他目前已發表的所有抗病毒藥物於死亡率均無明顯益處。然而，重症患者建議可使用非抗病毒藥 Dexamethasone 作為輔助治療，但未使用氧氣的輕症患者不宜。

關鍵詞：地塞米松、瑞德西韋、新冠肺炎、SOLIDARITY、世界衛生組織

* 通訊作者：許哲翰醫師 澄清綜合醫院中港分院 感染醫學科 臺中市西屯區台灣大道 4 號 966 號

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Original Article

The reality for Prolonged Mechanical Ventilation In Patients With Palliative Care

Szu-I Yu[1,3], Li YH[3], Yu-Chen Chen[4], Chen Yi Yu[4], Hueng-Chuen Fan[2,4,*]

[1]Department of Respiratory Therapy, [2]Department of Pediatrics, [4]Department of Medical Research, Tungs' Taichung Metroharbor Hospital, Taichung, Taiwan
[3]Department of Health Policy and Management, Chung Shan Medical University, Taichung, Taiwan

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Abstract

The number of patients who require prolonged mechanical ventilation increased during the last decade, resulting in a large population of chronically ill patients[1]. Palliative care is an indispensable part of continuing care in the end-of-life period and is a basic human right[2].

This study established the incidence of prolonged mechanical ventilation in the Ministry of Health and Welfare Information Science Center, Taiwan, and reported different characteristics of patients receiving prolonged mechanical ventilation (mechanical ventilation dependency, ≥21 days) and compared them with those receiving palliative care.

Key words: palliative care, respiratory care, prolonged mechanical ventilation-dependent, healthcare database

Introduction

The number of patients who require prolonged mechanical ventilation (PMV) increased during the last decade, resulting in a large population of chronically ill patients[1]. The World Health Organization (WHO) defined palliative care as an indispensable part of continuing care in the end-of-life period, emphasizing the importance of multifaceted integration in all physical, mental, and social problems, i.e., a basic human right[2]. Palliative care promotes patients' dignity and quality at the end-of-life and does not extend the dying process or respirator use to support the last breath[3,4]. PMV not only result in low quality of life of patients but also creates burden on the health insurance system[4]. Patient receiving PMV often have a high depression level and low self-esteem and are unable to express their inner pain[5]. PMV is associated with high morbidity, mortality, and disability rates, with declined functional status and 1-year costs of almost half a million dollars[6,7,8]. Therefore, the current status of patients receiving palliative care should be carefully understood, and necessary improvement should be made accordingly. This study reported different characteristics of patients receiving PMV (mechanical ventilation dependency, ≥21 days) and compared them with those receiving palliative care.

*Correspondence to: Hueng-Chuen Fan, MD, Department of Medical Research, Tungs' Taichung MetroHarbor Hospital, Department of Pediatrics, Tungs' Taichung MetroHarbor Hospital, No. 699, Sec. 8, Taiwan Blvd., Taichung, Taiwan (R.O.C.)

Method

Study Population

The study used a healthcare database of 100 million people sampling file, from Taiwan's National Health Insurance System collected by the Ministry of Health and Welfare Information Science Center, Taiwan, and screened for PMV-dependent patients age >17 years, from 2011 to 2013. They were intubated with ventilator support for >21 days, including invasive, negative pressure, and noninvasive ventilators, and patients in 2010 were excluded.

Data Collection

Data analysis was performed using the simple random sample with SPSS.20 program. Chi-square test and one-way analysis of variance were used to analyze the numbers, ratios, and disease varieties of patients with PMV who received palliative care from 2011 to 2013. A $p < 0.05$ was considered statistically significant. This study was carried out with an institutional review board approval (TTMHH-108C0014).

Results

PMV on patients receiving palliative care was analyzed and explored. Patients on respirators were found to have significant differences in gender, age, and place of residence. In the gender section, men accounted for 290 (60.5%), and women accounted for 189 (39.5%) and were 1.17 times more likely than men. With regard to age, 17 (3.5%) patients age 17–40 years, 151 (31.5%) age 41–60 years, 219 (45.8%) 61–80 years, and 92 (19.2%) age 81–10 years; with regard to the area of residence, 77 (16.2%) patients reside in the north, followed by 95 (19.8%) in the middle, 250 (52.1%) in the south, and 57 (11.9%) in the east (Table 1).

During the 3-year period, among the 79,399, 61,232, and 63,192 patients on PMV, 226 (0.28%), 133 (0.22%), and 479 (0.76%) received palliative care in 2011, 2012, and 2013, respectively ($P < 0.05$) (Fig. 1). Proportions of patients on PMV who received palliative care were low; however, the number of patients was increasing. Among patients with PMV who received palliative care in 2011, 2012, and 2013, 11 (4.9%), 5 (3.8%), and 22 (4.6%) patients were diagnosed with sepsis ($P = 0.47$); 150 (66.4%), 88 (66.1%), and 325 (67.8%) with malignant tumor ($P = 0.68$); 56 (24.7%), 33 (24.8%), and 110 (23.1%) with chronic illness ($P = 0.45$); and 9 (4%), 7 (5.3%), and 22 (4.5%) with late effects of motor vehicle accident, respectively ($P = 0.76$). These were among the analyzed patients on PMV who received palliative care (Fig. 2).

Table 1. 2011~2013 Initial Data Analysis (N=63192)

Variables	PMV compared with Palliative care Initial Data Analysis			
	TOTAL PMV compared with Palliative care.	Mean	SD	P value
Gender				.000
Male	290 (60.5%)			
Female	189 (39.5%)			
Age (years)				
17-40	17 (3.5%)			
41-60	151 (31.5%)	49.7	23.5	.000
61-80	219 (45.8%)			
81-100	92 (19.2%)			
Place of residence				
North	77 (16.2%)			
Central	95 (19.8%)			0.000
South	250 (52.1%)			
East	57 (11.9%)			
Chi-square test				*p<0.05*

Discussion

This study investigated a cohort of 63,192 patients requiring PMV, and the overall incidence of PMV for patients with acute respiratory failure requiring MV was 9.56% over 3 years. In another multicenter study conducted in Brazil, Loss et al.[9] investigated 218 patients requiring PMV, and the hospital death rate reached up to 65%. Outcomes for patients requiring PMV in Western countries varied according to different study settings and populations[4]. In Taiwan, our study had an in-hospital mortality rate similar with that in other countries. The difference

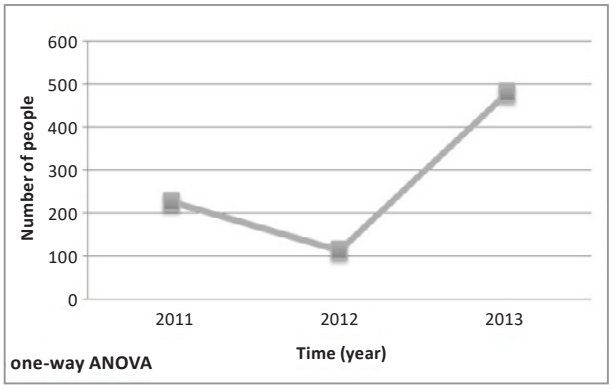

Fig. 1 PMV for receiving palliative care in Taiwan.

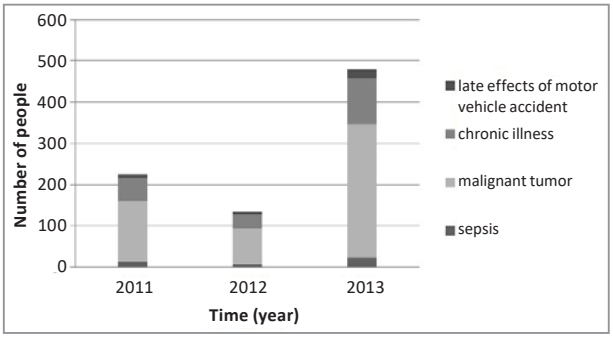

Fig. 2 PMV disease types receiving palliative care.

may be due to the high selectivity of patients transferred from the intensive care unit (ICU) to the Respiratory Care Center (RCC) to the Respiratory Care Ward. Second, patients with tracheostomy had better outcomes than those with translaryngeal intubation. Findings in our and a previous study indicate that a tracheostomy could lead to a higher survival rate in patients requiring PMV than patients who had translaryngeal intubation[10]. Therefore, physicians should consider performing a tracheostomy for these patients[4]. In conclusion, patients requiring PMV were selected based on the strict RCC admission criteria, and their in-hospital mortality rate was <20%[11]. Moreover, mortality was significantly associated with high disease severity, hypoalbuminemia, need for hemodialysis, and older age. In addition, the short-term mortality was 100% for patients with all five risk factors[4,11].

This study investigated a cohort of the 79,399, 61,232, and 63,192 patients on PMV, who received palliative care in 2011, 2012, and 2013, respectively. This study showed an increasing proportion of patients on PMV who received palliative care even though it remains low. The trend in providing palliative care can be attributed to promotions involving ineffective medical treatment and palliative care for critically ill and PMV patients since 2011 in Taiwan. Promotions not only increased the number of patients with malignancies but also different groups of disease types.

Conclusion

The study on patients with PMV constituted a distinct group of patients who were sicker on admission and exhibited higher mortality, longer hospital stays, and higher costs. This indicates a need to promote palliative care for patients receiving PMV to improve the quality of life and to reduce the burden on the health insurance system. We believe that increasing the use of palliative care will reduce suffering in patients on end-stage PMV.

Limitations

Our study had major limitations. First, only the in-hospital mortality rate was measured in this study. We did not assess outcomes of patients after discharge; therefore, long-term outcomes such as the 1-year survival rate are not indicated.[12] However, our study results should remain representative of this specific population.

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長期呼吸器依賴病人接受安寧緩和醫療照護之現況分析

游偲翌[1,3] 李亞欣[3] 陳玉珍[4] 陳怡妤[4] 范洪春[2,4,*]

童綜合醫療社團法人童綜合醫院 [1]呼吸治療科 [2]兒醫部 [4]醫學研究部
[3]中山醫學大學國際醫療管理所

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摘要

在過去的十年中，需要長期呼吸器依賴的病人人數有所增加，這產生了大量的慢性病病人 1。安寧緩和醫療是在人的生命中最後階段的持續照護中是不可或缺的一部份，它是一項基本人權。

本研究經由台灣衛生福利部信息科學中心了解了長期呼吸器依賴接受安寧緩和病人（呼吸器使用≥ 21 天）的人數及其不同的特徵。

關鍵詞：安寧緩和醫療照護，呼吸照護，長期呼吸器依賴，健保醫療數據庫

* 通訊作者：范洪春醫師 童綜合醫療社團法人童綜合醫院 兒醫部 台中市梧棲區台灣大道八段 699 號

Original Article

Flipped Classroom with Team-based Learning in Evidence-Based Nursing

Chin-Yi Huang[1], Yi-Cheng Liao[2], Ming-Tsung Lee[3], Li-Hsin Yu[4], Lon-Yen Tsao[5,*]

[1]*Department of Medical Education,*[2]*Department of Psychiatry,* [4]*Library and Learning Resources Center,*
[5]*Department of Pediatrics, Changhua Christian Children's Hospital, Changhua, Taiwan*
[3]*Research Assistant Center, Show Chwan Memorial Hospital, Changhua, Taiwan*

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Abstract

Background and purpose: Medical student and nurse's problem solving skills, team work and communication have been promoted in recent years through novel designs such as flipped classrooms with team-based learning curriculum.
Methods: Our hospital encourages the "*flipped classroom*" design so that the team-based learning method is combined with flipped classroom for the due appraisal of teaching literature. In this study, we share our experiences from course learning objectives, team composition, pre-course reading and an assigned homework and team-based learning activity design in order to elaborate and evaluate this training program.
Results: We have shown that implementing a "*flipped classroom*" with a team-based learning model in order to teach literature appraisal skills in evidence-based nursing is not only possible but may as well constitute an improved learning opportunity for nurses, providing a point of reference for clinical teachers who might want to implement the "*flipped classroom*" model of teaching.
Conclusion: Follow-up work is needed in order to evaluate the effectiveness of this model on both learning and clinical practices.

Key words: Evidence-based nursing; Systematic review; Meta-analysis; Flipped classroom; Appraisal skill; Team-based learning

Introduction

The Flexner Report in 1910 highlighted the ineffective teaching among many medical education programs in the United States [1]. From 1910s onwards, however, medical education was still largely characterized by passive educational strategies[2]. In late 1960s, McMaster University in Toronto, Canada began the first "problem-based learning" (PBL) curriculum[3], where by active educational approach learners were invited to focus on solving open-ended problems.

Typically, PBL was conducted in small groups which were led by faculty facilitators, which has been documented with a significant improvement in the practice of medical education[4]. Nevertheless, more evidence from PBL curriculums did not register noticeable improvements regarding the outcomes and was thus constrained in practice by the heavy manpower and extensive faculty development[5] that was needed.

In late 1970s, Larry Michaelson, a faculty member in business school at the University of Oklahoma, used group activities and assignments in smaller classes, which was effective in helping students learn how to apply concepts as opposed to simply learning about them[6]. Likewise, this "team-based learning" methodology can be used in academic settings such as in the field of medical education.

In 1993, Alison King illustrated the concept of

*Correspondence to: Lon-Yen Tsao, MD, MPH, Department of Pediatrics, Changhua Christian Children's Hospital, No. 135 Nanxiao Street, Changhua, 500, Taiwan (R.O.C.)

"*flipping a classroom,*"[7] which essentially shifts the traditional model of classroom instruction in which the teacher is typically the central focus of a lesson into a learner-centered model[8], of which the "flipped classroom" model represents a type of learning practice which blends both online and face-to-face learning[9]. To put it simply, learners review and learn the "teaching material" such as video outside the class, which will then communicate and discuss the topic with their respective classmates and teacher or instructor, ideally reaching a solution to the problem in a collective fashion.

Numerous studies related to flip teaching were able to prove that "flip classroom" learning methods can improve the effectiveness of students' motivation and satisfaction [10] as well as improving students' preparation before class (readiness) and their engagement in the classroom[11,12]. The performance of students participating in "flipped classrooms" is also said to be better than that of non-flipped classrooms[13-16]: Foldnes[17] shows that when students work alone, flipped teaching is not significantly different from traditional teaching compared to traditional teaching, but when students interact with their peers positive results are shown to be achieved.

In other words, the use of flip teaching strategies can improve students' readiness before class, make them actively participate in the curriculum and improve learning effectiveness. Additionally, "flip teaching" requires students to complete pre-class materials such as designated reading materials, lecture videos prepared by lecturers and PowerPoint slides. In their turn, class activities include review of difficult topics, team-based learning (TBL) activity courses and individual assessments. Team-based learning can also promote students' participation within their respective team while also increasing their overall knowledge [18]. Literature evidence points out that in contrast to traditional classroom teaching methods, the combination of "flipped classroom" teaching with team-based learning can improve student satisfaction and participation[19] and learning effectiveness[20,21].

The aim of this study, therefore, was to design and evaluate the said effectiveness of combining "*flipped classroom*" methods with team-based learning models to teach evidence-based nursing on the critical appraisal skills in a systematic review/meta-analysis article.

Methods

This program is mainly planned by the department of medical education of the study hospital. Using the in-hospital online registration system, nurses are able register for courses on the system. The number of participants for each course was based on the course content, and course participants are mainly N2-N3 nursing staff, of which a total of 72 nurses participated in this program. Finally, the present study is informed by a pre-test post-test design in order to make it possible to estimate the changes in outcomes before and after the required intervention.

Recruitment

Each team consists of 5 to 7 nurses and is as heterogeneous as possible.

Blended learning evidence-based medicine delivery

Every participant had to read and study the teaching material, "How to do a critical appraisal on systematic review/meta-analysis", online (around 20 minutes video) before the class. The content of the pre-class teaching material includes the important concept of critical appraisal, having also been assigned homework concerning the appraisal of a systematic review/meta-analysis article. Each participant had to accomplish this homework by SR CASP checklist and further discuss it with other participants and teacher in the classroom.

Specifically, the reading materials specified before the class were placed in the e-learning system, and researchers not only confirmed the reading experience of each participant on the system but also called before the class to remind them to finish reading the designated reading materials.

In-depth step-by-step workshop program

Step 1. Reading assurance (readiness assessment process, RAD), which includes individual and team testing. In total, this session takes 35 minutes and consists of 12 multiple choice test questions about the basic knowledge regarding the critical appraisal of a SR/MA article, which should be answered in 15 minutes while the team testing should be completed in the remaining 20 minutes.

Step 2. Asking questions followed by a moment of discussion and by the instructor's lecture. This step took 15 minutes to completion.

Step 3. In this session of 80 minutes all participants work on the pre-class assigned reading article for the discussion and try finding out the correct answers, during which the tutor is merely acting as a facilitator.

The multiple choice questions for testing the knowledge of the participants on critical appraisal on SR/MA are oriented by the following questions, (1) What is wrong regarding the review/overview article, (2) What is the difference between a narrative review and a systematic review? Which is right, (3) and What is wrong about meta-analysis, (4) In CASP systematic review checklist, which of the following descriptions correspond to the "inclusion and exclusion criteria" for the due selection of an article, (5) Was a comprehensive literature search done for the correct identification of all the relevant literature, (6) While doing a systematic review, which of the following processes need at least two reviewers and an independent review, (7) Has the reviewer addressed a clearly focused question and its research hypothesis, (8) Whose research is the most comprehensive? What is more comprehensive funnel plot, (9) From the forest plot, which study has included the greater number of participants? Was there a significant difference in the combined effect size? (10) Which is wrong in conducting a systematic review/meta-analysis, (11) In conducting a systematic review/meta-analysis, which of the following factors cause the least heterogeneity.

All participants are allowed to ask questions and discuss these questions collectively, and the teacher is invited to provide feedbacks and give a short lecture regarding the topics that were discussed. Usually, the teacher would synthesize and deliver the expert content, guide and encourage the participants to articulate their understanding the problem that was presented. Ideally, the facilitator of the team-based learning should share his or her own views regarding the applications or the problems presented to the participants.

The principle of team-based learning is "How to design an effective team-based activity." In general, all participants should participate in discussion, brainstorming and work together in order to solve a difficult problem.

We have used the *"Four Ss"* model proposed by Michaelson et al. [22] for creating and implementing an effective group assignment: (1) Significant (to students) problem; (2) Specific choice; (3) Same problem; (4) Simultaneous report.

After the team testing, all the participants would use the knowledge acquired from pre-class teaching materials to elaborate on a critical appraisal of an assigned homework based on a SR/MA article, discussing it together and raising a different color card at the same time to find out a specific answer. In this session, which takes 80 minutes, the teachers' role is to tell the participants what is the content they need to master, to create challenging problems for them to solve and to question and challenge their reasoning that made them reach their conclusion.

To put it briefly, the purpose of this design was to enhance the opportunities to learn, discuss and collaborate inter-group and intra-group.

Evaluation of the training program, data analysis and results

Regarding the evaluation of the effectiveness of this workshop we have used the Kirpatrick's four-level model to assess each outcome while also having developed a questionnaire with a five-point scale plus an open questionnaire in order to assess the participants' satisfaction regarding this workshop (reaction level) and the self-efficacy of the critical appraisal of SR/MA pre- and post-training program (learning level).

Table 1. Demographic characteristics (n=72)

variable	Frequency (%)
Age	
21-25	6(8.3)
26-30	18(25.0)
31-35	22(30.6)
36-40	20(27.8)
41-45	4(5.6)
45 ↑	2(2.8)
Leader	
N2	28(38.9)
N3	39(54.2)
N4	5(6.9)
Education	
College	6(8.3)
two-/four-year technical program	23(31.9)
Bachelor	31(43.1)
Master's degree	12(16.7)
Section	
Internal Medicine	14(19.4)
Surgery	12(16.7)
Obstetrics & Gynecology /Pediatrics	25(34.7)
Emergency & critical care	11(15.3)
else	10(13.9)

Table 2. Participant satisfaction questionnaire on the curriculum of this workshop

Item (Question)	Mean	SD
1. Was the time arrangement appropriate?	4.46	0.79
2. Was the main topic of this curriculum of this workshop clear?	4.49	0.72
3. Was the design of the workshop's activity more interactive than didactic?	4.46	0.68
4. Was the space of this workshop appropriate?	4.41	0.72
5. Was the content of the lecture practical?	4.46	0.66
6. Was the speaker's lecture interactive and lively?	4.46	0.66
7. Were you more familiar with the critical appraisal of the systematic review/meta-analysis of intervention article?	3.97	0.86
8. Were all the participants actively engaged in this workshop?	4.26	0.74
9. Was there enough time for participant's discussion and feedback?	4.23	0.73
10. Did this workshop improve the ability of critical appraisal of literature?	4.11	0.76
11. Did this workshop improve your understanding on teaching methods and capability to teach EBN?	4.06	0.76
12. Will you try to use the critical appraisal of literature method in your clinical practice?	4.09	0.78
13. In general, do you satisfy this workshop on EBN critical appraisal?	4.20	0.76

After the first draft of the questionnaire was completed, an expert validity assessment was performed and experts in related fields were invited to give their insights from which the final form of the questionnaire was determined. In this case Cronbach's alpha is often used in assessing the reliability of questionnaire, whose alpha value for its self-efficacy of participants' literature review was 0.96.

Finally, we have also encouraged and asked participants to complete a critical appraisal on an assigned SR/MA article (behavior level).

Statistical analysis

Paired t-test was used to compare changes before and after class regarding the self-efficacy of participants' literature review, having been executed with an experiment α-level of 0.05.

Ethical consideration

This project was exempted from an ethical approval by Changhua Christian Hospital Institutional Review Board (IRB No. 190718).

Results

The demographic characteristics of the 72 participants are presented in Table 1 and researchers briefly checked the e-learning system to see whether participants had completed their homework before class. The average correct answer rate was 70% for the test of basic knowledge of participants' literature review in-class.

Table 3. Qualitative data collected from the 72 participants

Item	Description
1.	More understanding the questions after discussion.
2.	Learn how to do a comprehensive critical appraisal of a literature from writing an assigned homework and teacher's lecture.
3.	Teacher (tutor) can give a correct answer to the difficult question.
4.	Learn how to do critical and systemic thinking.
5.	Easy to learn through group discussion, interaction and sharing.
6.	Learning a lot and very interesting in flipped classroom teaching method.
7.	I do not accustom to the flipped classroom model and cannot understand the content of the curriculum at all.

The result of the participants' satisfaction to this training program (Table 2) had shown that most of the participants had a higher satisfaction score, which overall was over 4.0 points, concerning the lecturers' content, in teams of practice, style of lecture and interaction as opposed to the normal didactic teaching method. Feedback from participants, whose key contents were analyzed and induced in Table 3, was divided as in the following: much easier to understand the problems and learned how to use the critical and comprehensive thinking techniques to solve the problems; much easier to learn through interaction and discussion within groups. There were, however, several participants who showed an inability to adapt

to this teaching method.

Participants' self-efficacy in the critical appraisal of SR/MA (Table 4) were statistically and significantly different (*p-value* <0.05) between pre- and post-training program, which proves that this training program is able to enhance the participants' skills regarding critical appraisal of literature and that all participants would certainly continue to practice these acquired skills in clinical settings.

Discussion

The aim of this study was to combine a "*flipped classroom*" method with a team-based learning model in order to teach EBN in a nursing training program. The results of this workshop shows participants were not only satisfied with the training program but it also had the ability to increase the participants' self-efficacy on how to critically appraise a SR/MA article.

There is very little research regarding this blended approach and specifically the "flipped classroom" model to teach EBN at a medical or a nursing school. From the previous experiences, however, implementing a "flipped classroom" model to teach EBM in a residency program is not only possible as it also enables more learning opportunities[23] and increases the overall knowledge[24] for residents. In this regard, and according to the results of the present study teaching critical appraisal skill on SR/MA article through the combination of the "*flipped classroom*" method with team-based learning to nurses is an interesting and practical method.

Even though the "flipped classroom" and team-based learning (FC/TBL) is a relatively new pedagogical model[25,26], it has enough potential to create opportunities for active learning, problem solving, engagement, and attitudes toward the value of teamwork and enhanced learning, the two most important outcomes of the FC/TBL model. Specifically, our findings suggest that FC/TBL is a suitable model for teaching critical appraisal of literature as demonstrated through the marginal improvements

Table 4. Assessment of the self-efficacy in the critical appraisal of SR/MA

Item (Question)	Pre/post test	Mean	SD	t value	p value
1. Critical appraisal of the validity and importance on SR?	pre	2.61	0.79	-7.55	< 0.001
	post	3.05	0.83		
2. Critical appraisal on: Did the review explicitly address a sensible clinical question?	pre	3.29	0.98	-3.39	0.002
	post	3.76	0.75		
3. Critical appraisal on: was the search for relevant studies detailed and exhausted?	pre	2.79	0.87	-5.98	<0.001
	post	3.53	0.76		
4. Critical appraisal on: were the Included primary studies assessed the risk of bias (quality of methodology)?	pre	2.58	0.72	-7.65	<0.001
	post	3.42	0.68		
5. Critical appraisal on: were Selection and assessment of studies reproducible?	pre	2.78	0.95	-7.41	<0.001
	post	3.62	0.68		
6. Critical appraisal on: was the "homogeneity test" done ?	pre	2.61	0.92	-7.22	<0.001
	post	3.50	0.69		
7. Critical appraisal on: how large was the effect size of the review?	pre	2.71	0.80	-6.59	<0.001
	post	3.47	0.56		
8. Critical appraisal on: Did the review address confidence and precision in effect estimation?	pre	2.66	0.85	-7.23	<0.001
	post	3.50	0.65		
9. Understanding "what is meta-analysis" ?	pre	2.79	0.84	-8.74	<0.001
	post	3.63	0.75		
10. Understanding "what is publication bias"?	pre	2.66	0.88	– 7.65	<0.001
	post	3.50	0.76		
11. Could you differentiate between systematic review and review article?	pre	2.89	0.95	-7.96	<0.001
	post	3.84	0.79		

noted on the following participants' assessments and feedbacks: "*Learn how to do a comprehensive critical appraisal of a literature from writing an assigned homework and teacher's lecture,*" and, "Easy to learn through group discussion, interaction and sharing." In this case, it is also worth pointing out the results of the present study were similar to a previous one made by Boysen-Osborn et al. [27].

Despite course evaluations of the participants' satisfaction having rated an average of 4.0 on a five-point scale, narrative participant feedback from our FC/TBL model was mixed. While the participants were overall satisfied with the training program, a conclusion which other studies have also previously reported, [20,21], there were still, however, a part of the participants who felt "I do not accustom to the "flipped classroom" model and cannot understand the content of the curriculum at all."

Although researchers were quick to remind participants they were to complete their homework before class, it was found that some of them were not actively engaged in the subsequent discussion by observing the participants' in-class behavior. Possible reasons were their poor readiness prior to class, their unfamiliarity to the topic that was being discussed, or their simple reluctance to participate. Looking into how to provide an incentive for participants to prepare for class, to increase participants' interest in the material that was provided, to assign interactive exercise pre-class, and to provide in-class activities that focus on higher level cognitive activities are the key issues for applying and continuing the FC/TBL model in clinical education.

Although most participants were satisfied with the FC/TBL model approach, however, our studies did not evaluate the effectiveness of the FC/TBL on performance. It is unknown that how this translated to improved performance. To effectively measure the learning associated with the FC/TBL, assessment needs to be realigned to capture higher level learning outcomes[28].

The strength of the present study was that this was a good start for designing a team-based learning and "*flipped classroom*" activities based on an important topic "critical appraisal of a SR/MA article," the cornerstone of EBM topic. The transformative potential of the "flipped classroom" method transcends beyond learning the factual content traditionally taught within a classroom setting, which typically and posteriorly assessed by written examinations.

Finally, there were several limitations in this study worth highlighting, such as the fact we did not have a control group to begin with and the formative and summative assessment on the critical appraisal skill was done very close to the end of the workshop. Further research is thus required to investigate the feasibility of implementing such training program in a larger cohort study.

Conclusions

The curriculum design of combining the "*flipped classroom*" method with team-based learning consists of the teachers providing participants with a short, pre-recorded video-lecture to deliver primary course contents outside the classroom, which allows participants to learn the material at their own pace. Once participants acquire the primary course contents outside the classroom, every participant has to take an in-class test and accomplish the assigned homework through a team-based learning approach, where participants can share and learn from each other and solve the problem as a collective. Conclusively, we have found that combining a "*flipped classroom*" with a team-based learning approach to teach literature appraisal is a good way to improve the learning experience and that, according to the results of the present study, teaching critical appraisal skills on SR/MA articles to nurses through this method is an interesting, innovative and practical approach to teaching.

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Conflicts of Interest

The authors declare they hold no conflicts of interest.

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結合翻轉課堂與團隊導向學習應用於實證護理教學

黃靜宜[1] 廖以誠[2] 李銘宗[3] 游立新[4] 曹龍彥[5,*]

彰化基督教醫院 [1]教學部 [2]精神科 [4]圖書館暨學習資源中心 [5]兒童醫院兒科部
[3]秀傳紀念醫院 研究輔佐中心

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摘要

背景及目的：近年來，透過新穎設計的翻轉課堂和團隊導向學習課程，提高了醫學生和護理人員的問題解決能力、團隊合作和溝通能力。
方法：本院鼓勵課堂教學的翻轉設計，因此將團隊導向學習方法與課堂教學相結合來進行文獻評讀的教學。在此研究中，我們分享了許多教學經驗，從課程學習目標、團隊組成、課前閱讀和作業指派、團隊導向學習活動設計到此訓練課程的評估。
結果：實施團隊導向學習模式的翻轉課堂，以教授實證護理文獻評讀技能，不僅是可能的，可為護理人員提供更好的學習機會，並且可做為臨床教師實施翻轉課堂教學之參考。
結論：此模式在學習和臨床實踐中的成效，仍需要進行後續追蹤來加以評估。

關鍵詞：實證護理、系統性回顧、統合分析、翻轉課堂、評讀技巧、團隊導向學習

* 通訊作者：曹龍彥醫師 彰化基督教醫院兒童醫院 兒科部 彰化市南校街 135 號

Case Report

Extrarenal Wilms' Tumor of the Ovary: A Case Report

Chun-Chen Hsu[1], Jong-Shiaw Jin[2], Meng-Yu Shi[3], Tien-Yung Wei[1,*], Chia-Jen Lee[4,*]

[1]Department of Obstetrics and Gynecology, [2]Department of Pathology, [3]Department of Medical Imaging, [4]Department of Medical Research, Tungs' Taichung Metro Harbor Hospital, Taichung, Taiwan

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Abstract

A primary extrarenal Wilms' tumor (ERWT) of the ovary is exceedingly rare. Here, the authors report the case of a 41-year-old woman who presented with lower abdominal pain and a palpable abdominal mass. Computed tomography examinations revealed a large solid mass located on the right side of her ovary and pelvic cavity. The patient was subsequently treated by surgical excision. Pathologic diagnosis of the neoplasm was ERWT of the ovary with a triphasic nephroblastoma comprising metanephric blastema, mesenchyme (stroma), and epithelial derivatives. In addition, the tumor occurred only in an extrarenal location without primary renal involvement. Immunohistochemical studies showed the tumor cells were positive for Wilms' tumor-associated protein 1, vimentin, and CD56, and were negative for CD99, estrogen receptor, progesterone receptor, smooth muscle actin, and S100. The patient was administered adjuvant chemotherapy according to recommendations from the National Wilms' tumor study and continued to be followed up for survival.

Key words: extrarenal Wilms' tumor (ERWT), triphasic nephroblastoma, blastema, stroma, epithelial derivatives

Introduction

Extrarenal Wilms' tumor (ERWT), excluding primary neoplasm in the kidney, accounts for less than 1% of Wilms' tumors[1]. The published literature indicates that ERWT can be located in the retroperitoneal, inguinal, sacrococcygeal, lumbosacral, or Para spinal lumbar regions, and in the coccyx, bladder, ovary, uterus, cervix, spermatic cord, testis, skin, mediastinum, and chest wall. Whether Wilms' tumor or ERWT, the diagnosis is almost always achieved based on histological features. Microscopically, there is no difference between Wilms' tumor and ERWT. Classical histological features of both Wilms' tumor and ERWT include a triphasic pattern of epithelial, stromal, and blastemal components[2]. The clinical course for extrarenal and renal Wilms' tumors appears similar; thus, similar staging and treatment guidelines can be followed. Here we present the case of a 41-year-old woman with an ERWT arising from the right ovary.

*Correspondence to: Dr. Chia-Jen Lee, Department of Medical Research, Tungs' Taichung Metro Harbor Hospital
Dr. Tien-Yung Wei, Department of Obstetrics and Gynecology, Tungs' Taichung Metro Harbor Hospital, No.699, Sec.8, Taiwan Blvd., Wuqi District, Taichung 43503, Taiwan (R.O.C.)

Case Report

A 41-year-old woman who initially presented with leiomyoma of the uterus was transferred to our gynecology clinic from the local community hospital. Her chief complaint was a palpable abdominal mass and lower abdominal pain since2–3 weeks earlier. Preoperative evaluation included chest radiography, computed tomography (CT), and laboratory studies. Her chest radiograph revealed a small right pleural effusion and mild atelectasis in the right basal lung. Neither the diaphragm nor the chest wall showed significant findings. Preoperative CT scan of the abdomen showed a heterogeneously enhanced solid and cystic mass measuring approximately 20.9× 20.5 cm and 20.6× 8.2cm, respectively, on the right side of

the lower abdomen and pelvic cavity (Fig. 1A and 1B). No abnormality was detected inside the kidneys. Her routine hematological and biochemical parameters and the urine analysis were normal. Carbohydrate antigen 125 (CA-125, also known as mucin16) was significantly high, with a level of 519.6 U/ml(levels below 35.0 U/ml are accepted as normal), where as other tumor markers such as carcinoembryonic antigen, α-fetoprotein, and human β-chorionic gonadotropin were within the normal range. CA-125 is recommended for clinical use in ovarian cancer screening. Therefore, the patient›s preliminary diagnosis was malignant neoplasm of the right ovary.

For reproductive-age patients with ovarian cancer, the decision to elect either conventional radical surgery or fertility-sparing surgery is complex and involves tradeoffs between the risks and advantages of each therapy. Before surgery, the clinician offers their expert opinion about the treatment options available to and the patient and the patient takes part in the treatment plan by following the approach of shared decision making. The pathologic evaluation of an intraoperative ovarian lesion is indicated for the diagnosis of ovarian mass for differentiating the neoplastic from the non-neoplastic. The differential diagnosis, as measured by intraoperative frozen sections (IFS),could achieve an accurate diagnosis and influence a patient›s treatment options and alternatives to undergoing surgery. The patient's ovarian and pelvic tumors were both diagnosed as

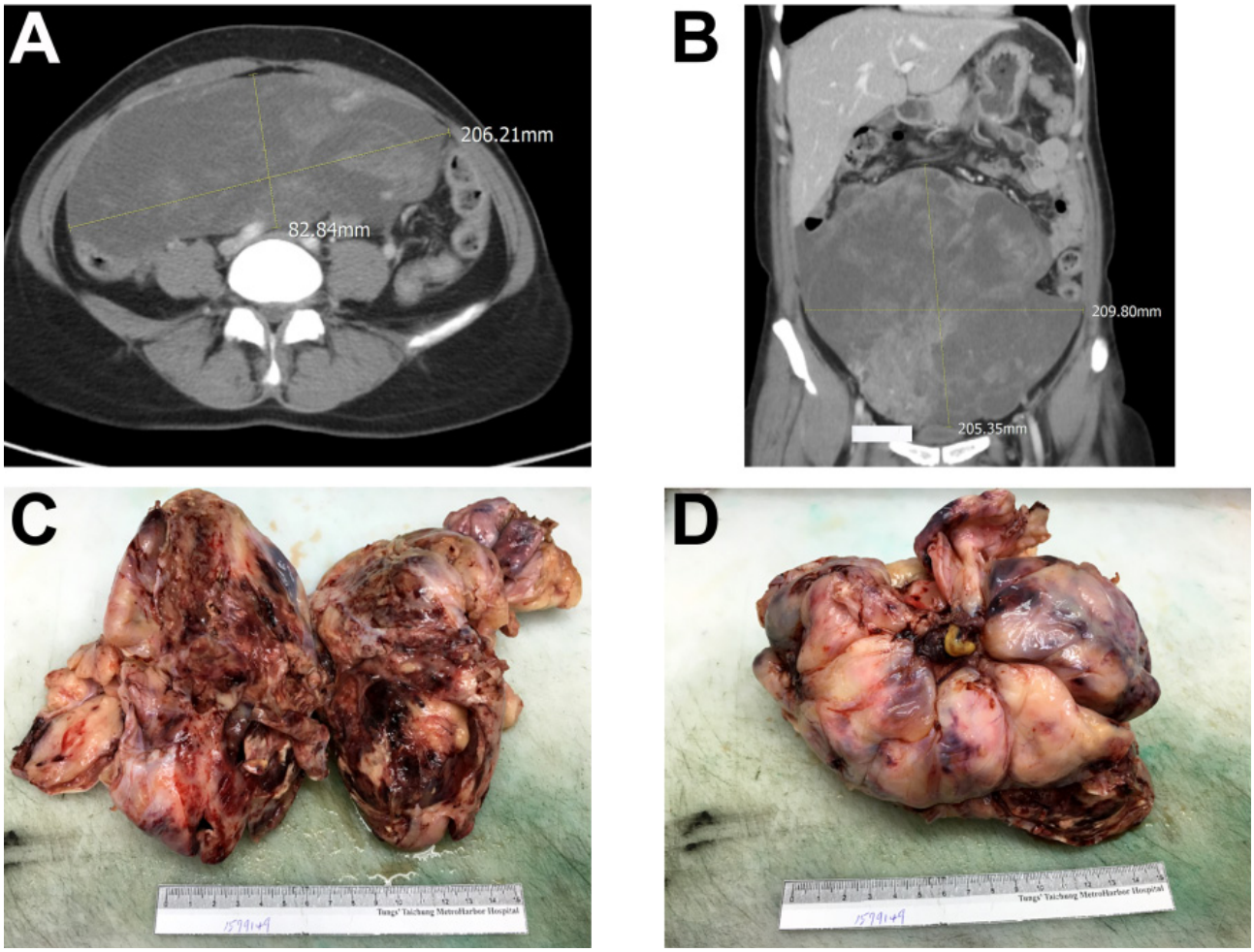

Fig. 1 Extrarenal Wilms' tumor of the ovary. Images from both triple-contrast CT scan and contrast CT of the *abdomen* and pelvis revealed a heterogeneously enhanced round mass in the patient with pelvic tumor (A, B). Gross pathology. The surface of the ovarian tumor was a brown-red color with ruptured capsule, multifocal hemorrhage, and necrosis, measuring approximately 20×17×5.5 cm (C). The surface of the pelvic tumor was a brown-red color with well encapsulated, multifocal hemorrhage, measuring approximately16×15×4 cm (D).

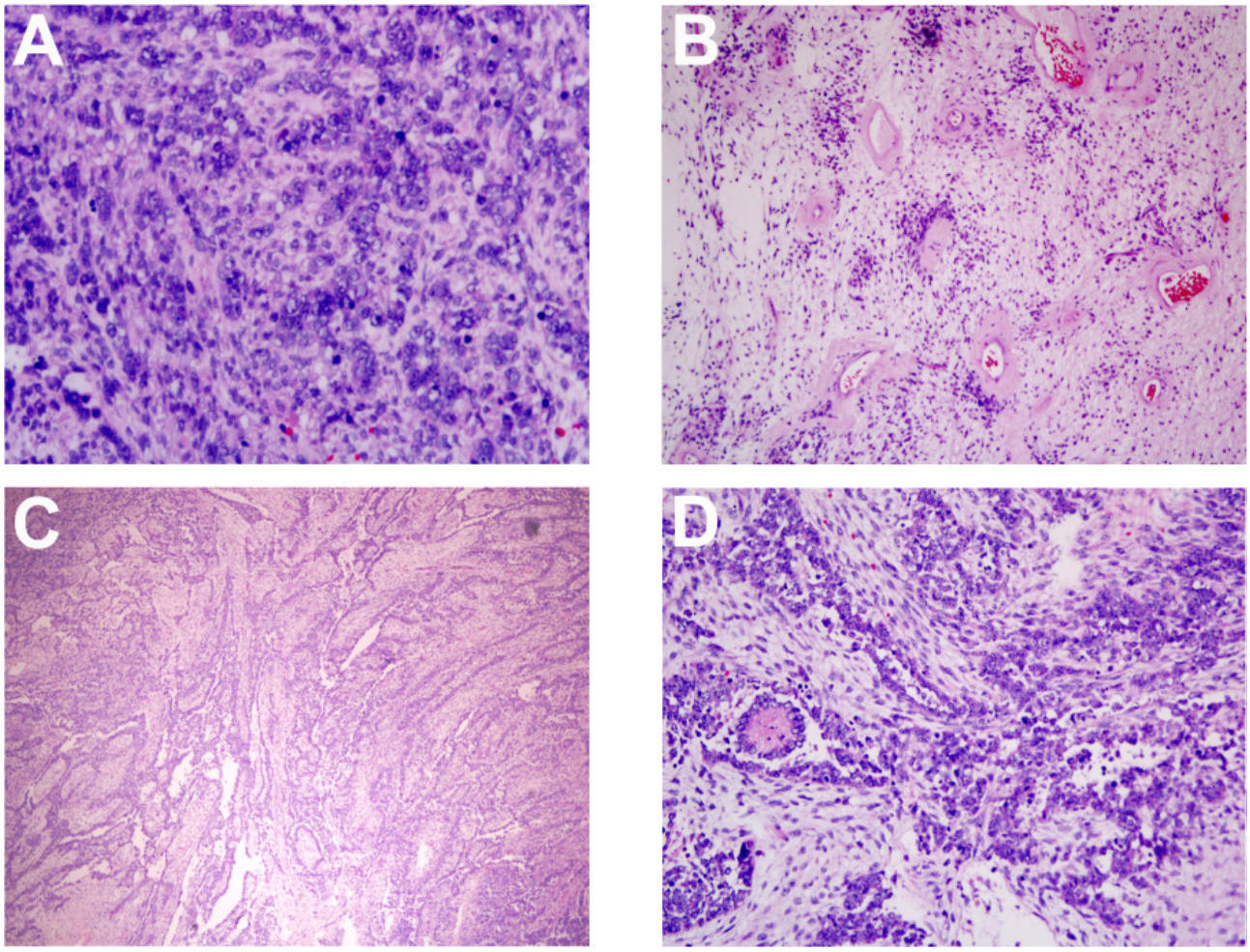

Fig. 2 Histopathology of the resected masses showing favorable histology of extrarenal Wilms' tumor consistent with triphasic nephroblastoma. Triphasic neoplasm consisting of blastemal, stromal, and epithelial elements was revealed (A-C). One of the sections contained focal primitive rosettes (D). Hematoxylin and eosin staining with magnification ×400, ×200, ×100, and ×200 (A-D, respectively).

malignant, and a differential diagnosis was of sarcoma or lymphoma was achieved.

According to the differential diagnosis of intraoperative biopsy, she was thereby taken for exploratory laparotomy, which revealed 1 mass located in the lower abdomen originating from the right ovarian region, and another mass located in the right pelvic cavity with pelvic wall involvement. Perioperatively, a 2-section mass comprising the right ovary with tumor (20×17×5.5 cm) and a right pelvic wall tumor(16×15×4 cm) were excised (Fig. 1C and 1D).

Overall, the ovarian tumor and pelvic wall tumor were brown-red in color. Only the ovarian tumor showed a ruptured capsule. Solid nodules with hemorrhage and extensive necrosis were noted on a cut section of the ovarian tumor and pelvic tumor. The fallopian tube was dilated, showed hydropic change, and was not involved. Microscopically, the sections of the 2 tumor masses all showed the following:

1. Triphasic growth pattern, including blastemal cells, stromal cells, and epithelial differentiation with a renal tubule-like structure (Fig. 2A, 2B, and 2C).

2. Both diffuse and serpentine blastemal patterns.

3. Focal primitive rosette formation (Fig. 2D).

4. Poorly differentiated tumor cells showing frequent mitoses, high N/C ratio, and small nucleoli.

5. According to the results of immunohistochemical staining, the tumor cells were strongly positive for Wilms' tumor-associated protein 1 (WT1), vimentin, and CD56.Moreover, the specimens were negative for CD99, estrogen receptor, progesterone

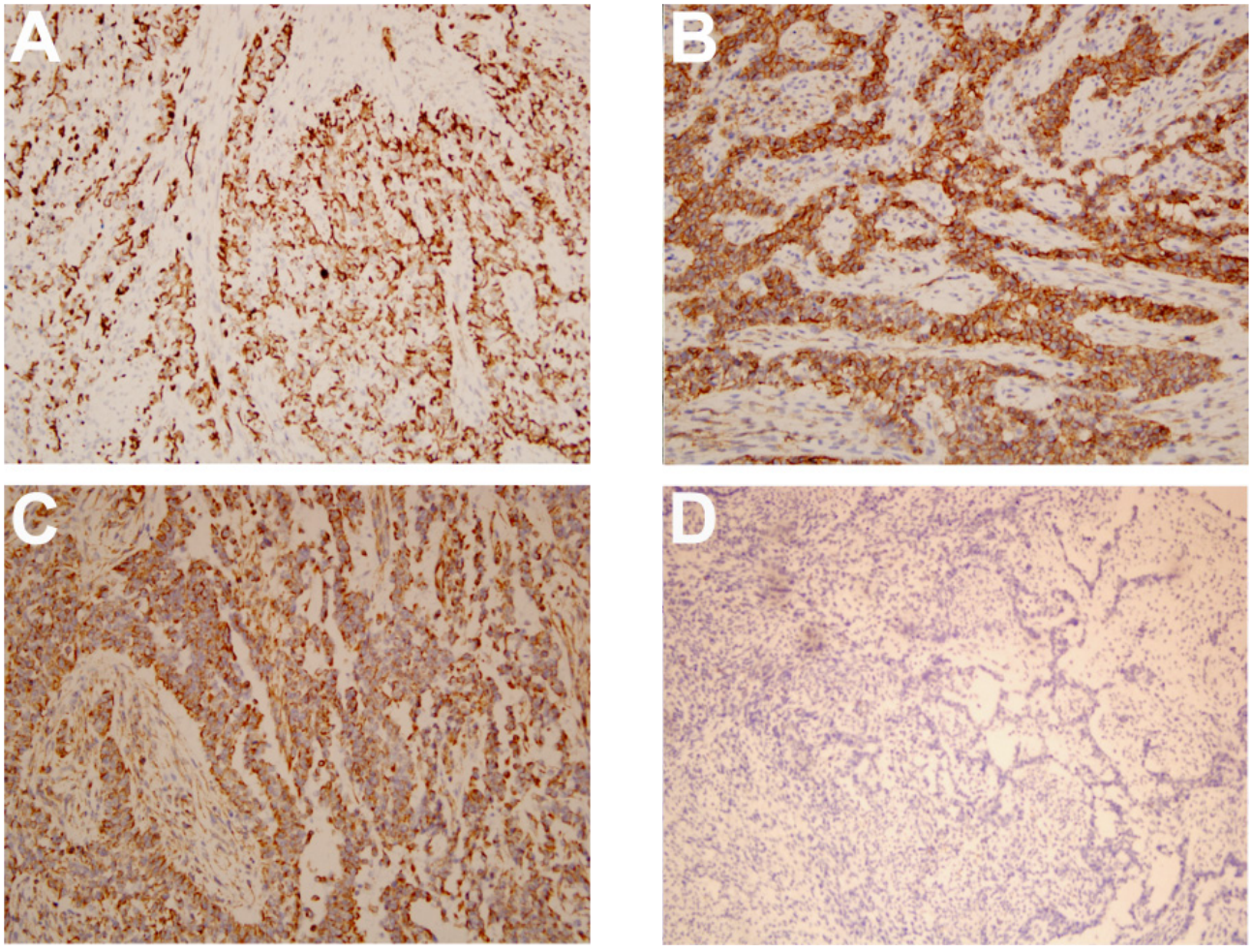

Fig. 3 Immunohistochemicalstaining. Representative immunohistochemical images of WT1 (A), CD56 (B), vimentin (C), and CD99 (D) staining in tissue sections from extrarenal Wilms' tumor of the ovary (IHC staining×200).

receptor, smooth muscle actin, and S100 (Fig. 3, data not shown). Although none of the immunohistochemical markers were specific for Wilms' tumor, the indisputable evidence of triphasic neoplasm led to the diagnosis of right ovarian Wilms' tumor with pelvic wall involvement, stage 2B.

The patient received therapy as per the National Wilms' tumor study (NWTS) IIB protocol, which included chemotherapy treatment with 2 drugs, Paraplatin and Phyxol. The patient is alive and recurrence-free with an 8-month follow-up.

Discussion

Ovarian cancer is at present the eighth leading cause of death and is among the world's most common cancers[3]. In fact, ovarian cancer refers to more than 30 different types of cancer that form in or on an ovary. The diagnosis of ovarian cancer starts with physical examinations (including pelvic examination and pelvic ultrasound),blood tests (including CA-125 and other biomarkers), and a CT examination. CA-125 levels in premenopausal women over 200 U/mL could indicate ovarian cancer, as may any elevation in CA-125 above 35 U/mL in postmenopausal women[4]. The diagnosis of ovarian cancer must be confirmed with examination of histological tissue sections from surgical excision. The histopathological diagnosis of ovarian cancer dictates many aspects of clinical treatment, management, and prognosis. Differential diagnosis of IFS is also a reliable method for the surgical management of patients with an ovarian mass.

Ovarian cancer typically has a relatively poor

prognosis. This poor prognosis could be because it lacks a clear early detection or screening test, and it metastasizes early in its development. Ovarian cancers shed cells into fluid within the abdominal cavity. These cells can subsequently implant on other peritoneal structures, including the bowel, uterus, urinary bladder,and lining of the bowel wall, leading to the formation of new tumors at those sites. For these reasons, ovarian cancers have been regarded as among the deadliest gynecological cancers.

The WT1 gene, identified as a tumor suppressor gene located at 11p13, is involved in the development of the genitourinary tract, mesothelial structures and spleen in the embryonic period [5]. There is growing evidence that the WT1 suppressor gene behaves as an oncogene in numerous types of cancer. Goyal *et al* have reported that the proportion of WT1 positivity in Wilms' tumors was 100%compared with 26.7% in non-Wilms' tumors (P<0.001) [6]. Recent reports have shown that WT1 is detected in the nucleus of tumor cells from Wilms' tumor and ovarian serous cancers; therefore, immunohistochemical detection of WT1 has been considered a diagnostic marker for these tumors [7]. CD56 is also frequently positive, but might not be an entirely specific marker in Wilms' tumors[8]. Altogether, these data suggest immunostaining of WT1 and CD56 could differentiate Wilms' tumors from other tumors.

ERWT occurs mainly in childhood; it is seldom reported in adults. In terms of the mechanism underlying ERWT occurrence, because the number of reported cases is very small, there is thus far no consensus. Thus, the therapeutic model currently still follows the procedure for the treatment of Wilms' tumor. However, the exact mechanism of ERWT has a positive correlation with Wilms' tumors originating from the ectopic metanephric blastema, which are tissues of primitive mesodermal origin and support Connheim's cellrest theory[9-11].

In the ovary, only 8 cases of ERWT have been reported[12]; thus, the number of cases is insufficient to provide a protocol for patient treatment. ERWT of the ovary originating from outside renal tissue is a rare type of tumor histologically characterized by a triphasic morphology comprised of blastema, stroma, and epithelial cells. Once it has been diagnosed, treatment typically involves surgery and chemotherapy. Additionally, radiotherapy should be recommended for patients with residual, metastatic or recurrent tumors according to the NWTS treatment guidelines[13].

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腎外的威爾姆氏卵巢腫瘤：病例報告

許俊正[1] 金忠孝[2] 施孟好[3] 魏添勇[1,*] 李嘉仁[4,*]

童綜合醫療社團法人童綜合醫院 [1]婦產部 [2]病理科 [3]放射科 [4]醫學研究部

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摘要

原發性腎外的威爾姆氏卵巢腫瘤非常罕見。我們報告一名 41 歲女性患者的病例，該女性因下腹部疼痛與可觸及的腹部腫塊而前來就診。電腦斷層掃描（CT）檢查顯示位於卵巢和骨盆腔右側出現巨大實質腫塊。經手術切除的腫瘤病理切片診斷此二腫塊皆為腎外腎母細胞瘤（ERWT）－因其具有包括胚基，間質（基質）和上皮衍生物的三相腎母細胞瘤組織。此外，腫瘤僅發生在沒有原發性腎臟轉移的腎外位置。免疫組織化學染色的結果顯示腫瘤對 WT1、Vimentin 與 CD56 呈陽性，對 CD99、ER、PR、SMA 與 S100 呈陰性。目前正依據威爾姆氏腫瘤研究小組（NWTS）所建議的治療方針對患者進行輔助化療，並持續進行追蹤中。

關鍵詞：腎外威爾姆氏腫瘤、三相腎母細胞瘤、胚基、基質、上皮衍生物

* 通訊作者：李嘉仁助理研究員 童綜合醫療社團法人童綜合醫院 醫學研究部
魏添勇醫師 童綜合醫療社團法人童綜合醫院 婦產部 43503 台中市梧棲區台灣大道八段 699 號

Case Report

Successful Late Preterm Delivery with Dehiscent Caesarean Scar Repair in Early Second Trimester: A Case Report

Kim-Seng Law[1,2,*], Cheng-Chun Lee[3]

[1]*Department of Obstetrics and Gynecology,* [3]*Department of Medical Imaging, Tungs' Taichung Metroharbor Hospital, Taiwan*
[2]*Department of Early Childhood and Family Educare, Chung Chou University of Science and Technology, Changhua, Taiwan*

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Abstract

Background: The incidence of uterine scar dehiscence in gravid women is increasing because of increasing rates of cesarean section and other uterine surgeries. Most previous reports have described expectant management without proactive measures. This report describes the successful early second trimester repair of a partially dehiscent uterine scar.

Case presentation: A 29-year-old woman was found to have a dehiscent cesarean scar on routine ultrasonography performed at 9 weeks' gestation. Surgical repair was performed at 13 weeks to reduce the protruding gestational sac and close the uterine scar. The patient's recovery was uneventful and she underwent a successful cesarean delivery at 36 weeks.

Conclusion: The early detection and timely repair of a dehiscent scar in pregnant women may prevent maternal and fetal complications.

Key words: Caesarean scar dehiscence, caesarean section, second trimester surgery, uterine rupture

Introduction

Uterine scar dehiscence or rupture is an important differential diagnosis of intermenstrual bleeding in women with a previous cesarean delivery. It should also be considered in the routine examination for new pregnancies after cesarean delivery, even in the absence of specific symptoms[1-3]. The early detection of a potential scar disruption is essential, and scheduled surgical intervention is advisable for women at high risk of subsequent uterine rupture[2,4,9]. The devastating complications of uterine scar dehiscence include preterm delivery, massive maternal blood loss, and the death of both mother and child. The expectant management of the dehiscent scar has been reported, with only a few studies describing proactive measures to prevent the complications of uterine rupture and preterm delivery[5-9]. This report describes a patient managed with early (13 weeks' gestational age) primary repair of the disrupted uterine scar with successful delivery of a healthy baby in the late preterm.

*Correspondence to: Dr. Kim-Seng Law, Department of Obstetrics and Gynecology, Tungs' Taichung Metroharbor Hospital, No. 699, Sec. 8, Taiwan Blvd., Wuqi Dist., Taichung City 43503, Taiwan (R.O.C.)

Case Report

A 29-year-old, gravida 4 para 2, woman presented at 5 weeks' gestation for an early ultrasound examination. She had undergone 2 cesarean deliveries (for breech presentation and placenta previa). Five months prior to presentation, she underwent an elective termination at 5 weeks' gestation because of lower segment implantation. Transvaginal ultrasonography revealed a hypoechoic linear defect over the lower segment of the uterus, which was indicative of a cesarean scar defect. A fundal gestational sac without a fetal pole indicated intrauterine pregnancy.

Magnetic resonance imaging (MRI) at 9 weeks' gestation revealed a thin (3-mm) cesarean scar defect and an amniotic fluid-filled sac over the previous lower segment incision site with otherwise normal findings (Fig. 1). Surgical intervention with the intent of primary repair of the defect was scheduled at 13+ weeks after a comprehensive discussion with the mother.

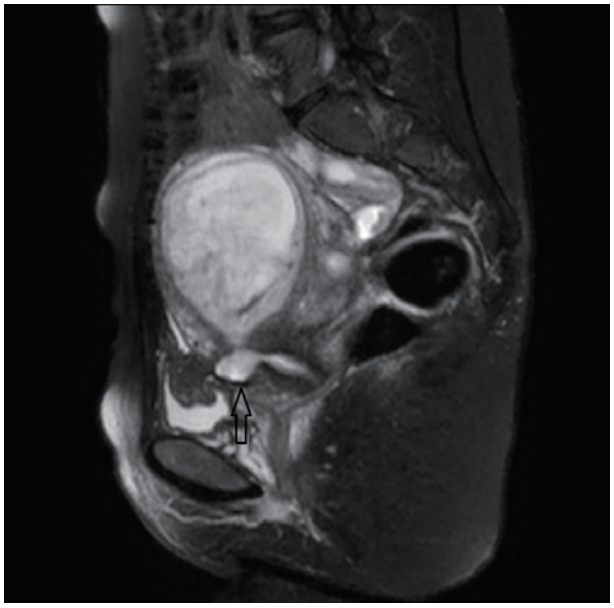

Fig. 1 Magnetic resonance image at 9 weeks. A T2W1 sagittal image showing a 1.2-cm pouch (black open arrow) in the lower segment of the uterus, over the cesarean scar. The pouch is filled with amniotic fluid. The anterior wall of the pouch is 3-mm thick.

After epidural anesthesia, a mini-laparotomy was performed. On entering the pelvic cavity and peeling off the uterine serosa, a dehiscent scar measuring approximately 1.5 cm in length was noted with the protrusion of the gestational sac (Fig. 2A). After reducing the sac using a moistened 1-cm cotton tip while taking care not to puncture the sac (Fig. 2B), the defect was repaired with 1-0 chromic catgut followed by the placement of a 3 × 2 cm segment of Mersilene® mesh (Ethicon, Somerville, NJ) with 1-0 Dexon. A secondary layer repair of the uterine muscle was completed, with sutures between the muscle and serosa layers to reinforce the defect. Suture removal was planned during the scheduled cesarean section. The abdominal cavity was closed layer by layer according to standard procedure after verifying a normal fetal heartbeat using a sterile sonar transducer. The patient was discharged uneventfully 2 days later. Routine antenatal care was provided with close follow-up of the repaired scar via serial ultrasonography. Another pelvic MRI at 24 + 6 weeks showed an intact scar and mesh and a viable fetus with an appropriate growth curve (Fig. 3). A cesarean section was scheduled for the late preterm because of a breech presentation and frequent contractions, which were controlled with oral ritodrine. A preterm baby was delivered

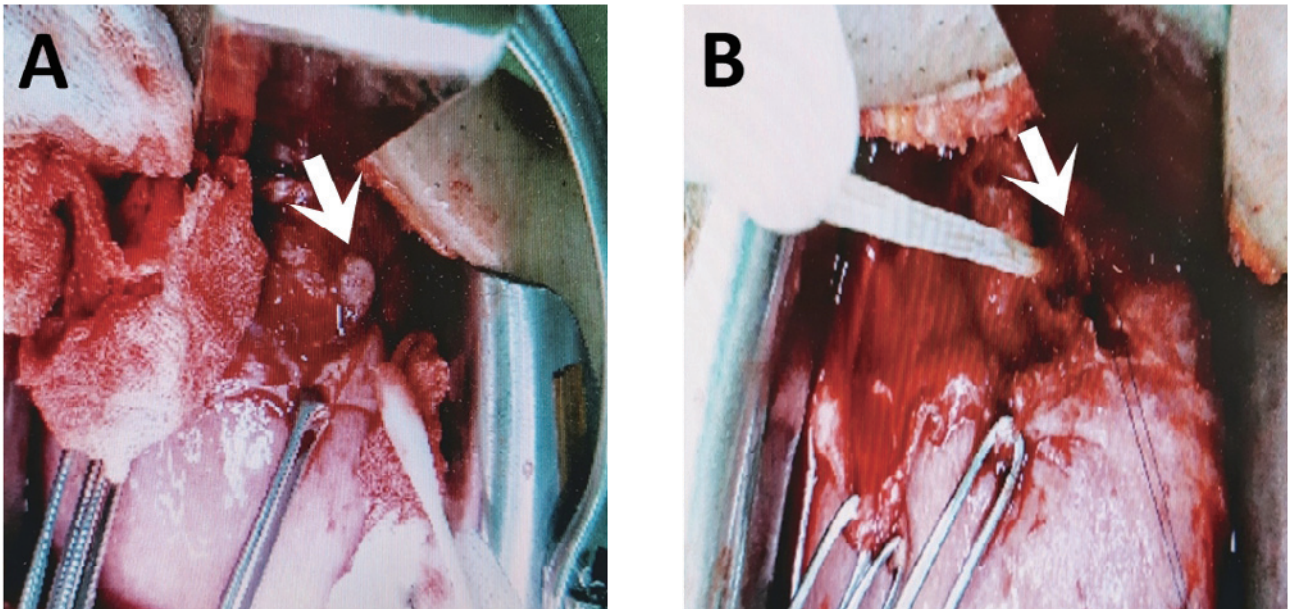

Fig. 2 Intraoperative management of the ruptured dehiscent scar. (A). The amniotic sac was seen protruding from the uterine cavity after the uterine serosa was peeled off. (B) The protruding sac was gently reduced using a moistened cotton tip. Care was taken to avoid puncturing the sac.

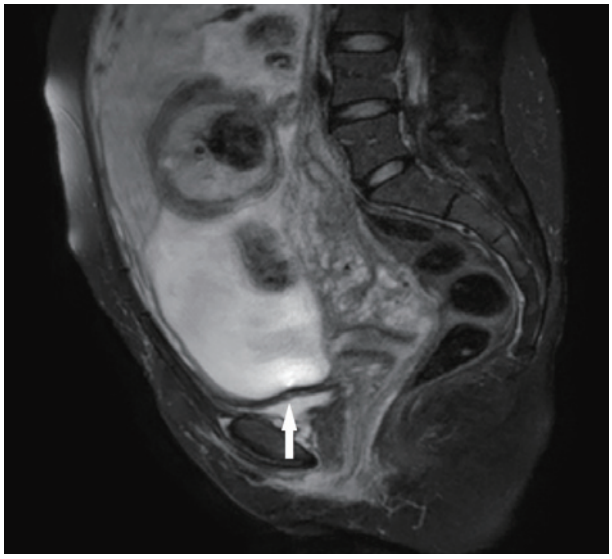

Fig. 3 Magnetic resonance image after surgical repair. T2W1 sagittal image showing the Mersilene® mesh (white arrow) with a subtle magnetic susceptibility artifact at the lower segment of the uterus. No pouch can be seen. The fetus is in the upper portion of the uterine cavity.

with Apgar scores of 8 and 10 at 0 and 5 minutes, respectively. The wound was closed with two layers of 1-0 Dexon and the mesh was removed. The mother and baby were discharged uneventfully 5 days after delivery.

Postoperative hysteroscopy 2 months later showed an intact scar with scattered tiny gestational tissue inside the uterine cavity. The mother's menses resumed 3 months later without prolonged spotting. The patient was followed up at our clinic regularly for 1 year without complications.

Discussion and Conclusion

Uterine scar dehiscence or rupture is rare (0.05%)[3,5]. Dehiscence refers to the disruption of the myometrial muscle layer by intact uterine serosa, while rupture is defined as the intra-amniotic contents or fetal parts actually protruding into the peritoneal cavity. With the advancement in imaging studies, it is possible to detect scar dehiscence as early as in the first trimester; however, the optimal treatment is unclear.

Most reports of dehiscent scars detected during the second trimester involved expectant management or pregnancy termination[4-9,10], with a few descriptions of surgical repair at the discretion of the caregiver. Only nine cases of primary repair of the disrupted scar have been reported to date, with the gestational age at repair ranging from 14 to 26 weeks[6-9]. In the current case, uterine scar dehiscence and potential rupture were detected by transvaginal ultrasonography and MRI in the early first trimester. To our knowledge, this report presents the earliest diagnosis and repair of uterine scar dehiscence, with pregnancy continuing up to the late preterm without complications.

The early detection of uterine scar dehiscence in high risk groups, such as those with previous cesarean deliveries, hysterotomy, or myomectomy, placenta previa or accreta, or preterm delivery, can be accomplished with more advanced imaging techniques[1-3]. Timely repair of the defect should be performed when the thickness of the myometrium is less than 3 mm. The reduction of the protruding amniotic sac can be more easily facilitated with two-layer suturing, with the patient in the appropriate Trendelenburg position during the procedure.

Postoperative evaluation should include monitoring the residual thickness of the myometrium and the well-being of the fetus, while aiming to prevent uterine contractions and preterm labor. The early detection of scar dehiscence and the timely repair of the defect can prevent uterine rupture and help preclude poor maternal and fetal prognoses.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

KSL was responsible for protocol/project development, manuscript writing, data analysis, and patient care. CCL contributed to data collection, data analysis, and patient care. Both authors read and approved the final manuscript.

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第二孕期前期進行子宮剖腹疤痕修復後成功的在第三孕期成功分娩 - 個案報告

劉錦成[1,2,*] 李政君[3]

童綜合醫療社團法人童綜合醫院 [1]婦產部 [3]放射科
[2]中州科技大學 幼兒保育與家庭服務系

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摘要

背景：隨著剖宮產率和其他子宮手術率的增加，妊娠婦女子宮瘢痕裂開的情況也跟著上升。在以往的研究報告中，皆未執行任何手術加以管理妊娠婦女子宮瘢痕裂開的情況。本個案中，我們順利的在第二孕期前期對此妊娠婦女進行子宮剖腹疤痕修復後並成功的在第三孕期成功分娩。
案例：一名 29 歲的女性在妊娠 9 週時進行常規超聲檢查後發現有開裂性剖宮產瘢痕。我們在妊娠第 13 週時進行手術修復突出的妊娠囊並縫合了子宮瘢痕。患者的預後良好，並在 36 週時成功地進行剖腹產。
結果：結果顯示及早發現和及時修復孕婦子宮上的開裂疤痕可以預防孕產婦和胎兒併發症的產生。

關鍵詞：剖宮產瘢痕裂開、剖宮產、妊娠中期手術、子宮破裂

*通訊作者：劉錦成醫師 童綜合醫療社團法人童綜合醫院 婦產部 43503 台中市梧棲區台灣大道八段 699 號

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Case Report

Central Anticholinergic Syndrome Due to Cyproheptadine Overdose in a Child: A Case Report and Literature Review

Chuen-Ming Lee[1], Hung-Ming Wu[2], Mei-Yu Kuan[3], Chih-I Hung[3], Ching-Shiang Chi[1], Hueng-Chuen Fan[1,4,*]

[1]Department of Pediatrics, [3]Department of Nursing, [4]Department of Medical Research, Tungs' Taichung Metroharbor Hospital, Taichung, Taiwan
[2]Department of Post Baccalaureate Medicine, China Medical University, Taichung, Taiwan

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Abstract

Central anticholinergic syndrome is common and its clinical manifestations include agitation, confusion, dry mouth, tachycardia, and hypertension. Cyproheptadine is a first-generation antihistamine with anti-serotonergic and anti-cholinergic effects and a common medication used for treating various allergic symptoms. The pharmaceutical technology has been improving the taste of the pharmaceutical formulations, including the syrups, without affecting their pharmacological effects, leading, however, to a risk of overdose, especially in children. This study reports a clinical case of a girl with a typical central anticholinergic syndrome due to taking excessive amounts of cyproheptadine. A high index of suspicion, anamnesis, and an astute physical examination are the main key to the most accurate diagnosis and the appropriate treatment.

Key words: Anticholinergic syndrome, Cyproheptadine, overdose

Introduction

Cyproheptadine, which is an antihistamine, is commonly used for the treatment of various allergic symptoms, such as red, irritated, itchy, watery eyes, sneezing, and runny nose. Other conditions, including fever, itchy skin conditions, blood products transfusion related allergic reactions, and life-threatening allergic reactions are also treated with this drug since 1961[1]. In addition to anti-allergic properties, cyproheptadine is an antagonist of the muscarinic, H-1 histaminic, and serotonin receptors[1]. The diverse properties of cyproheptadine allow it to cater to a large variety of clinical purposes, including feeding intolerance, appetite stimulation, Cushing's Syndrome, and migraine. Common side effects associated with the use of cyproheptadine, include excessive sedation, impairment of motor function, confusion, dizziness, blurred vision, dry mouth and throat, palpitations, tachycardia, abdominal distress, constipation, headache, urinary retention, and acute narrow angle glaucoma[1]. According to the pharmaceutical perspective, cyproheptadine is a white to slightly yellow crystalline powder that is odorless and has a slightly bitter taste[1,2]. The pharmaceutical industry has successfully turned the bitter nature of several drugs, including cyproheptadine to a more tasty syrup without affecting their pharmacological effects, which can lead to a higher risk of overdose, especially in children[2-5]. This clinical case reports a female child that presented bizarre behaviors, a dry mouth, hypertension, and tachycardia due to the intake of excessive amounts of cyproheptadine. A high index of suspicion associated with a careful anamnesis and an astute physical examination are the main key toward the accurate and precise diagnosis, which will allow

*Correspondence to: Dr. Hueng-Chuen Fan, Department of Pediatrics, Tungs' Taichung Metroharbor Hospital, No. 699, Sec. 8, Taiwan Blvd., Wuqi Dist., Taichung City 43503, Taiwan (R.O.C.)

the establishment of an appropriate treatment for the cyproheptadine-induced central anticholinergic syndrome.

Case Report

A previously healthy and fully immunized 2 year and 7-month-old girl was brought to the emergency department due to the presence of bizarre behaviors, including agitation, slurred speech, stumbling, falling, disoriented to person, place, time, and situation for one and a half hour. There was no previous history of febrile convulsions, neurological events, dog bite, recent travel, toxin exposure, animal contact, or hemorrhagic disease, and intake of any salicylic acid before this visit. Family history did not yield any remarkable findings. The family was advised to bring all household medications to the emergency department, which included several intact sacks of powdered Ambroxol Hydrochloride 1 mg/kg/day, Dextromethorphan 1 mg/kg/day, Pseudoephrine 0.5 mg/kg/day, and a syrup bottle of cyproheptadine 120 ml (48 mg), which were prescribed by the patient's family physician for her previous upper airway infection. The mother reported that the girl was playing with the bottle on the floor, and later the full bottle was founded empty. After approximately one and a half hours, the girl was transported to the emergency department. Upon physical examination, the child's weight was 12.8 kg (15th–50th percentile) and height was 91 cm (15the–50th percentile). Her body temperature, pulse rate, respiratory rate, blood pressure, and oxygen saturation were, 36.8°C, 180/min, 30 breaths/min, 170/113 mmHg, and 100%, respectively, on room temperature. The child showed confused and agitated behavior, and meaningless speech. The glasgow coma scale (GCS) was evaluated with a total score of 12, being E4M5V3 (Eye, Motor, Verbal). Her skin was intact and dry without apparent petechiae, purpura, or any abnormalities. Her pupils were 4–5 mm, equal, reactive, and dilated. Her pharynx was not erythematous or with less salivation. Auscultation of the child's heart revealed tachycardia without any significant murmurs. Her chest wall was symmetric and in full expansion with a clear breathing sound. Her abdomen was soft without a liver or a spleen enlargement and therefore not palpable. The child's four limbs were active with fine tremors with purposeless atheoid movements. Her deep-tendon reflex was enhanced (2/2, in both knees and ankles), while her pupillary reflex and corneal reflex were preserved. No meningeal signs were found and the bilateral Babinski sign was absent. Although her brainstem reflexes were intact, the child was admitted to the pediatric intensive care department due to the hemodynamic instability, bizarre manifestations, and confusion. The blood analysis revealed a total white cell count of 7500/mm^3, a hemoglobin concentration of 12.7 g/dl, a platelet count of 256,000 /mm^3, and a C-reactive protein concentration <0.02 mg/dl. The blood glucose, serum electrolytes, coagulation profile, ammonia, lactate, bilirubin, liver, and kidney function profiles were within the normal range. In addition, the urine analysis was normal. An electrocardiogram showed the presence of a sinus tachycardia at 178 beats per minute with normal intervals. The QRS axis was +45 degree. The QTc (corrected QT interval) was 469 milliseconds. The overall findings of this case were mostly consistent with an anticholinergic overdose caused by a drug with anticholinergic properties with predominantly central effects. The child's urine toxicology screen was negative, including the investigated drugs, namely benzodiazepine, barbiturate, morphine, cocaine, cannabinoids, acetaminophen, and alcohol. The toxicology service recommended that the patient needed to be admitted overnight for observation. The family of the child refused gastric lavage with activated charcoal and physostigmine treatment. Meanwhile, the patient's level of consciousness progressively improved (GCS: 15; E4M6V5) 8 hours after the metabolization of this drug. Then, the patient was transferred to the ordinary ward and discharged the next day without any complications.

Discussion

Histamine has been recognized as a major mediator in allergic effects, being a bronchoconstrictor, vasodepressor, ileum spasmogenic, can cause anaphylactic shock, and increase gastric secretion in laboratory animal models[6]. In addition, anxiety, depression, schizophrenia, migraine, appetite, and drug abuse are related to the 5-HT(serotonin) receptor[7]. The chemical structure of cyproheptadine resembles the phenothiazine, a H_1-antagonist. This drug acts by competing with histamine for the H_1-receptor sites on effector cells, having a potent 5-HT antagonist

activity through its 5-HT_{2A} receptor-blocking action. Despite its central depressant properties, the 5-HT antagonist effect of cyproheptadine may reduce the ACTH (adrenocorticotropic hormone) production because 5-HT can stimulate both CRH (corticotropin-releasing hormone) and/or ACTH secretion[8]. Moreover, it is used off-label as an appetite stimulant and for the treatment of cyclic vomiting. Therefore, it becomes a common medication that can be used to treat a wide variety of diseases.

In this clinical case, however, the exact mechanism by which the overdose of cyproheptadine caused the hypertension, pupil dilation, dry mouth, and skin consciousness disturbance in the patient remain unclear. In this regard, the antimuscarinic nature of cyproheptadine with its anticholinergic properties may contribute to these signs[4]. Pathophysiologically, acetylcholine transmits essential signals in the autonomic ganglia, namely in the parasympathetic nerve endings, muscle junctions, and synapses within the central nervous system in order to alter neuronal excitability, influencing synaptic transmission, and inducing synaptic plasticity and the neurons firing coordination[9]. The clinical characteristics of anticholinergic toxicity can be divided into central and peripheral effects. The central effects manifested by emotional and conscious disturbances, movement discordance, circulatory, respiratory and neurological dysfunction, hyperthermia, and seizures, while the peripherical effects are manifested by dysrhythmias, decreased gastrointestinal motility, dysphagia, salivation, hyperthermia, hemodynamic instability, decreased sweating, and urinary retention (Table 1)[5]. Apart from signs and symptoms, a central anticholinergic syndrome can occur without any peripheral anticholingeric manifestations[10]. Several medicines, such as dextromethorphan and pseudoephedrine in high doses may cause similar signs and symptoms as the serotonin syndrome[11,12]. The patients with serotonin syndrome may have a febrile response and athetoid movement with a relatively longer return to the baseline status[13]. The metabolism of the dextromethorphan/pseudoephedrine is approximately 4 hours[11,12]. In this case, it took 8 hours for her level of consciousness progressively improved, suggesting that the medications with different metabolism mechanisms and clearance times may have distinct clinical manifestations

Cyproheptadine was approved by the Food and Drug Administration for allergic diseases in children with ages above 2 years and the recommended dose for patients between 2- and 6-years-old is 0.25 mg/kg/ day[1,2]. The lethal dose for cyproheptadine is between 25 mg/kg to 250 mg/kg[2]. However, the use of lower doses can also be harmful, such as the case presented herein. Thus, this case report showed an unexpected complication of a toxic psychosis caused by a drug in a child that was taken only 4 times the therapeutic dose[3]. The suspected maximum dose consumed by this girl was 48 mg or 3.75 mg/kg, which is 15 times the therapeutic dose. Although the patient exhibited signs and symptoms that were consistent with anticholinergic toxicity, the anti-serotonergic and anti-histaminic effects of cyproheptadine

Table 1. Central and peripheral anticholinergic effects

Central	Peripheral
Agitation	Decreased bronchial and nasal secretions
Amnesia	Decreased bowel motility, Dysphagia
Anxiety	Dysrhythmias, including atrial and/or ventricular tachycardia abnormal conduction, bundle branch blocks, AV dissociation
	Hyperthermia
Aphasia	Hypertension
Ataxia	Hypotension
Choreoathetoid movements	Decreased salivation
Circulation collapse	Decreased sweating
Coma	Urinary retention
Confusion	Vasodilation
Delirium	
Disorientation	
Dysarthria	
Hallucination	
Hyperactivity	
Hyperthermia	
Lethargy	
Somnolence	
Myoclonus	
Nystagmus	
Respiration failure	
Seizures	

Modified from [5]

may be synergistically involved in the child's clinical manifestations.

The therapy for anticholinergic toxicity is usually supportive and conservative. The priority should be the monitoring of heart-lung functions and the management of the patient's airway, breathing, and circulation. Activated charcoal and gastric lavage may also decrease absorption and enhance drug elimination. Physostigmine is the only medication that can penetrate blood-brain barrier and reverse acetylcholinesterase. Physostigmine should be considered in the case of patients with both central and peripheral anticholinergic effects, namely cardiac arrhythmia, coma, respiration depression, and hypotension. Generally, physostigmine is administered 0.5 mg in children or 1–2 mg in adults, slowly being infused over 5 minutes until the cholinergic symptoms, such as salivation, lacrimation, urination, or defecation occur. Contraindications for physostigmine administration, include cardiovascular, bronchospastic, intestinal or bladder obstruction, or in the use of choline esters or depolarizing neuromuscular blocking agents[5]. However, the child's family refused the use of physostigmine and the girl spontaneously recovered without any complications. In conclusion, this case highlights the importance of the first-line doctors to identify the cyproheptadine-induced central anticholinergic syndrome early in the pediatric patients. A misdiagnosis of the disease may lead to life-threatening events.

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Cyproheptadine 過量在兒童引發中樞抗膽鹼症候群：一病例報告

李春銘[1] 巫宏明[2] 關美玉[3] 洪芝怡[3] 遲景上[1] 范洪春[1,4,*]

童綜合醫療社團法人童綜合醫院 [1]小兒部 [3]護理部 [4]醫學研究部
[2]中國醫藥大學學士後中醫學系

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摘要

中樞抗膽鹼症候群（central anticholinergic syndrome）並不罕見，臨床表現為躁動，神智不清，口乾，心博過速過速和高血壓。Cyproheptadine 是治療各種過敏症狀的常用藥物，是第一代抗組胺藥，具有額外的抗 5- 羥色胺和抗膽鹼作用。由於先進的製藥技術使此具苦味的化合物變成了美味的糖漿而不影響其藥理作用，特別是在兒童更會有增加藥物過量的風險。因此，我們報告一位女童，因為服用過量的 cyproheptadine 而表現典型的中樞抗膽鹼症候群。臨床高度懷疑，小心的病史詢問和仔細身體檢查是發現此病和適當治療的主要關鍵。

關鍵詞：中樞抗膽鹼症候群、cyproheptadine 、藥物過量

*通訊作者：范洪春醫師 童綜合醫療社團法人童綜合醫院 小兒部 43503 台中市梧棲區台灣大道八段 699 號

Case Report

Cerebral Venous Thrombosis: A Rare Cause of Stroke

Entzu-Liu[1], Chi-Chiang Yang,[2,*]

[1]Department of Critical Care Medicine and [2]Neurology Tungs' Taichung MetroHarbor Hospital, Taichung

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Abstract

Cerebral venous thrombosis (CVT), a life-threatening disease, is often underdiagnosed or the diagnosis is delayed due to the variety of clinical manifestations. We herein present a case of CVT with initial symptoms including consciousness disturbance and weakness in both legs. The patient was successfully treated with an anticoagulant, direct catheter thrombolysis, mannitol, and hyperbaric oxygen therapy.

Key words: cerebral sinus venous thrombosis, cerebral venous thrombosis, clinical manifestation, diagnosis, treatment

Introduction

Cerebral venous thrombosis (CVT), a rare disease, is present in approximately 0.5% of all strokes. The onset is typically at younger than 50 years of age[1]. Symptoms such as headache, reduced consciousness, motor deficit, or occasional seizures, are versatile and nonspecific, easily leading to misdiagnosis[2]. Therefore, an early diagnosis and proper treatment of this potentially life-threatening disease is a considerable challenge to first-line clinicians. Here, we present a case of successfully treated CVT and full recovery of neurological deficits.

Case presentation

A 37-year-old woman presented to a teaching hospital with sudden onset of consciousness disturbance and bilateral leg weakness. She had been taking oral contraceptives for the past 2 years for birth control. Two days before this admission, she complained of severe global headache with thrombosing sensation without aura. The pain improved after taking painkillers. On examination, her consciousness level was E4V1M4. Her vital signs were stable. Neurologic examination showed both lower limbs with muscle power 2, without sensory impairment. The D-dimer level was 657 ng/mL and her platelet count was 541 x 10^3/uL. Her coagulation tests were normal. An echocardiogram did not detect any vegetation or regional wall motion abnormality. A computed tomography (CT) scan found edema in the bilateral thalami, as well as basal ganglia and asymmetric edema in the right lateral temporal lobe. Magnetic resonance venography revealed an absence of flow at the right transverse and sigmoid sinus in combination with remarkable venous congestion in the bilateral thalami and bilateral basal ganglia (Figs. 1-3). She was still drowsy and her muscle power remained weak even though heparin was administered and the dose was adjusted according to the international normalized ratio. As more aggressive treatment, she received a direct catheter thrombolysis to the sinus on the third day of admission, accompanied by an anticoagulant, mannitol, and hyperbaric oxygen (HBO). Her consciousness level reached E4V5M6 and she achieved a full recovery in her limb muscle power on the nineteenth day of admission.

Discussion

CVT is a rare neurological disease that is difficult to diagnose. Its treatment is often delayed and results

*Correspondence to: Dr. Chi-Chiang Yang, Neurology Tungs' Taichung MetroHarbor Hospital, No. 699, Sec. 8, Taiwan Blvd., Wuqi Dist., Taichung City 43503, Taiwan (R.O.C.)

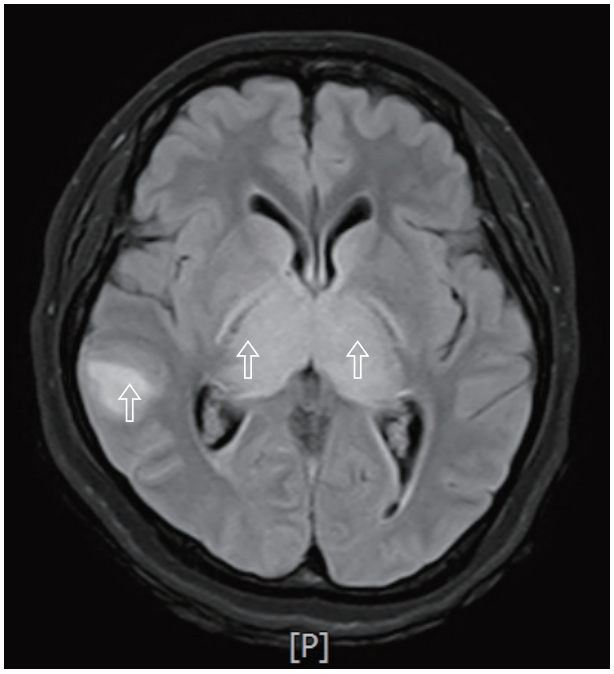

Fig. 1 Magnetic resonance imaging showing marked venous congestion in the bilateral thalami, bilateral basal ganglia, and right lateral temporal lobe.

in a poor prognosis and death. CVT is female predominant; the ratio for females to males is 3:1[1]. Half of woman with CVT could have an exposure history of oral contraceptives. CVT can be linked to prothrombotic conditions, head injury, infection, inflammation, and malignancy[2]. Regarding the diagnosis, the sign in noncontrast CT is a hyperdensity in the dual sinus and an "empty delta" sign in CT with contrast.[3] One-third of patients of CVT have been found to have a normal result on brain CT scan[3]. The most common CVT-involved location is the superior sagittal sinus and the transverse sinus. More than 70% of patients have multiple venous sinus involvement[4]. Whether focal brain injury and/or increased intracranial pressure may cause patients with this disease showing varied clinical presentations[5]. However, the clues for CVT are based on clinical findings, and brain imaging can confirm the diagnosis. Unlike arterial infarcts, venous infarcts are not strictly confined to a specific territory. In CVT, different brain lesions in imaging studies correspond to different sinuses' involvement. In our case, occlusions of the straight sinus presented symmetric abnormal signals and edema in the bilateral

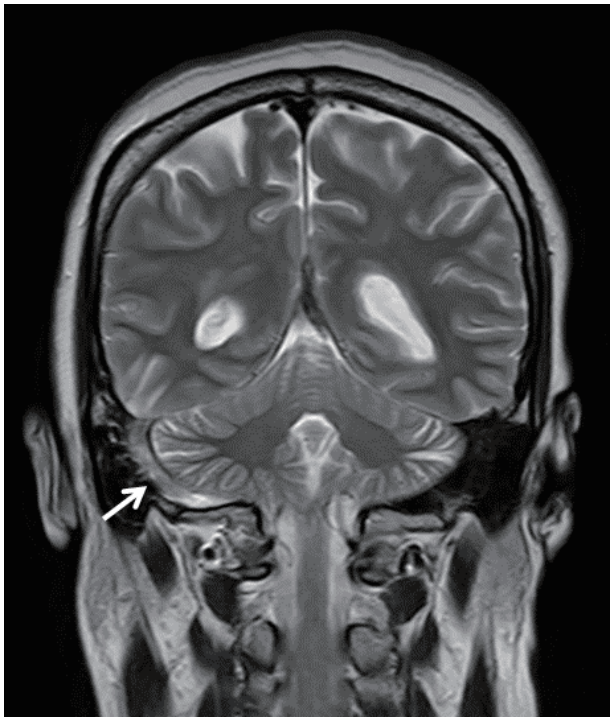

Fig. 2. Coronary section T2-weighted image showing loss of flow signal at right sigmoid sinus.

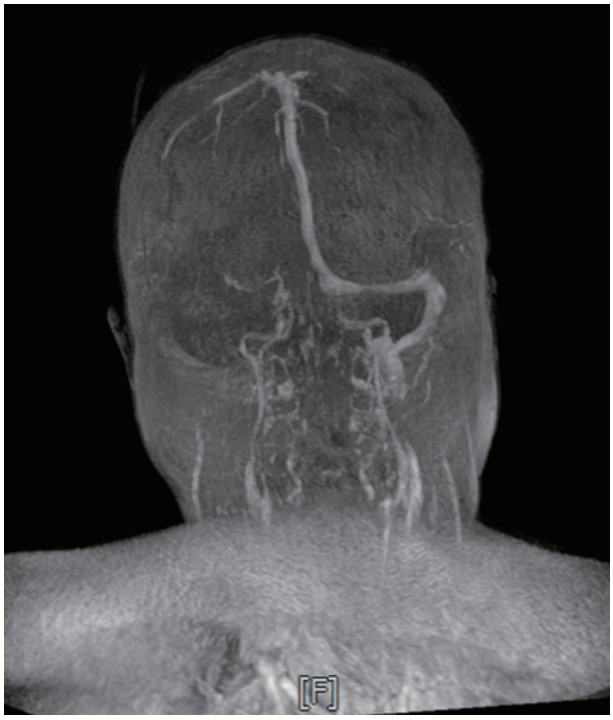

Fig 3. Magnetic resonance venography of brain showing absence of flow at right transverse and sigmoid sinus.

thalami and basal ganglia. The therapeutic plans for CVT should immediately resolve the underlying conditions and an anticoagulant should be administered[5]. Approximately 40% of patients with CVT progress to intracerebral hemorrhage[6], which is not a contraindication for the use of anticoagulation[7]. Some 9%–13% of patients with CVT have a poor outcome, although anticoagulant therapy and fibrinolytic therapy can provide benefit these patients[8]. The purpose for our use of HBO was to improve the patient's cerebral blood flow, although the medical evidence for this therapy is weak. However, she did make a full recovery after a combination of fibrinolytic therapy, mannitol, HBO, and medical care provided by a well-trained team.

Conclusion

CVT is a rare neurological disease. Delays in its diagnosis can cause death and poor neurological outcome. Patients with risk factors and new-onset headache accompanied by focal neurological deficits should be suspected as having CVT.

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腦靜脈竇栓塞：一種罕見的腦中風

劉恩慈[1] 楊自強[2,*]

童綜合醫療社團法人童綜合醫院 [1]重症醫學部 [2]神經內科

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摘要

腦靜脈栓塞是一種威脅生命的疾病。由於臨床表現多變，它經常被漏診及延遲診斷。我們在此報告一個以意識障礙和雙腿無力表現的腦靜脈血栓的病患，她在接受抗 凝劑，直接導管溶栓，甘露醇和高壓氧合併治療後病情順利恢復。

關鍵詞：腦靜脈竇栓塞、腦靜脈栓塞、臨床表現、診斷、治療

* 通訊作者：楊自強醫師 童綜合醫療社團法人童綜合醫院 神經內科 43503 台中市梧棲區台灣大道八段 699 號

Image

Septic Pulmonary Embolism

Min-Wei Cheng[1,*], Chih-Chuan Kao[2], Chih-Hao Yeh[3]

[1]Department of Emergency, [2]Department of Infection, [3]Department of Radiology, Tungs' Taichung MetroHarbor Hospital, Taichung

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Abstract

Septic pulmonary embolism is a rare condition that is always associated with a microorganism in the primary site and metastasis to the lung through hematogenous dissemination. This patient presented to the Emergency Room (ER) with fever, right-sided chest pain and a chest X-ray revealed a small pneumonia-like lesion. Further, as his CRP level was high (17.6 mg/dl), a chest computer tomography was acquired, which revealed multiple discrete consolidated nodules in bilateral. The patient was diagnosed with septic pulmonary embolism and we discuss etiology, symptoms, pathophysiology, imaging findings, and treatment for septic pulmonary embolism.

Key words: Septic pulmonary embolism

Case presentation

A 33-year-old man presented to the ER with a chief complaint of a fever of 40°C in the night and right-sided chest pain for the last 2 days. His medical history appeared unremarkable except for a right chest contusion after an accidental fall 2 days ago. A comparison of his chest X-rays (Fig. 1) revealed previously absent radiopaque patches with infiltrations and consolidation over the right lower lobe, along with pleural effusion. His CRP level was 17.6 mg/dl, and as such high levels could not be accounted for by the small lesion on X-ray, a chest computer tomography (Fig.2) was acquired, which revealed multiple discrete consolidated nodules in the peripheral and subpleural spaces with a few cavitations in all lobes of the right lung and the lingual segment of the left upper lobe. Blood culture requested during admission grew *Staphylococcus aureus*, and an oscillating soft tissue mass, about 0.7 x 0.7 cm, was noted in the tricuspid valve. Based on these findings, the patient was diagnosed with pulmonary septic emboli with concurrent infectious endocarditis and he also confessed to heroin drug abuse.

*Correspondence to: Dr. Min-Wei Cheng, Department of Emergency, Tungs' Taichung MetroHarbor Hospital, No. 699, Sec. 8, Taiwan Blvd., Wuqi Dist., Taichung City 43503, Taiwan (R.O.C.)

Discussion

Septic pulmonary embolism is a rare condition wherein the thrombus is transported to the lungs through circulation and invariably contains microorganisms from the primary infection site. The source(s) are typically right-sided endocarditis or valve vegetation, drug abuse, iatrogenic such as after catheter implantation, liver abscesses, pelvic thrombophlebitis in post-partum women, or internal jugular vein thrombophlebitis due to severe throat infection (Lemierre's syndrome)[1].

Although the *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Escherichia coli* are the most likely pathogens, fungal emboli from Aspergillus, Mucor, or Candida species have also been reported in immunocompromised patients. Microorganism stasis in distal pulmonary vasculature can produce cytotoxins, and enzymatic and inflammatory mediators then induce immune reaction, which promote local thrombus formation. Apart from localized parenchymal inflammation reaction, the thrombus also serves as the nidus for future bacterial proliferation[1].

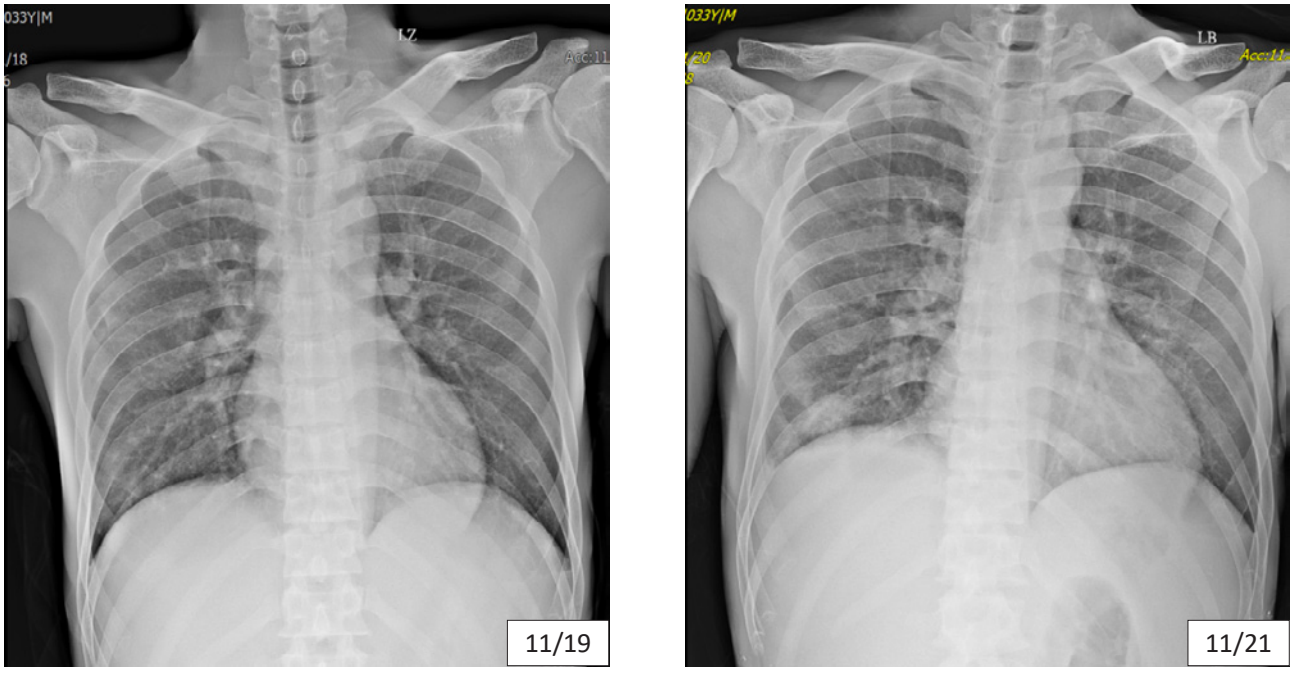

Fig. 1 CXR in the left panel was obtained on 11/19 and shows no specific lesion.CXR in the right panel was obtained on 11/21 and shows patches and pleural effusions that were not previously seen.

Clinical signs of septic pulmonary embolism vary from unspecific illness to septic shock and may be concurrent with fever, cough, shortness of breath, or pleuritic chest pain[2]. Diagnosis is often based on chest radiograph or computer tomography findings, such as diffuse peripheral pulmonary nodules with feeding vessel sign, wedge-shapes lesions, or unilateral or bilateral pleural cavitation[3]. Based on imaging findings, differential diagnoses should consider benign tumors, malignant metastases, abscesses, necrobiotic pulmonary nodules, Wegener granulomatosis, arteriovenous malformation, and pulmonary embolism[3].

Broad-spectrum antibiotic management must be initiated when septic embolism is suspected, and the antibiotic regimen must be adjusted based on culture results and clinical response such that the treatment course lasts for 4-6 weeks[1]. Although extensive use of antibiotics has decreased the mortality rate in septic embolism, the prevalence of methicillin or vancomycin resistant *S. aureus* has also increased. Further, determining the source of the microorganism and providing early intervention, such as valve replacement or liver abscess drainage, are also essential. Complications of septic pulmonary embolism range from localized empyema or pneumothorax to systematic organ failure due to bacteremia[3].

Reference

1. Thomas R. Wojda, Kristine Cornejo, Andrew Lin, Anthony Cipriano, Sudip Nanda, Jose D. Amortegui, et al. Septic Embolism: A Potentially Devastating Complication of Infective Endocarditis. Contemporary Challenges in Endocarditis. IntechOpen ,2016 : 144-157. DOI: 10.5772/64931.
2. Wong KS, Lin TY, Huang YC et-al. Clinical and radiographic spectrum of septic pulmonary embolism. Arch. Dis. Child. 2002;87 (4): 312-5.DOI:10.1136/adc.87.4.312
3. Website: Radiopaedia.org . Accessed 08/11, 2019, at https://radiopaedia.org/articles/septic-pulmonary-emboli

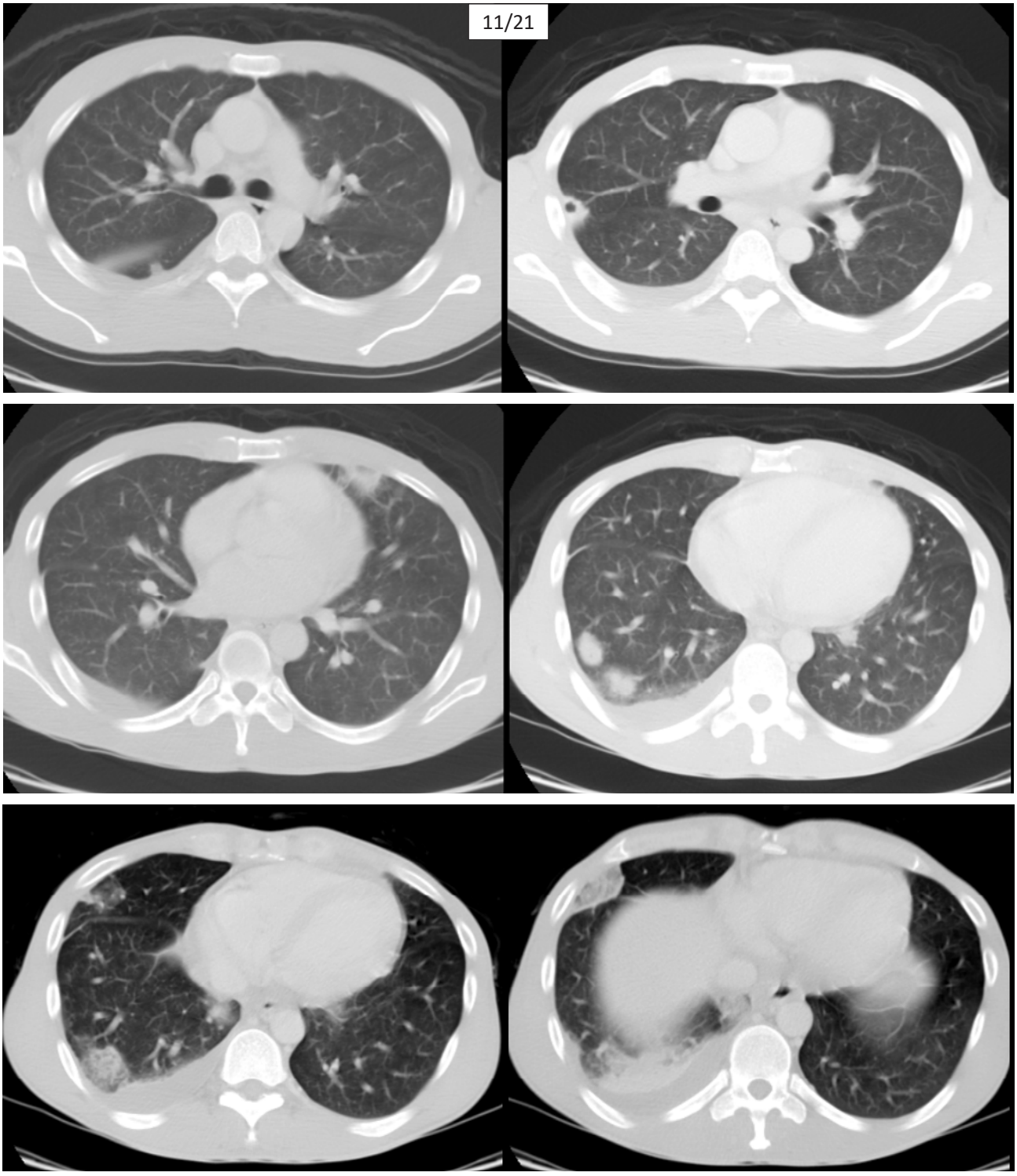

Fig. 2 Multiple discrete consolidative nodules can be seen in the peripheral and subpleural space, along with cavitations in bilateral lung fields.

敗血性肺栓塞 - 影像判讀

鄭閔瑋[1,*] 高智泉[2] 葉治浩[3]

童綜合醫療社團法人童綜合醫院 [1]急診部 [2]感染科 [3]放射科

受文日期：民國 108 年 08 月 12 日；接受刊載：民國 108 年 10 月 14 日

摘要

敗血性肺栓塞是一種罕見的疾病。該疾病的發生往往與原發於其他部位的微生物感染有關，並通過血行性轉移到肺部。案例裡的患者因發燒和右胸疼痛來到急診，根据他的胸部 X 片，初始的診斷比較傾向是輕微的肺炎。但由於 CRP 數值很高與臨床表現不一致，因此安排了胸部電腦斷層掃描做進一步的診斷。

本文將討論敗血性肺栓塞的病因，症狀，病理生理學，圖像發現和治療。

關鍵詞：敗血性肺栓塞

* 通訊作者：鄭閔瑋醫師 童綜合醫療社團法人童綜合醫院 急診部 43503 台中市梧棲區台灣大道八段 699 號

童綜合醫學雜誌投稿相關規則

95.9.01 製訂
110.06.23. 修訂（第 13 版）

童綜合醫學雜誌線上投稿暨評閱系統：http://www.ipress.tw/J0143。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）

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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。
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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

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稿件種類	字數限制		參考文獻	圖 / 表
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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

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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，並編行號及頁碼，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。
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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。
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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.

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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」。

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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。

＊＊內文文獻標示以中括號、數字、上標呈現。

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.

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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].

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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.

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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.

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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.

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Tel：〈04〉26581919 ext 59045　Fax：〈04〉26582193

印 刷 者：
大光華印務部　Tel：〈02〉2302-3939（代表號）
地址：10851 台北市萬華區廣州街 32 號 6 樓　Fax：〈02〉2302-2036