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CONTENTS IN BRIEF

IMAGE

Editorial

Molecular Mechanisms of Cetrimonium Bromide Involved in the Epithelial to Mesenchymal Transition of Liver Cancer

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Abstract

Liver cancer is one of the most common malignant tumors and is currently the fourth leading cause of cancer-related mortality worldwide. Due to its rapid progression, the prognosis of patients with liver cancer is poor. Nowadays, alternative anticancer approaches or medicines should be explored to reduce the risk of disease progression. In particular, several studies have shown that cetrimonium bromide (CTAB) can be administered as a cytotoxic agent against some types of cancer by playing an anti-viability effect through a mitochondria-mediated apoptotic pathway. Nevertheless, our previous study demonstrated that CTAB played a strongly suppressive effect on the migration and invasion of different hepatocellular carcinoma (HCC) cell lines, such as SK-Hep1, Mahlavu, and HA22T/VGH cells. Specifically, CTAB was found to be involved in modulating canonical and non-canonical transforming growth factor-β (TGF-β), fibroblast growth factor (FGF), and c-Met/phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB, also known as Akt)/mammalian target of rapamycin (mTOR)-mediated mesenchymal phenotype, and CTAB could be a potent medical agent used to control the epithelial to mesenchymal transition (EMT) of hepatic cancer.

Key words: liver cancer, cetrimonium bromide (CTAB), epithelial-to-mesenchymal transition (EMT)

Introduction

Liver cancer is the seventh most common malignancy and the fourth leading cause of cancer-related deaths worldwide[1]. Incidence rates of liver cancer are high in Eastern Asia and sub-Saharan Africa, accounting for approximately 80% of liver cancer cases worldwide. Current therapeutic strategies for liver cancer include surgical excision, liver transplantation, and molecular-targeted therapy, e.g., kinase and immune checkpoint inhibitors depending on the liver cancer stage. However, recrudescence and metastasis frequently occur due to ineffective treatments or the emergence of drug resistance, which supports the need to clarify the molecular mechanism and pathogenesis underlying the uncontrolled cell invasion in liver cancer to develop new potential approaches or medicines.

Cancer metastasis may occur based on the physiological state of the cells, including epithelial to mesenchymal transition (EMT), subsequently mesenchymal to epithelial transition (MET), and eventually leading to colonization at other sites.[2] Thus, disruption of mesenchymal features in cancer cells is considered as the prime prerequisite for restraining cancer cell motility and invasiveness.[3] In liver cancer tissues, several transcription factors, including Snail, Slug, ZEB1, and Twist, which are all modulated by miscellaneous signaling pathways, such as PI3K, Akt, and signal transducer and activator of transcription 3 (STAT3), have been identified to play decisive roles in EMT[4]. Simultaneously, large numbers of cellular EMT regulatory components are involved, such as those of extracellular matrix (ECM)

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and matrix metalloproteinases (MMPs). In EMT procedures, MMPs act a critical role in interacting with and degrading the basement membrane of ECM to remodel it for migration and invasion of metastatic cells to target tissues, thereby contributing to tumor cell metastasis[5]. Thus, targeting these molecules may be effective in liver cancer therapy.

Cetrimonium bromide (CTAB, $[(C_{16}H_{33})N(CH_3)_3]Br$), a substance of quaternary ammonium compounds (Quats), is widely used as an antiseptic agent against bacteria and fungi.[6] Quats are known to have anticancer properties by restraining cell proliferation, causing loss of mitochondrial membrane potential, elevating the cytosolic Ca^{2+} level, and finally leading to cell death[7]. A more recent research has proven that CTAB is cytotoxic against human head and neck cancer cell lines via the mitochondria-mediated apoptosis pathway[8]. In this report, molecular targets of CTAB with regard to signaling pathways controlling hepatic EMT and its potential effects as a drug for liver cancer therapy are critically reviewed.

Molecular targets of CTAB for liver cancer

CTAB suppresses liver cancer cell migration and invasion based on the following mechanisms: I) altering the precise balance between MMP levels and tissue inhibitors of metalloproteinases (TIMPs); II) downregulating the canonical and non-canonical TGF-β signaling pathways; III) exerting an influence on c-Met/PI3K/Akt/mTOR signaling pathway; and IV) inhibiting the expression of FGF signaling and EMT-associated proteins[9-11].

CTAB effects on the EMT-mediated mechanism

EMT is not only a physiological process but also the prime step for the invasion progression and metastatic course of tumors. Remodeling and degradation of ECM were based on MMPs, thereby enabling tumor cells to migrate, invade, and metastasize to particular secondary sites following the EMT, where they form metastases. Through the upregulation of TIMPs, CTAB inhibits cellular migration and invasion due to MMP downregulation. CTAB is considered to be an effective tumor inhibitory substance among Quats, which reduces the EMT promotion by suppressing expression of genes associated with EMT, such as Snail, Slug, and Twist. In addition, CTAB could cause reverse protein expression of cadherins, including E- and N-cadherin. For example, CTAB upregulated the expression of poorly expressed E-cadherin in Mahlavu cells. Moreover, the morphological change also suggests that Mahlavu cells might undergo EMT reversal with CTAB exposure[11].

CTAB targets in TGF-β signaling

TGF-β signaling plays a crucial role for the promotion of EMT and mediates tumor metastasis and progression, including abrogation of cell-cell adhesion, contribution to mesenchymal phenotypes, and invasive capabilities of liver cancer cells[12]. TGF-β signaling is attenuated during hematotumorigenesis but is retained during the malignancy of hepatocellular carcinoma cells[13]. TGF-β ligands activate downstream signaling pathways, including both Smad-dependent and Smad-independent pathways (such as Ras, PI3K/Akt/mTOR,and p38 mitogen-activated protein kinase).

Our recent study has proved that CTAB downregulated phosphorylation levels of Smad2/3 and PI3K p85/Akt/mTOR/p70S6K in a dose-dependent manner[9]. Furthermore, this study has demonstrated that CTAB not only downregulated the expression level of Snail, Slug, Twist, vimentin, fibronectin, N-cadherin, and β-catenin but also upregulated the cellular protein level of claudin-1 as compared to TGF-β1 treatment. Therefore, CTAB is suggested to potentially block the TGF-β/Smad and PI3K p85/Akt/mTOR signaling pathways, thereby arresting the EMT process progression. These results suggest that CTAB exerts its anti-EMT effects through the canonical and non-canonical TGF-β pathways[9].

CTAB targets in c-Met/PI3K/Akt/mTOR signaling

The HGF/its cell surface receptor tyrosine kinase c-Met axis play an important role in cell migration and invasion through EMT modulation[14]. Dysregulation of the HCF/c-Met signaling has been involved in HCC carcinogenesis, progression, and prognostic parameter[14]. PI3K interacts with Akt to trigger a certain number of substrates to perform various functions in the MMP regulation, including MMP-2 and MMP-9[15]. In addition, PI3K/Akt oncogenic signaling and tumor suppressor functions of phosphatase and tensin homolog (PTEN) and glycogen synthase kinase 3β (GSK3β) are frequently observed in HCC[16]. Therefore, PI3K/Akt-mediated signaling would be an attractive target in HCC chemotherapy.

CTAB attenuates c-Met, PI3K, and Akt and diminished the phosphorylation levels of c-Met and its downstream proteins. Moreover, treatment with CTAB in HA22/VGH HCC cells also reduces the protein expression of mesenchymal markers, including vimentin, N-cadherin, and Twist. Based on these findings, CTAB seems to be an attractive approach in HCC therapy.

CTAB targets in FGF signaling

FGFs function as ligands that bind to multiple FGFRs to activate its designated tyrosine kinase domain. Activated receptor signals exert various physiological and pathological processes and functions, such as cell migration, invasion, proliferation, angiogenesis, drug resistance, and metastasis through multiple downstream signaling, including PI3K/Akt, Ras-MAPK, or PLCγ[17]. FGF signaling has been reported to play a critical role in carcinogenesis such as HCC. The PI3K/Akt signaling pathway is the principal component upstream of EMT and is involved in metastasis and tumor invasion in HCC[18]. The PI3K/Akt signaling cascade is also involved in MMP-mediated cell invasion.[19] Furthermore, FGF can promote EMT through Akt/GSK3β/Snail signaling cascade, inducing tumor cell motility[20]. Our previous study demonstrated that CTAB could regulate cellular signaling pathways, such as FGFR and PI3K/Akt pathways. CTAB might cause the downregulation of PI3K/Akt through FGFR signaling, thereby reducing migratory and invasive capabilities of human Mahlavu HCC cells.

Future perspective

The available evidence suggests that CTAB, a substance of Quats, exerts an anticancer impact by triggering signals of the mitochondrial apoptotic pathway. Our recent studies have reported that CTAB targets EMT–MET modulators in tumor progression and metastasis. By comparing our studies to those of other related research findings, interference with cellular signaling pathways was positively correlated with inhibition of malignant tumor properties, such as proliferation, migration, invasion, and metastasis. Effects of CTAB on liver cancer can potentially establish new cancer therapies targeting cancer metastasis. However, the mechanism by which CTAB regulates the EMT might be highly complex, because other new or undiscovered signaling pathways might exist. Further study will identify other unmentioned signaling pathways that play a role in the regulation of liver cancer invasion and metastasis by modulating the EMT. Consequently, further extensive investigation is required to obtain an understanding of the function of EMT-related signaling and target proteins involved in antimetastatic activities of CTAB.

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溴化十六烷基三甲銨參與肝癌細胞上皮向間質轉換的分子機制

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摘要

肝癌不論是在腫瘤的發生率或相關致死率皆排名在各類惡性腫瘤的前十名內。由於肝癌的癌化進程快速，導致肝癌患者普遍預後較差。所以研發替代現有的抗癌模式或藥物，以減緩疾病進程顯得刻不容緩。之前的研究顯示，溴化十六烷基三甲銨（cetyltrimethylammonium bromide, CTAB）可經由影響粒線體的凋亡途徑抑制特定癌細胞存活。我們的研究也發現 CTAB 對不同的肝細胞癌細胞株，例如 SK-Hep1，Mahlavu 與 HA22T/VGH 細胞等，在癌細胞的遷移和侵襲方面具有抑制的能力。具體而言，我們發現 CTAB 分別參與典型和非典型乙型轉化生長因子（transforming growth factor-beta, TGF-β）、成纖維細胞生長因子（fibroblast growth factors, FGF）與酪氨酸蛋白激酶 Met（c-Met）/ 磷脂肌醇 -3- 激酶（phosphoinositide 3-kinase, PI3K）/ 蛋白激酶 B（Protein kinase B, PKB, also known as Akt）/ 哺乳動物雷帕黴素靶蛋白（mammalian target of rapamycin, mTOR）等所調控的癌症轉移的關鍵機制 – 上皮向間質轉換。期能藉由探討 CTAB 對肝癌的影響模式，深入了解肝癌上皮向間質轉換的相關分子機制，藉此找到抑制肝癌轉移的目標靶點，提供治療肝癌更有效的方法。

關鍵詞：肝癌、溴化十六烷基三甲銨、上皮向間質轉化

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Review Article

Review of ATP-binding Cassette Super-family G member 2 (ABCG2)

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Abstract

ATP-binding cassette sub-family G member 2 (ABCG2), a subclass of the human ATP-binding cassette (ABC) transporter family, can facilitate the extrusion of a wide array of unrelated chemicals and molecules from cells. The multidrug transport nature of cancer cells impedes the effects of chemotherapy. Overcoming intrinsic and acquired drug resistance is a major challenge in treating cancer patients since chemoresistance is associated with recurrence, cancer dissemination, and death. The tumor microenvironment plays a crucial role in tumor progression and is associated with the therapeutic effects of cancer treatment. Hypoxia is a key feature of the tumor microenvironment, as it contributes to cancer progression and mediates chemotherapy resistance. Hypoxia-inducible factor-1 (HIF-1) is a master regulator of the transcriptional response to oxygen deprivation in cancer cells. This mini-review aimed to describe our current knowledge of the roles and functions of ABCG2 and HIF-1 in mediating chemoresistance in hypoxic conditions in breast cancer.

Key words: ATP binding cassette (ABC), ATP-binding cassette super-family G member 2 (ABCG2), hypoxia, Hypoxia-inducible factor-1 (HIF-1), chemoresistance

Introduction

Chemoresistance and metastasis in breast cancer

Of all cancer types, worldwide, breast cancer has the highest incidence rate in women and is the second most common cancer. It accounts for 23% of all cancer cases and 14% of all cancer deaths[1]. Breast cancer not only has a high incidence rate worldwide, but it has also become the primary cause of death in women[2, 3]. The incidence rates of breast cancer in the United States, Western Europe, and Taiwan are 127.5, 89.7, and 73 per 100,000 women-years, respectively[4, 5]. Compared with women, men with breast cancer account for fewer than 1% of all breast cancer cases[6]. In Taiwan, the standardized prevalence of breast cancer was 186.46 per 100,000 individuals in 1997 and 834.37 per 100,000 individuals in 2013. Although the prevalence and incidence of breast cancer have been rising globally[7], the rapid 4.5-fold increase in the prevalence of breast cancer within the past 6 years has forced the Taiwanese government to establish a national biennial mammography screening program for women between the ages of 40 and 69 years[8]. However, although one study indicated a rising trend in the prevalence and incidence of breast cancer in Taiwan[9], the 5-year mortality rate has not changed significantly (4.5% in 1997 and 4.4% in 2008)[9], which suggests that breast cancer is one the most important health issues in Taiwan.

Recently, there has been an explosion of advanced therapies for breast cancer, which has brought new hope and excitement to the field. The multidisciplinary approach to this cancer includes the prevention, early detection through appropriate

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screening, treatment of localized tumors, and management of an advanced disease. The primary forms of treatment used in the management of breast cancer consist of surgery, radiotherapy, chemotherapy, hormone therapy, targeted therapy, and immunotherapy[10]. Although breast cancer is responsive to a wide array of single and combination chemotherapy regimens, the eventual emergence of tumor re-growth at the original site and at new sites is common[11], and approximately 30% of women who are initially diagnosed with early-stage disease will ultimately develop metastatic lesions, which often occurs months or even years later[12]. Although clinicians administer different chemotherapeutic agents as soon as patients develop progressive disease after initial chemotherapy, the therapeutic effects of these subsequent agents usually weaken due to the development of chemoresistance, which is associated with metastasis. Over 90% of breast cancer deaths are due to the metastasis of breast cancer to other sites of the body, such as the bone, lungs, liver, and brain[13]. Insights into the cellular and molecular mechanisms of metastatic spread may broaden our understanding of the development of chemoresistance and may contribute to the discovery of better therapies against this cancer.

Multidrug resistance

Clinical drug resistance remains a significant impediment to the successful treatment of cancer. One mechanism by which cancers develop drug resistance is through multidrug resistance (MDR), which leads to subsequent cancer relapse after therapy and is a widespread problem in breast cancer patients[14]. Multidrug transporters (MDTs) can recognize several chemical substrates and pump them out of cells to reduce the intracellular levels of these substrates, thereby causing treatment failure, which leads to MDR[15]. MDTs, also called ATP-binding cassette transporters (ABC transporters), comprise one of the largest families of membrane proteins, which are universally expressed in all living organisms on Earth[16]. To date, 48 ABC genes have been identified, the majority of which are membrane-bound primary transporters that actively transport various molecules across all cell membranes via ATP hydrolysis. The typical structure of ABC transporters consists of a pair of nucleotide-binding domains (NBDs), which are located on the cytoplasmic side of the membrane, and two sets of transmembrane domains (TMDs), which each contain six transmembrane-spanning α-helices (TMHs) (Fig. 1). The function of NBDs is to bind and hydrolyze ATP to provide energy for substrate transport, whereas the TMD participates in substrate recognition. According to the homology of the NBD sequences, the ABC transporter family is classified into the following 8 subfamilies: ABCA (12 members), ABCB (11 members; including P-glycoprotein (Pgp) (*ABCB1* or *MDR1* gene)), ABCC (13 members; including MRP1 (*ABCC1* gene)), ABCD (4 members), ABCE (1 member), ABCF (3 members), and ABCG (5 members; including ATP-binding cassette sub-family G member 2 (ABCG2)), which are expressed in both normal and malignant cells. ABC transporters with at least two TMDs and two NBDs are considered full transporters, while those with one of each domain are considered half transporters[17]. ABC transporters are involved in the transport of many substances, the excretion of toxins, and limiting the permeation of toxins into vital structures, such as the brain, placenta, liver, kidneys, and gastrointestinal tract[17]. Among these transporters, Pgp (Fig. 1A) and multidrug resistance-related protein (MRP) (Fig. 1B) are by far the most intensely studied ABC transporters, and both are overexpressed in breast cancer cells. Both have a similar structure that includes 12 TMHs, which are divided into two halves forming TMD1 and TMD2, as well as 2 NBDs (NBD1 and NDB2)[18, 19]. MRP1 may play a general physiological role as a protector against toxins as well as drugs[19]. Pgp can transport several chemotherapeutic agents including the anthracyclines, vincas, taxanes, etoposide, and mitoxantrone; and Pgp expression in cancer cells indicates a poor prognosis[20].

ATP-binding cassette sub-family G member 2 (ABCG2)

The discovery of ABCG2 helped explain the puzzle of non-Pgp and non-MRP-mediated mechanisms that are observed in some tumors[21]. Unlike Mrp1 and Pgp, ABCG2, which is also known as breast cancer–resistance protein (BCRP), ABC transporter in placenta, and mitoxantrone-resistance transporter (MXR1), is a half-transporter that must homodimerize to acquire transport activity and is a 655 amino acid protein encoded by the *ABCG2* gene located on chromosome 4q22 (Fig. 1C). ABCG2 is expressed in the placenta, intestine, liver, blood–testis barrier,

blood–brain barrier, hematopoietic progenitors, and in several types of tumors, including breast cancer, gastric carcinoma, hepatocellular carcinoma, endometrial carcinoma, colon cancer, small cell lung cancer, and melanoma[22], and is associated with resistance due to its active extrusion of diverse therapeutic compounds[14]. Therefore, understanding the molecular mechanisms of drug transport by ABCG2 is crucial for the improvement of anticancer therapies.

Hypoxia-inducible factor-1 (HIF-1)

Hypoxia occurs when the oxygen concentration is below the level required to maintain the physiological O_2 tension in a particular tissue. Like normal tissues, tumors require an adequate supply of oxygen, and if hypoxia is severe or prolonged, cell death occurs. Hypoxia is considered a property of many tumor types because highly proliferating tumors rapidly extinguish the vascular supply, which results in a hypoxic microenvironment[23]. Through the use of oxygen microelectrodes, the mean oxygen tension in normal tissues has been found to lie between 40 and 50 mmHg, but the corresponding values in cancerous tissues are between 5 and 10 mmHg or lower. Such a hypoxic environment results in the transcriptional induction of numerous hypoxia-responsive genes, including those encoding glucose transporters, glycolytic enzymes, and growth factors as well as those involved in gluconeogenesis, high-energy phosphate metabolism, erythropoiesis, heme metabolism, iron transport, vasomotor regulation, and nitric oxide synthesis[23, 24]. Hypoxia is one of the hallmarks of cancer, and the occurrence of hypoxia has been demonstrated in different types of solid tumors, including breast cancer[25]. Malignant cells can undergo genetic and adaptive changes that allow them to escape death due to oxygen deprivation. These changes are associated with a more aggressive malignant phenotype as well as with resistance to chemotherapy and radiotherapy, which results in a poor prognosis[26]. Among these transcriptional pathways, the hypoxic response depends critically on the expression of hypoxia-inducible factor-1 (HIF-1).

HIF-1 is a transcriptional activator that functions

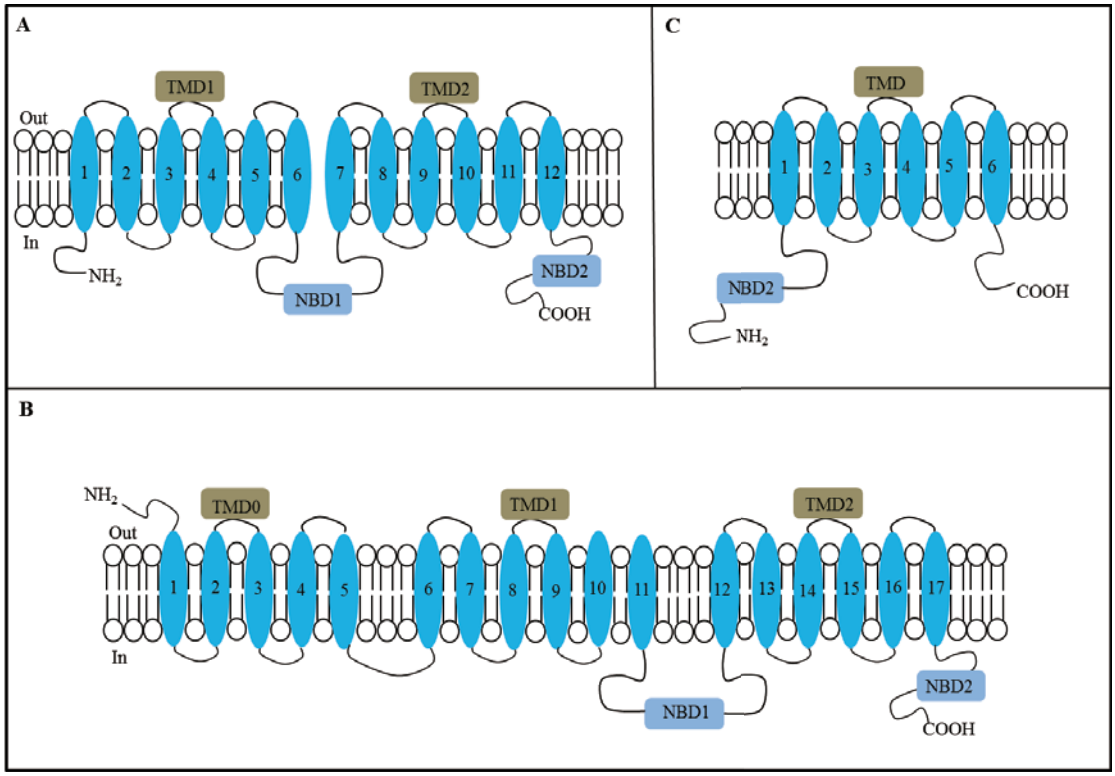

Fig. 1 Representation of ABC proteins. (A) Human P-glycoprotein (P-gp). P-gp, a full-transporter, contains twelve transmembrane-spanning α-helices (TMHs) and two transmembrane domains (TMDs), each with a nucleotide-binding domain (NBD). (B) Representation of human multidrug resistance-associated protein 1 (MRP1). MRP1, a full-transporter, contains three transmembrane domains, including five extra transmembrane segments toward the N-terminus and two NBDs. (C) Representation of ABCG2, a half-transporter, which contains only six TMHs and one NBD. NBD, nucleotide-binding domain; CL, cytoplasmic linker.

as a master regulator of cellular and systemic oxygen homeostasis[23]; it is a heterodimeric complex composed of the 120-kDa HIF-1α and 94-kDa HIF-1β subunits, both of which belong to the basic-loop-helix Per-Arnt-Sim protein family[27]. HIF-1β is constitutively expressed[28], whereas HIF-1α is degraded by the ubiquitin–proteasome pathway and is thus maintained at a low level in cells in normoxic conditions; in contrast, the level of HIF-1α protein is increased under hypoxic conditions[29]. The degradation of HIF-1α is affected by the Von Hippel–Lindau (VHL) protein in normoxia[30] (Fig. 2). Clinically, HIF-1 expression has been detected in many solid tumors including those in the brain, bladder, breast, colon, ovary, pancreas, kidney, and prostate, whereas no expression has been detected in the surrounding normal tissue or in benign tumors, such as breast fibroadenoma and uterine leiomyoma[31]. In addition, HIF-1 overexpression is potentially a marker of highly aggressive disease and has been associated with a poor prognosis and treatment failure in breast cancer[32]. At least 100 putative hypoxia-inducible genes have been found to be directly regulated by HIF-1[33]. The ability of HIF-1 to promote both tumor cell survival and angiogenesis strongly suggests that HIF-1 overexpression is important for tumor vascularization and metabolic adaptation to hypoxia[34]. HIF-1 expression is correlated with tumor grade and vascularity, and VHL-inactivated tumors are highly vascular and overproduce angiogenic factors, such as VEGF. VEGF is one of the most potent angiogenic cytokines and is transcriptionally regulated in large part by HIF-1, which suggests that the ability to downregulate HIF-1 expression would have a positive impact on cancer control[23]. The level of the HIF-1α protein is inversely related to the oxygen tension in cultured cells *in vitro* and *in vivo*. Under normoxic conditions, the HIF-1α protein is rapidly degraded through the ubiquitin–proteasome pathway; thus, only very low levels of HIF-1α protein are detected. However, a significant amount of HIF-1α protein accumulates in response to hypoxia. HIF-α then dimerizes with HIF-1β and translocates to the nucleus, where this protein can activate hypoxia-sensitive genes by binding to the consensus sequence 5′-RCGTG-3′ (where R is any purine) in the hypoxia response element (HRE) of various target genes, and enhances the hypoxia-inducible gene transcription rate[23].

Regulation of the HIF-1α: oxygen-independent pathway (Figures 3 and 4)

Hypoxia is not the only condition in which HIF-1α is activated and stabilized; HIF-1α protein can also be detected in normoxic conditions, and many mechanisms involving the increase, stabilization, and activation of HIF-1 expression in tumor cells include the following:

1. Growth factors: several growth factors

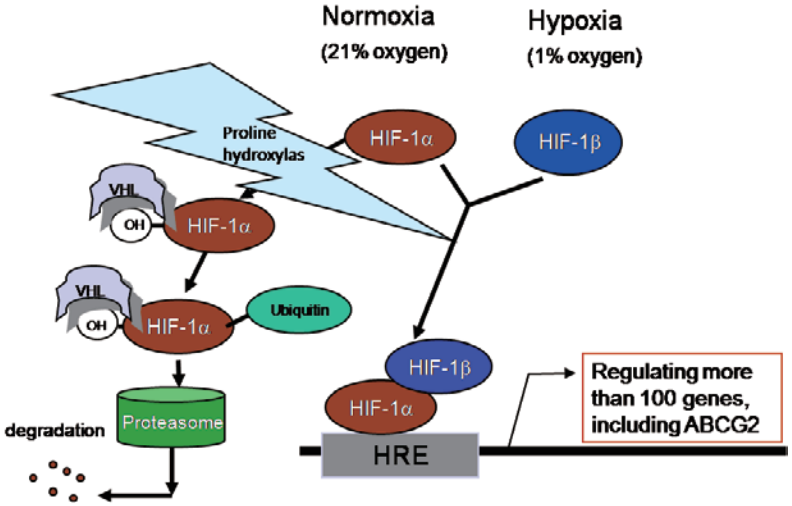

Fig. 2 The life and death of HIF-1. HIF-1 is composed of HIF-1α and HIF-1β. HIF-1α is hydroxylated in the presence of oxygen, and Von Hippel–Lindau protein recognizes and interacts with prolyl-hydroxylated HIF-1α. After ubiquitination by VHL, HIF-1α is degraded in the proteasome. Under hypoxic conditions, HIF-1α is translocated to the nucleus and dimerized to its partner HIF-1β, which is constitutively expressed, forming HIF-1 to actively transcribe more than 70 genes that harbor hypoxia-responsive elements (HREs).

including insulin, insulin-like growth factors 1 and 2, fibroblast growth factor 2, platelet-derived growth factor, transforming growth factor β1, and inflammatory cytokines, such as interleukin-1, and tumor necrosis factor-α, can trigger HIF-1 activation through the PI3K-AKT pathway under normoxic conditions. Epidermal growth factor receptor (HER2) signaling has been shown to increase HIF-1 protein synthesis through the phosphatidylinositol (PI)-3-kinase (PI3K)-Akt signaling cascade, while activation of the intracellular signal transduction protein Akt, has been found to be a central signaling event in experimental models of chemoresistance[35].

2. Receptors: epidermal growth factor receptor (EGFR) can activate the JAK/STAT3, PI3K/Akt/mTOR, src/FAK /Reactive oxygen species (ROS), and SOS/Grb2/Ras pathways and is involved in differentiation, proliferation, survival, and transformation. EGFR overexpression can activate NF-κB and STAT3, which leads to chemoresistance and poor outcomes. The mutant form of EGFR is still active and confers chemoresistance in glioma and lung cancer. In lung cancer cells, cisplatin resistance is associated with heme oxygenase (HO)-1, whose expression is decreased through the EGFR-mediated PI3K/Akt and NF-κB pathways; its expression is in turn restored by

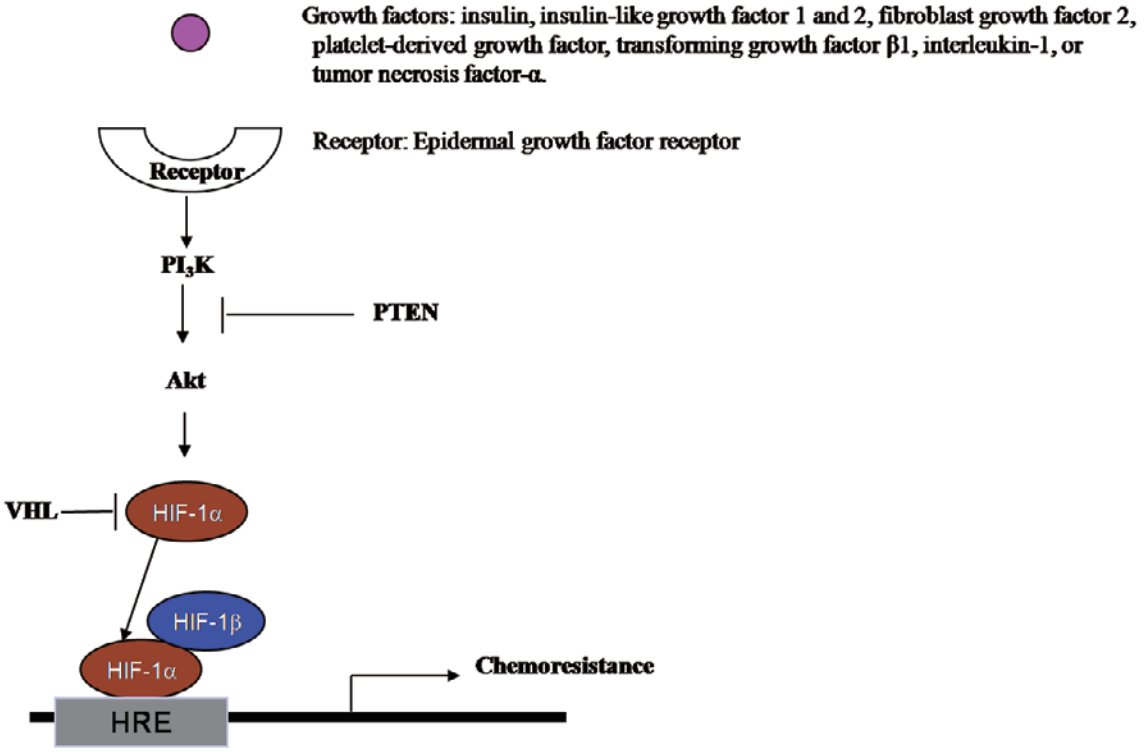

Fig. 3 The signal transduction pathway of HIF-1α regulation in normoxia. The PI3K-Akt pathway is activated in response to oncogenes (such as *PTEN*) or growth factors. These responses react to a different extent in cell type- and stimulus type-specific manners.

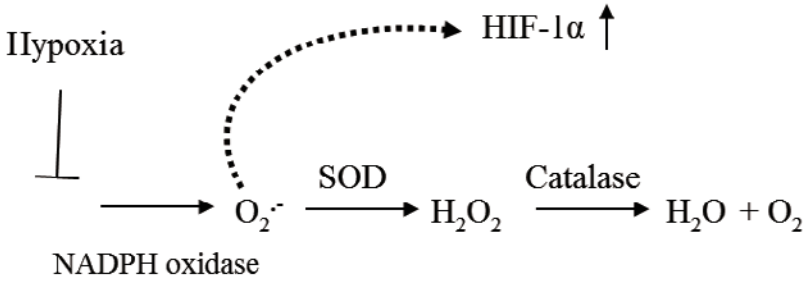

Fig. 4 Model for the production of ROS from NADPH oxidase under hypoxic conditions.

EGFR-selective tyrosine kinase or Akt inhibitors[36]. In one study, exposure to the anti-EGFR monoclonal antibody C225 reduced EGFR expression and the phosphorylation of its downstream proteins Akt and MAPK, which reversed cellular radioresistance[37].

3. Phosphoinositide 3-kinase (PI3K)-Akt pathway: Many tumor suppressor genes/oncogenes are activated or triggered by the PI3K-Akt pathway and are then able to influence HIF-1 expression levels in normoxia. PI3Ks are divided into three subgroups: class I, class II, and class III. These classifications are based on the structure and regulatory mechanism of the PI3K as well as on its *in vitro* lipid substrate specificity. PI3Ks are responsible for the recruitment of different upstream signaling components and can activate signal transduction pathways. PI3Ks have also been implicated in cell survival and metabolism. In tumor cells, PI3Ks are generally overactivated[38, 39]. PI3K-Akt pathways have been shown to regulate HIF-1α activity in response to growth factors and other signals. In a study of breast cancer cells, the results indicated that HIF-1α and VEGF expression could be induced by bFGF (basic fibroblast growth factor) in a time- and dose-dependent manner and that the mechanisms were related to the bFGF-regulated phosphorylation of Akt, which suggests that PI3K/Akt pathways can regulate HIF-1α activation by bFGF[40]. Akt is a serine/threonine-specific protein kinase that is involved in apoptosis, proliferation, transcription, and cell migration. Akt can also activate NF-κB and upregulate the transcription of pro-survival genes. Akt overexpression results in resistance of NSCLC cells to chemotherapeutic agents. The PI3K/Akt pathway is inactivated by doxorubicin and etoposide, and wortmannin can increase the sensitivity of gastric cancer cells to chemotherapy[41].

4. VHL and PTEN: these proteins are the two main factors that regulate hypoxia-related pathways. *VHL* is a tumor suppressor gene that, when mutated, causes VHL disease, which is a familial cancer syndrome that includes the development of hemangioblastomas, clear cell renal carcinoma, and polycythemia. HIF-1α is recognized by the VHL protein, which acts as an E3 ubiquitin ligase[42]. Ubiquitinated HIF-1α then undergoes rapid degradation through the proteasome pathway, and the loss of VHL results in HIF-1α accumulation[30]. The PI3K pathway is also negatively regulated by the tumor suppressor gene *PTEN* (phosphatase and tensin homolog, deleted on chromosome 10), which is commonly deleted in breast cancer. Loss of the tumor suppressor function of PTEN augments HIF-1α-mediated gene expression, and restoration of PTEN expression can inhibit HIF-1α expression[43]. These data may lead to further studies considering the role of VHL and PTEN in the ability of the HIF-1α pathway to regulate ABCG2 expression.

5. Reactive oxygen species: oxygen radicals and other toxic species produced by NADPH oxidase and myeloperoxidase function in killing microorganisms. Recently, ROS were discovered to play a significant role in hypoxia-related signal transduction. ROS are continuously produced by NADPH oxidase, which reduces O_2 to superoxide anion (O_2^-); this molecule is subsequently converted to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD), and thus, a reduction in the molecular oxygen concentration would be followed by a reduction in ROS levels[44]. One study showed that an increase in ROS was related to an increase in chemoresistance[45], which suggests that ROS production in hypoxic conditions might occur through HIF-1 stability[46] and result in the upregulation of chemoresistance-related proteins, such as ABCG2, and the increased survival of breast cancer cells treated with mitoxantrone. Therefore, a decrease in ROS generation could be either a direct or indirect marker of HIF-1 activation.

6. Mitochondria: mitochondria are the centers of cellular energy generation, and as such, they represent a key intracellular signaling hub that functions in certain processes related to cancer progression, including metabolic reprogramming, acquisition of metastatic capability, and response to chemotherapeutic drugs[35]. Mitochondrial dynamics are characterized by fission and fusion, which allow cells to adapt to specific metabolic/stem states. During genomic DNA replication, mitochondria are always hyperfused and produce more ATP. Mitochondrial fusion and subsequent efficient ATP production and transport are more frequently observed in chemoresistant rather than chemosensitive gynecological cancer cells[47]. Oliva et al.[48] demonstrated that the acquisition of temozolomide chemoresistance was closely correlated with high mitochondrial coupling and low ROS production in glioma cells.

Cytochrome c oxidase (COX) is the main oxygen acceptor during respiration in aerobic organisms[49]. The energy generated during respiration is stored via oxidative phosphorylation (OxPhos) in the form

of ATP, which is the general energy intermediate found in living cells, or it is released as heat. During the evolution from bacteria to mammals, the complexity of OxPhos regulation increased as a result of COX, namely due to an increased number of subunits, the expression of subunit isoforms, which are specific to tissue type, developmental stage, and oxygen concentration, and by reversible phosphorylation. In a study that was performed to understand MDR in breast cancer cells, the COX subunit VIc was reported to be overexpressed along with 15 other proteins in cultured cells that were resistant to mitoxantrone. This suggests that the overexpression of the COX subunit VIc, ATP synthase, and ABCG2 is involved in pumping the drug from the inside to the outside of cells, and thus, is also involved in chemoresistance[45].

Conclusion

Cancer cells can undergo genetic and adaptive changes that allow them to escape death due to oxygen deprivation. Hypoxia is a main factor that causes cancer cells to become more aggressive and to undergo malignant transformation, recurrence, and dissemination, and is responsible for resistance to chemotherapy and radiotherapy, which results in a poor prognosis. A HIF-1-mediated response to hypoxia can generally regulate hundreds of target genes. One of these genes is *ABCG2*, which is expressed in several cancers and is associated with resistance due to its active extrusion of diverse therapeutic compounds to the outside of the cell. HIF-1 is a master regulator that affects cancer cell chemoresistance under hypoxic or normoxic conditions, and the expression and activity of HIF-1 are influenced by oxygen tension in hypoxia and by several other factors, including growth factors, receptors, and signaling pathways (e.g., PI3K pathways, VHL and PTEN, ROS, and mitochondrial pathways) in normoxia. For these reasons, approaches that target HIF-1-associated factors, those that disrupt the interaction between HIF-1 and ABCG2, and genetic knockdown techniques against HIF-1 and ABCG2 may hold therapeutic promise as a means of overcoming chemoresistance in cancer.

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腺嘌呤核苷三磷酸結合盒轉運蛋白超家族 G 第 2 成員 (ABCG2) 的文獻回顧

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摘要

ABCG2 是腺嘌呤核苷三磷酸結合盒轉運蛋白（ABC）的亞類，可以促進細胞排出多種彼此無關的化學物質和分子。癌細胞中的多藥抗藥性質會阻礙化學治療的效果。治療癌症患者時，克服內源性和外源性癌症抗藥性是重大的挑戰，因為抗藥性會導致癌症復發，擴散和死亡。腫瘤的微細環境在腫瘤的進展中扮演關鍵角色，而且與癌症治療中的療效有關。缺氧是腫瘤的微細環境的關鍵特徵之一，可導致癌症進展並媒介癌症對化學治療產生抗藥性。缺氧誘導因子 -1（HIF-1）是癌細胞中對缺氧的轉錄反應的主要調節因子。這篇文獻回顧的目的是聚焦在 ABCG2 的作用和功能以及 HIF-1 在缺氧以及正常氧壓下對乳癌介導化學抗藥性的了解。

關鍵詞：腺嘌呤核苷三磷酸結合盒，腺嘌呤核苷三磷酸結合盒轉運蛋白超家族 G 第 2 成員，缺氧，缺氧誘導因子 -1，化學抗藥性

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Original Article

Investigation of the Atrial Fibrillation Risk in Hemodialysis Patients: A Population-Based Cohort Study

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Abstract

***Background and Purpose*:** Previous studies have reported that hemodialysis (HD) patients generally are at higher risk of cardiovascular diseases; however, the association between HD patients and atrial fibrillation risk is still inconclusive. Therefore, we explored the incidence and risk of atrial fibrillation among hemodialysis patients in Taiwan.
***Methods*:** A total of 15,622 HD patients were selected from Taiwan's National Health Insurance Research Database. A total of 54,243 individuals without chronic kidney disease were randomly selected as controls. A hazard ratio (HR) and 95% confidence interval (CI) were used to estimate the risk of atrial fibrillation using a Cox proportional hazards model.
***Results*:** We observed that 6188 controls and 5902 HD patients had new-onset atrial fibrillation. The incidence rate ratio for atrial fibrillation was 2.29 (95% CI 2.13–2.46) and the adjusted HR for atrial fibrillation risk was 1.95 (95% CI 1.76–2.17) in the HD patients. In particular, those HD patients with an older age, diabetes mellitus, hypertension, hyperlipidemia, or ischemic heart disease had a significantly higher risk of atrial fibrillation.
***Conclusions*:** Our results revealed that older hemodialysis patients with certain comorbidities had an increased risk of atrial fibrillation. We should pay particular attention to the clinical care of hemodialysis patients with these specific risk factors.

Key words: Atrial fibrillation, Chronic kidney disease, Hemodialysis, National Health Insurance Research Database

Introduction

Chronic kidney disease (CKD) is an important health issue, and the National Health Insurance program covers approximately NT$23 billion for dialysis annually in Taiwan[1]. Patients with end-stage renal disease (ESRD) typically receive hemodialysis, peritoneal dialysis, or renal transplantation. More than 65,000 patients with ESRD receive renal replacement therapy[1]. The selection of a dialysis modality for patients is influenced by national policies, physicians, and other aspects, such as education status and cultural and economic factors.

CKD-related medical costs, with relevant comorbidities, are rising annually. Cardiovascular diseases contribute greatly to higher morbidity and mortality in patients with CKD. Atrial fibrillation is of critical clinical interest, given its prevalence is higher in dialysis patients than in the general population[2-4]. A

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relationship between renal function and atrial fibrillation risk has been reported in previous studies[5-7]. Sympathetic activity and renin–angiotensin–aldosterone system activation have been found to promote arrhythmogenesis in patients with CKD[8-10]. Chronic inflammation and anemia in patients with CKD also play a role in the genesis of atrial fibrillation[11]. Structural and electrical changes in cardiac chambers related to fluid and electrolyte changes are risk factors for atrial fibrillation in this population.

Several studies have revealed that atrial fibrillation is associated with cardiovascular mortality among patients with renal disease[12-15]. A recent study revealed paroxysmal atrial fibrillation as a strong predictor of mortality in these patients[13]. A study by Genovesi et al in 476 dialysis patients revealed that patients with atrial fibrillation had a 65% higher risk of death[14]. In the Framingham study, Kannel et al revealed that atrial fibrillation was associated with a 2–3-fold increase in mortality among patients with CKD[15]. This higher mortality might be due to the fact that atrial fibrillation represents a spectrum of cardiovascular diseases leading to left atrial remodeling; these disorders lead to vascular calcification and stiffness associated with chronic kidney disease-mineral bone disorder in these patients[16]. Patients with atrial fibrillation and those with CKD can share similar comorbidities, including hypertension, diabetes mellitus, and coronary artery disease[17,18], which contribute to mortality. As in the general population, the higher incidence of stroke in atrial fibrillation might also lead to higher mortality in this population[19].

Although atrial fibrillation is prevalent among patients with CKD, the incidence of atrial fibrillation in these patients employing various renal replacement therapies is still unclear. Thus, we performed this study to investigate the incidence and risk of atrial fibrillation among hemodialysis patients in Taiwan.

Methods

Data resources

The National Health Insurance program has been administered since March 1995 by the National Health Insurance Administration (NHIA), Ministry of Health and Welfare, Taiwan. The National Health Insurance Research Database (NHIRD) was released by the NHIA for academic purposes. The NHIRD includes the insured population's registration files and medical claims data, such as demographics, inpatient and ambulatory care, diagnostic codes, medical expenditures, operations, prescriptions, and examinations. The diagnostic codes are listed in the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). This study protocol was approved by the Taipei Medical University-Joint Institutional Review Board. Given that the personal identification data were transformed and encrypted to protect the privacy of the study participants, this study was exempt from the full review (Approval No. 201712042).

Study population

The hemodialysis (HD) patients were selected from those patients who were diagnosed with ESRD (ICD-9-CM 585) and started renal replacement therapy (HD). All these HD patients had catastrophic illness registration cards. The index date for HD patients was the date of their first diagnosis of ESRD with hemodialysis. Furthermore, we excluded those younger than 18 years or older than 85 years of age, those who had a history of malignancies before the index date, those without available information for age and sex, and those who did not receive dialysis. Ultimately, a total of 15,622 individuals were selected as HD patients between January 1, 2007 and September 30, 2016.

Individuals who did not have CKD, selected from the NHI beneficiaries in the NHIRD between January 1, 2007 and September 30, 2016, were identified as the controls. Among the controls, their first use of healthcare in this year served as their index healthcare use. We also excluded individuals who had a history of malignancies before the index date, those without information regarding age and sex, and those aged younger than 18 or older than 85 years. Finally, a total of 54,243 study subjects were selected randomly with frequency matching for sex, age, and the year of the index date for HD patients. Both HD patients and controls were followed from the index date to the new onset of atrial fibrillation or until September 30, 2016.

Parameter estimation

The age distribution was classified into 4 subgroups: ≤49, 50–59, 60–69, and ≥70 years. Patients with atrial fibrillation were identified as those who

had 3 outpatient atrial fibrillation (ICD-9-CM 427.31) claims. "Comorbidities" were also defined as individuals who had 3 outpatient claims before the index date. These comorbidities included diabetes mellitus (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), hypertension (ICD-9-CM 401-405), and ischemic heart disease (ICD-9-CM 410-414).

Statistical analysis

The person-years were estimated for each individual from the date of the index ambulatory care visit to the date of new-onset atrial fibrillation, the date of death, or the end of this study. The incidence rate was calculated by dividing the number of incident atrial fibrillations by the person-years of follow-up as the denominator. The Cox proportional hazards model was applied to calculate the hazard ratio (HR) and its 95% confidence interval (CI). The HR was adjusted for age, sex, geographic area, and relevant comorbidities of hypertension, diabetes mellitus, hyperlipidemia, and ischemic heart disease. The SAS statistical package (version 9.3, SAS Institute Inc., Cary, NC, USA) was employed for all the statistical analyses. A *P* value of <0.05 was considered statistically significant.

Results

Basic characteristics

This study aimed to investigate potential differences in relevant features between HD patients and controls. The findings for the comparison of basic characteristics between controls and HD patients are shown in Table 1. The mean age was 58.7±14.1 years in the controls and 60.7±13.5 years in the HD patients. A greater proportion of HD patients than controls had certain comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, and ischemic heart disease (Table 1).

Incident atrial fibrillation among controls and hemodialysis patients

For calculating the incidence rate, we excluded individuals who had a history of atrial fibrillation

Table 1. Basic demographic characteristics for controls and hemodialysis patients

Parameter	Controls (N=54,243)	HD patients (N=15,622)	P value
	n (%)	n (%)	
Age (years)			
£ 49	14484 (26.7)	3389 (21.7)	<.0001
50-59	11757 (21.7)	3314 (21.2)	
60-69	13725 (25.3)	4176 (26.7)	
70+	14277 (26.3)	4743 (30.4)	
Mean ± SD	58.7±14.1	60.7±13.5	
Sex			
Male	25947 (47.8)	7560 (48.4)	<.0001
Female	28296 (52.2)	8062 (51.6)	
Geographic area			
Northern	23,637(43.6)	6,502(41.6)	<.0001
Central	11,379(21.0)	3,263(20.9)	
Southern	16,960(31.3)	5,147(32.9)	
Eastern	2,267(4.2)	7,10(4.5)	
Co-morbidities			
Diabetes mellitus	6081 (11.2)	7808 (49.9)	<.0001
Hypertension	12757 (23.5)	11534 (73.8)	
Hyperlipidemia	5110 (9.4)	4097 (26.2)	
Ischemic heart disease	4732 (8.7)	4239 (27.1)	

HD: Hemodialysis; SD: Standard Deviation.

before the beginning index date. During the follow-up period, 12,090 patients had new-onset atrial fibrillation (5902 in the HD patients and 6188 in the controls). The incidence rate of atrial fibrillation was 157.63/1000 person-years for the HD patients as well as 62.77/1000 person-years for the controls. The incidence rate ratio (IRR) for atrial fibrillation was higher among the HD patients than that in the controls (IRR 2.29, 95% CI 2.13–2.46). In addition, the adjusted HR for atrial fibrillation was 1.95 (95% CI 1.76–2.17) for the HD patients after adjusting for age, sex, geographic area, and comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, and ischemic heart disease (Table 2).

Stratification analysis for the risk of atrial fibrillation

In Table 3, the adjusted HR for atrial fibrillation was estimated by adjusting for age, sex, geographic area, and comorbidities, including diabetes mellitus, hypertension, hyperlipidemia, and ischemic heart disease in Model 2. Increased atrial fibrillation risks of 6.60, 2.90, and 1.66 were found for the age groups ≤49, 50–59, and ≥60 years, respectively. Both the female and male participants had a similar increased risk of atrial fibrillation. Regarding the subgroup analysis stratified by certain comorbidities, significantly increased atrial fibrillation risks of 2.07, 1.94, 3.39, and 2.26 were found for those who had a history of diabetes mellitus, hypertension, hyperlipidemia, and ischemic heart disease, respectively (Model 2).

Discussion

The present study found that hemodialysis patients have a significantly higher risk of atrial fibrillation after adjustment for age, sex, geographic area, and other comorbidities. Some potential reasons might contribute to this significant association. Electrolyte changes, especially from the decrease in potassium and variations in the extravascular volume, can lead to atrial fibrillation during the hemodialysis process[20-22]. Although dialysis had been proposed to be a risk factor for the development of atrial fibrillation, however, no larger studies regarding the association between hemodialysis and the risk of atrial fibrillation have been conducted[22]. Therefore, our findings provide useful information for monitoring the relevant complications among patients with CKD receiving hemodialysis.

Age has been reported to be a major risk factor for atrial fibrillation in both HD patients and the general population[2]. The effect of age on atrial

Table 2. Incidence rate and risk of atrial fibrillation for controls and hemodialysis patients

Parameters	Controls	HD patients
Mean follow-up period (years)	5.03	3.42
Number of events	6,188	5,902
Person-years at risk	98,580	37,441
Incidence rate†	62.77	157.63
IRR (95% CI)	1.00 (reference)	2.29 (2.13-2.46)
Estimation of HR (95% CI)*	1.00 (reference)	1.95 (1.76-2.17)

CI: Confidence interval; HR: Hazard ratio; IRR: Incidence rate ratio.
†Per 1,000 person-years.
*Adjustment for age, sex, geographic area, diabetes mellitus, hypertension, hyperlipidemia and ischemic heart disease.

Table 3. Risk of atrial fibrillation for hemodialysis patients stratified by covariates

Covariates	HD patients	
	Model 1	Model 2
	HR (95% CI)	HR (95% CI)
Age (years)		
≤ 49	8.08 (5.46-11.95)	6.60 (3.62-10.12)
50-59	4.05 (3.07-5.33)	2.90 (2.09-4.03)
≥ 60	1.89 (1.70-2.11)	1.66 (1.48-1.87)
Sex		
Female	2.29 (2.00-2.61)	1.95 (1.68-2.25)
Male	2.35 (2.05-2.70)	1.94 (1.67-2.26)
Diabetes mellitus		
No	2.08 (1.56-2.79)	1.89 (1.39-2.56)
Yes	2.48 (2.16-2.85)	2.07 (1.79-2.39)
Hypertension		
No	1.52 (1.31-1.77)	1.50 (1.28-1.76)
Yes	1.97 (1.56-2.48)	1.94 (1.54-2.45)
Hyperlipidemia		
No	2.67 (2.03-2.54)	1.91 (1.69-2.16)
Yes	3.65 (2.02-6.61)	3.39 (1.78-6.49)
Ischemic heart disease		
No	1.27 (0.92-1.76)	1.27 (0.89-1.81)
Yes	2.54 (2.25-2.87)	2.26 (1.98-2.58)

CI: Confidence interval; HD: Hemodialysis; HR: Hazard ratio.
* Model 1: Adjustment for age, sex and geographic area;
Model 2: Adjustment for age, sex, geographic area and comorbidities including diabetes mellitus, hypertension, hyperlipidemia and ischemic heart disease.

fibrillation risk in the present study was consistent with previous findings. Moreover, both female and male HD patients have a significantly higher risk of atrial fibrillation.

As to the effects of comorbidities, including diabetes mellitus, hypertension, hyperlipidemia, and ischemic heart disease, we found that these comorbidities were more common in HD patients compared with controls. This finding is consistent with previous studies, and these cardiovascular disorders might increase the risk of atrial fibrillation among hemodialysis patients[23-26].

The present study investigated patients with incident atrial fibrillation during an average follow-up period of 8–10 years. Our results are consistent with previous studies, which revealed HD patients have better blood pressure and fluid control, possibly due to more medical care in the dialysis center[27-30]. Severe left ventricular hypertrophy has typically been found among long-term dialysis patients[27,31]. Both hemodialysis and peritoneal patients have access to medical resources according to their health care policy. These factors could explain the difference in incident atrial fibrillation between the United States Renal Data System and the National Health Insurance Research Database in Taiwan.

In addition, recent studies have reported that peritoneal patients are at higher risk of cardiovascular diseases including left ventricular hypertrophy and atrial fibrillation, which will increase the mortality rate[32-34]. A possible causal mechanism could be the loss of residual renal function in peritoneal patients with fluid retention, which might explain the underlying mechanism of atrial fibrillation for these patients. Whether incident atrial fibrillation represents earlier phenomena of residual renal function loss with fluid overload in dialysis patients still needs further exploration.

This study has some limitations. Relevant personal information, such as smoking, alcohol drinking, and physical activity were unavailable in this study, which might influence the risk of atrial fibrillation. In particular, there are differences between rural and urban health care, which are influenced by various factors, such as socioeconomic status and lifestyle[35,36]. The lack of medical resources in rural areas and less access to relevant medical care is a noteworthy health problem. Therefore, we included geographic area in model 1 to adjust for potential differences. Moreover, the lack of data on body mass index, the severity of comorbidities, residual renal function, and blood pressure should be noted in this study. Finally, our study also lacked information on the intake and output recordings during the dialysis procedure, specific medications, and the duration of dialysis for individual patients. Therefore, we found an association, not a causality, between hemodialysis modality and the risk of atrial fibrillation.

In conclusion, hemodialysis itself is independently associated with incident atrial fibrillation among dialysis patients. The loss of residual renal function with volume overload could be the mechanism underlying the development of atrial fibrillation. Our findings indicated that intensive monitoring of dialysis patients is clinically important, deserves further prospective studies, and could improve the quality of life among patients with CKD.

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探討血液透析病人罹患心房顫動的風險：以群體為基礎的世代研究

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摘要

背景及目的：過去的研究發現血液透析病人會具有較高罹患心血管疾病的風險。然而，對於血液透析病人罹患心房顫動的關係仍有待進一步釐清。因此，本研究主要目的在探討血液透析病人與心房顫動的發生率及風險之相關性。

方法：本研究係利用全民健康保險研究資料庫（2007 年 1 月 1 日至 2016 年 9 月 30 日）選取 15,622 位長期接受血液透析的慢性腎臟病患者。另外，篩選出 54,243 位非慢性腎臟病者作為對照組個案。運用 Cox 比例風險模式估計血液透析病人罹患心房顫動的風險對比值及其百分之九十五信賴區間。

結果：本研究發現在對照組及血液透析病人於追蹤期間分別有 61,88 及 5,902 位新發的心房顫動個案。相較於對照組個案，血液透析病人的心房顫動發生率比為 2.29（95% CI = 2.13-2.46）。調整相關危險因子後，血液透析病人罹患心房顫動的風險對比值為 1.95（95% CI = 1.76-2.17）。分層分析的研究結果顯示血液透析病人同時具有糖尿病、高血壓、高血脂及缺血性心臟病等共病時亦會有顯著較高罹患心房顫動的風險。

結論：本研究結果發現年齡較大及同時具有其他共病的血液透析病人會有較高罹患心房顫動的風險。未來對於這些具有較高罹患心房顫動風險的血液透析病人的臨床照護需要更加注意，以期提高透析病人的生活品質。

關鍵詞：心房顫動、慢性腎臟病、血液透析、全民健康保險研究資料庫

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Original Article

Exploring Factors Related to Human Papillomavirus Vaccination Intention Among Nurses

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Abstract

Background: Human papillomavirus (HPV) is a double-stranded DNA virus that can cause anogenital infection. Nonetheless, the novel Gardasil 9 HPV vaccine has been developed, in which nurses play an important role in the recommendations and prevention of this disease.
Purpose: The study aimed to explore factors related to the HPV vaccination intention of nurses in central Taiwan.
Methods: This quantitative cross-sectional study utilized the health belief model as a theoretical framework along with a self-administered online QR code questionnaire. We conducted random cluster sampling and recruited 701 in-service clinical nurses aged 20 years or above. Factors related to the HPV vaccination intention of the participants were examined using SPSS 22.0 statistical software, descriptive statistics, and binary logistic regression.
Results: The nurses did not have sufficient knowledge of HPV. They had greater intention for free vaccination than self-financed vaccination of HPV. Age, employment in the general medicine service division, and health beliefs regarding prophylactic vaccination were the factors affecting self-financed HPV vaccination intention. The factors affecting free HPV vaccination intention were age, average monthly household income, lack of care experience in patients with cervical cancer, lack of friends or family members with HPV infection, knowledge of friends or family members with HPV infection, lack of friends or family members with cervical cancer, lack of HPV knowledge, knowledge of HPV vaccine, and health beliefs regarding prophylactic vaccination.
Conclusion: Understanding the factors affecting HPV vaccination intention among nurses and providing HPV-related knowledge and information facilitate schools and medical staff-related units in increasing the rate of HPV vaccination.

Key words: Nurses, HPV vaccine, health belief model

Introduction

According to the latest report from the International Agency for Research on Cancer[1], cervical cancer is the fourth and seventh most common malignancy among women and in the world, respectively. According to the annual report of statistics on the causes of death in Taiwan in 2016, uterine cancer and cervical cancer ranked eighth and tenth, respectively, in the ten leading causes of cancer deaths among women[2].

In the medical staff-related studies conducted by Jeyachelvi, Juwita, & Norwati[3], Mojahed, Karimizarchi, Bokaie, & Salimi[4] and Wong et al.[5], approximately 1500 physicians, nurses, and medical assistants from Kelantan (Malaysia), Hong Kong, and Iran were surveyed. According to the study results, the medical staff lacked knowledge of human papillomavirus (HPV) vaccination. People's decision about receiving HPV vaccine is affected by several factors, including vaccine protection, long-lasting immunity, good antibody response, and vaccine safety.

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Currently, nurses, in general, have an insufficient knowledge of the HPV vaccine, and obstetric nurses are more willing to recommend vaccination[6].

If nurses can provide more information regarding HPV vaccination, people in Taiwan will possibly be more willing to avail self-financed vaccinations, thereby reducing their chance of contracting HPV[7].

According to a study by Cancer Council Victoria[8], nurses' actions may affect the completion rate of the second and third doses of the HPV vaccine. Hence, the present study aimed to determine and understand nurses' opinions on HPV vaccination and related influencing factors and to facilitate the implementation of in-service education or public lectures to assist nurses and promote the concept of vaccination.

Methods

Research Design

In this quantitative cross-sectional study, we utilized the health belief model as a theoretical framework and conducted random cluster sampling to explore factors related to the intention of nurses regarding HPV vaccination.

Research Participants

This study enrolled in-service nurses aged 20 years and above from various divisions in a medical center in central Taiwan and four regional teaching hospitals. Data were collected using a structured, self-administered QR code questionnaire. Our research plan was reviewed and approved by the institutional review board of the medical institution where the data was collected (106033). We collected 701 questionnaires from January 16 to April 15 of 2018. The valid response rate was 93%.

Research Tools

The questionnaire was developed by referencing relevant foreign and local studies. Five Taiwanese experts and scholars who work in the fields of local gynecological cancer, public health, clinical nursing, nursing education, and obstetrics and gynecology were invited to offer their opinions; the content validity of the questionnaire was 1.0. Based on the research purpose and the variables to be measured, the Cronbach's α coefficient of the structured questionnaire was.80, and the research title was "Exploring the human papillomavirus vaccination intention of nurses and related factors." The questionnaire contained 13 questions on demographic characteristics (age, gender, educational background, service division, marital status, financial status, knowledge about disease, prior disease experience, and prior disease nursing experience); 20 questions on the knowledge of HPV, cervical cancer, and HPV vaccine; 28 questions on vaccination-related health beliefs; and 2 questions on HPV vaccination intention. The responses were based on the numbers 1, 2, and 3, with 1 meaning "no," 2 meaning "yes," and 3 meaning "do not know." In the final analysis, a correct answer corresponded to 1 point, while an incorrect answer or a "do not know" response corresponded to 0 points. The higher the score, the better the nurse's knowledge of HPV, cervical cancer, and HPV vaccine. The vaccination-related health beliefs had six main facets: 3 questions on "perceived susceptibility to HPV-related diseases," 5 questions on "perceived severity of HPV-related diseases," 3 questions on "perceived benefits of HPV vaccination," 8 questions on "perceived barriers to HPV vaccination," 5 questions on "self-efficacy of disease prevention," and 4 questions on "cues to action that result in HPV vaccination." These questions were scored using a 5-point Likert scale ranging from 1, meaning "strongly disagree," to 5, meaning "strongly agree." The higher the score, the more the participant agreed with the question.

Statistical Methods

After the questionnaires were collected, the data were analyzed using the SPSS 22.0 statistical software. We used descriptive statistics to present the demographic characteristics of the research participants in terms of number, percentage, and mean, knowledge of "HPV, cervical cancer, and HPV vaccine," "health beliefs regarding prophylactic vaccination," and HPV vaccination intention of nurses. For the dependent variables, nurses were classified into those who agreed with self-financed HPV vaccination and those who were into free HPV vaccination. To explore the factors that affect the HPV vaccination intention of nurses, we employed binary logistic regression to analyze the variable distribution of these two groups in terms of demographic characteristics, knowledge of "HPV, cervical cancer, and HPV vaccine," and "health beliefs regarding prophylactic vaccination."

Results

Demographic Variables

A total of 701 participants were included. The average age was 31.65 ± 8.16 years, with the majority of the participants aged 25 years old (7.8%). Women accounted for 92%, whereas men made up the remaining 8%. Most of them were unmarried (59.5%), attained the university level of education (70.8%), worked in the internal medicine division (28.4%), and obtained an average monthly household income of NT$30,000–60,000 (inclusive) (41.5%). Meanwhile, 11.6% of the participants had been diagnosed with genital infection or gynecological conditions. In addition, 66.2% had never been asked HPV vaccine-related questions, while only 33.8% had been asked. Participants who had taken care of patients with cervical cancer accounted for 48.1%. Those with friends or family who had contracted HPV accounted for 6.1%, whereas those who did not know whether or not their friends or family had contracted HPV accounted for 26.2%. Participants who had friends or family diagnosed with cervical cancer accounted for 11%. In terms of knowledge, participants who had heard of HPV and those who had heard of the cervical cancer vaccine or HPV vaccine accounted for 92.7% separately, implying that those who had never heard of such topics only accounted for 7.3% each.

Knowledge Scale of HPV, Cervical Cancer, and HPV Vaccine

The overall scale was divided into three dimensions, namely, the average scores of the HPV knowledge scale (5.91 ± 1.63), cervical cancer knowledge scale (4.21 ± 1.03), and HPV vaccine knowledge scale (4.90 ± 1.51). These three dimensions obtained an average score of 15.01 ± 3.45.

Health Beliefs Regarding Prophylactic Vaccination

Participants obtained an average score of 2.60 ± 1.10 for their perceived susceptibility to HPV-related diseases, 4.00 ± 0.63 for their perceived severity of contracting HPV-related diseases, 3.80 ± 0.67 for their perceived benefits of HPV vaccination, 2.80 ± 0.67 for their perceived barriers to HPV vaccination, and 3.57 ± 0.71 for the self-efficacy of disease prevention. For the question "How did you obtain information on the HPV vaccine?," the majority responded "TV" (24.2%), followed by the "Internet" (16.6%), "books" (15.30%), "newspapers, magazines" (14.90%), "family, friends, or colleagues" (14.80%), "relevant seminars" (9.80%), and "advertising posters" (4.40%). For the question "Have you ever received any self-financed vaccinations?," 59.3% of the participants answered "yes." For the question "Have you received HPV vaccine?," 77% answered "no." For the question "Do you have family members who have received HPV vaccine?," 78.3% answered "no."

HPV Vaccination Intention

For the question "Would you be willing to receive HPV vaccine at your own expense?," 66.2% of the participants answered "yes." Participants who answered "no" indicated they could not afford the total cost of the three doses of HPV vaccination, which costs NT$6,400 on an average. For the question "Would you be willing to receive HPV vaccine if it was fully covered by the government?," 91.3% answered "yes."

Factors Affecting HPV Vaccination Intention

Factors that affect self-financed HPV vaccination were analyzed by binary logistic regression. The results for the demographic variables showed that for each additional year of age, the odds of intention to receive self-financed HPV vaccination were 0.955 times those of the original figure (*Wald* = 9.32, *P* = 0.02). With the general medicine division used as the reference group, the odds of intention of the participants in the surgery division to receive self-financed HPV vaccination were 0.372 times (*Wald* = 5.887, *P* = 0.015) those of the participants in the general medicine division. Meanwhile, such odds of the participants who worked in community and long-term care were 0.312 times (*Wald* = 4.15, *P* = 0.042) those of the participants in the general medicine division. Likewise, the odds of intention to receive self-financed HPV vaccination of the participants in the psychiatry division were 0.179 times (*Wald* = 8.382, *P* = 0.004) those of the participants in the general medicine division. Moreover, the impact of the variable "knowledge of HPV, cervical cancer, and HPV vaccine" was not statistically significant. In the variable "health beliefs regarding prophylactic vaccination," the odds of intention to receive self-financed HPV vaccination increased 1.217 times (*Wald* = 4.877, *P* = 0.027) for each additional unit of the "perceived susceptibility to HPV-related diseases," 1.928 times (*Wald* = 14.535, *P* < 0.001) for each additional unit of the "perceived

benefits of HPV vaccination," 0.536 times (*Wald* = 15.341, *P* < 0.001) for each additional unit of the "perceived barriers to HPV vaccination," and 1.580 times (*Wald* = 9.083, *P* = 0.003) for each additional unit of the "self-efficacy of disease prevention." In "cues to action that result in HPV vaccination," the odds of intention to receive self-financed HPV vaccination for the participants who had never received a vaccine at their own expense were 0.570 times (*Wald* = 10.604, *P* = 0.001) those of the participants who had; the odds for the participants who had never received the HPV vaccine were 0.099 times (*Wald* = 36.331, *P* < 0.001) those of the participants who had; the odds for the participants who had no family members with HPV vaccination were 0.596 times (*Wald* = 3.995, *P* = 0.046) those of the participants who had. These results are shown in Table 1.

In terms of demographic variables, the odds of intention to receive free HPV vaccination increased 0.882 times (*Wald* = 15.374, *P* < 0.001) for each additional year of age. For the participants with monthly incomes of NT$30,000–60,000 (inclusive), NT$60,000–90,000 (inclusive), and NT$90,000–120,000 (inclusive), such odds were 3.327 (*Wald* = 5.313, *P* = 0.021), 5.180 (*Wald* = 7.532, *P* = 0.006), and 10.667 (*Wald* = 9.935, *P* = 0.002) times those of the participants with monthly incomes of NT$120,000–150,000 (inclusive) or above, respectively. For the participants who had never taken care of patients with cervical cancer, such odds were 0.334 times (*Wald* = 6.803, *P* = 0.009) those of the participants who had. In addition, for the participants who had and who did not have friends or family with HPV infection, the odds were 0.24 (*Wald* = 6.981, *P* = 0.008) and 0.049 (*Wald* = 8.201, *P* = 0.04) times those of the participants who did not know, respectively. For the participants who did not have friends or family with cervical cancer, the odds were 0.039 times (*Wald* = 5.185, *P* = 0.023) those of the participants who had. For the participants who had never heard of HPV, the odds were 0.260 times (*Wald* = 6.604, *P* = 0.014) those of participants who had. Meanwhile, in the variable "knowledge of HPV, cervical cancer, and HPV vaccine," the odds of intention to receive free HPV vaccination increased 1.603 times (*Wald* = 11.384, *P* = 0.001) for each additional unit of "knowledge of HPV vaccine." In the variable "health beliefs regarding prophylactic vaccination," such odds increased 2.918 times (*Wald* = 11.112, *P* = 0.001) for each additional unit of "perceived severity of HPV-related diseases." In addition, for each additional unit of "perceived benefits of HPV vaccination," the odds increased 2.543 times (*Wald* = 7.18, *P* = 0.007). For each additional unit of "perceived barriers of HPV vaccination," the odds increased 0.307 times (*Wald* = 11.15, *P* = 0.001). In "cues to action that result in HPV vaccination," for the participants who had never received a vaccine at their own expense, the odds of intention to receive free HPV vaccination were 0.548 times (*Wald* = 4.606, *P* = 0.032) those of the participants who had. These results are listed in Table 2.

Discussion

This study aimed to understand the factors related to the intention of nurses regarding HPV vaccination. We found that nurses had a low correct response rate for HPV-related knowledge, probably because we included newly employed staff in our study population that resulted in less HPV-related knowledge.

In terms of obtaining information on HPV vaccine, TV was the most popular source. In Kuo's[9] study, less than 10% of the research participants obtained accurate information from relevant professional seminars, possibly because of the lack of relevant seminars at the medical centers where the participants worked.

Regarding HPV vaccine intention, nurses had a greater intention for free HPV vaccination than for self-financed HPV vaccination. The average cost for self-financed HPV vaccine was NT$6,400. However, the accepted cost is far from the NT$16,500 required for the latest Gardasil 9 vaccine announced by the Ministry of Health and Welfare. Thus, cost may be a barrier for self-financed HPV vaccination.

With regard to the factors affecting self-financed HPV vaccination, the intention to receive self-financed HPV vaccination was lower for each additional year of age, possibly because the WHO recommends that the main target recipients of the HPV vaccine are girls aged 9 to 14 years. In terms of service divisions, Yao et al.[6] revealed that the self-financed HPV vaccination intention of participants from the obstetrics and gynecology division was not significantly higher than those from other divisions. A possible explanation could be that the region or grade of the hospital where they worked could relay different

HPV-related information. For the variable "health beliefs regarding prophylactic vaccination," Tsai[10] and Huang et al.[11] compared nurses, recipients aged 9–26 years, and parents of adolescents, and they found that "health beliefs regarding prophylactic vaccination" is the factor that affects self-financed HPV vaccination intention.

Moreover, Schulein et al.[12] inferred that knowledge of HPV-related disease, prior disease experience, and prior disease care experience are factors that affect free HPV vaccination. In terms of the variable "knowledge of HPV, cervical cancer, and

Table 1. Binary logistic regression analysis of factors that affect self-financed HPV vaccination intention in terms of demographics, relevant knowledge, and health beliefs regarding prophylactic vaccination (N=701)

Variable	Wald	Exp(B)
Age (reference group)	9.32**	0.955
Gender		
Male (reference group)		
Female	0.016	0.957
Educational Background		
Graduate School (including M.S. and Ph.D.), reference group	3.687	
General or Vocational High School	1.113	0.325
Junior College	0.178	1.209
University	0.879	1.482
Service Division		
General Medicine (reference group)	12.457	
Internal Medicine	2.994	0.497
Surgery Division	5.887*	0.372
Obstetrics and Gynecology	1.843	0.513
Pediatrics	1.08	0.618
Community and Long-Term Care	4.15*	0.312
Outpatient	1.711	0.481
Psychiatry	8.382**	0.179
Emergency Room	1.534	0.546
Marital Status		
Separated (reference group)	0.217	
Unmarried	0.000	0.000
Married	0.000	0.000
Divorced	0.000	0.000
Monthly Household Income		
Above 12,000-15,000 (inclusive) (reference group)	0.636	
Below 30,000 (inclusive)	0.063	1.132
30,000-60,000 (inclusive)	0.008	1.027
60,000-90,000 (inclusive)	0.009	0.971
90,000-120,000 (inclusive)	0.277	1.200
Have you ever been diagnosed with genital infections or gynecological conditions?		
Yes (reference group)		
No	1.909	1.464
Have you ever been asked HPV? vaccine-related questions?		
Yes (reference group)		
No	0.805	0.827
Have you ever taken care of a cervical cancer patient?		
Yes (reference group)		
No	0.001	0.994
Do you have friends or family who have contracted an HPV infection?		
Do not know (reference group)	2.146	
No	0.222	0.906
Yes	2.146	0.531
Do you have friends or family who have had cervical cancer?		
Yes (reference group)		
No	0.258	0.849
Have you ever heard of human papillomavirus or HPV?		
Yes (reference group)		
No	0.146	0.862
Have you ever heard of the cervical cancer vaccine or HPV vaccine?		
Yes (reference group)		
No	2.089	0.565
HPV-related knowledge	2.501	1.119
Cervical cancer-related knowledge	0.213	1.052
HPV vaccine-related knowledge	1.135	1.082
Perceived susceptibility to HPV-related diseases	4.877*	1.217
Perceived severity of HPV-related diseases	1.538	0.818
Perceived benefits of HPV vaccination	14.535***	1.928
Perceived barriers to HPV vaccination	15.341***	0.536
Self-efficacy of disease prevention	9.083**	1.580
Cues to action that result in HPV vaccination		
Have you ever received any self-financed? vaccinations?		
Yes (reference group)		
No	10.604***	0.570
Have you received the HPV vaccination?		
Yes (reference group)		
No	36.331***	0.099
Do you have family members who have received? the HPV vaccination?		
Yes (reference group)		
No	3.995*	0.596

Note: 1.*.P<0.05 **. P<0.01 ***. P<0.001

2. This scheme will yield:

$$\ln\left(\frac{p}{1-p}\right) = -0.046\,(\text{age}) - 0.990\,(\text{surgery division}) - 1.165\,(\text{community and long-term care}) - 1.723\,(\text{psychiatry}) + 0.196\,(\text{perceived susceptibility to HPV-related diseases}) + 0.656\,(\text{perceived benefits of HPV vaccination}) - 0.623\,(\text{perceived barriers to HPV vaccination}) + 0.458\,(\text{self-efficacy of disease prevention}) - 0.563\,(\text{have never received any self-financed vaccine}) - 2.311\,(\text{have never received HPV vaccination}) - 0.518\,(\text{no family members who have received HPV vaccination})$$

Where p is the rate of self-financed HPV vaccination intention.

HPV vaccine," the greater the knowledge of the HPV vaccine, the greater was the intention to receive free HPV vaccination. In terms of the variable "health beliefs regarding prophylactic vaccination," the intention to receive free HPV vaccination increased as the participant agreed with the perceived severity of contracting HPV as well as the perceived benefits of HPV vaccination; however, the intention decreased as the participant agreed with the perceived barriers to HPV vaccination. In addition, participants who had never

Table 2. Binary logistic regression analysis of factors that affect free HPV vaccination intention in terms of demographics, relevant knowledge, and health beliefs regarding prophylactic vaccination (N=701)

Variable	Wald	Exp(B)
Age	15.374***	0.882
Gender		
Men (reference group)		
Women	0.667	1.624
Educational Background		
Graduate School (including M.S. and Ph.D.), reference group	0.45	
General or Vocational High School	0	1.21E+18
Junior College	0.281	1.586
University	0.445	1.682
Service Division		
General Medicine (reference group)	6.632	
Internal Medicine	0.376	1.527
Surgery Division	1.233	2.22
Obstetrics and Gynecology	0.547	2.181
Pediatrics	2.532	4.027
Community and Long-Term Care	0.045	1.302
Outpatient	0.811	3.068
Psychiatry	0.016	0.886
Emergency Room	0.195	0.714
Marital Status		
Separated (reference group)	1.794	
Unmarried	0	1.27E+10
Married	0	2.48E+10
Divorced	0	8.79E+09
Monthly Household Income		
Above 12,000-15,000 (inclusive) (reference group)	12.213	
Below 30,000 (inclusive)	1.012	2.381
30,000-60,000 (inclusive)	5.313*	3.327
60,000-90,000 (inclusive)	7.532**	5.18
90,000-120,000 (inclusive)	9.935**	10.667
Have you ever been diagnosed with genital infections or gynecological conditions?		
Yes (reference group)		
No	1.197	1.877
Have you ever been asked HPV? vaccine-related questions?		
Yes (reference group)		
No	0.47	1.362
Have you ever taken care of a cervical cancer patient?		
Yes (reference group)		
No	6.803**	0.334
Do you have friends or family who have contracted an HPV infection?		
Don't know	10.305	
No	6.981**	0.240
Yes	8.201**	0.049
Do you have friends or family who have had cervical cancer?		
Yes (reference group)		
No	5.185*	0.039
Have you ever heard of human papillomavirus or HPV?		
Yes (reference group)		
No	6.064*	0.260
Have you ever heard of the cervical cancer vaccine or HPV vaccine?		
Yes (reference group)		
No	1.504	0.486
HPV-related knowledge	0.555	0.908
Cervical cancer-related knowledge	0.026	0.971
HPV vaccine-related knowledge	11.384***	1.603
Perceived susceptibility to HPV-related diseases	0.086	0.947
Perceived severity of HPV-related diseases	11.112***	2.918
Perceived benefits of HPV vaccination	7.18**	2.543
Perceived barriers to HPV vaccination	11.15***	0.307
Self-efficacy of disease prevention	1.972	1.575
Cues to action that result in HPV vaccination Have you ever received any self-financed? accinations?		
Yes (reference group)		
No	4.606*	0.548
Have you received the HPV vaccination?		
Yes (reference group)		
No	1.922	0.540
Do you have family members who have received? the HPV vaccination?		
Yes (reference group)		
No	0.236	0.825

Note: 1.*.P<0.05 **. P<0.01 ***. P<0.001

2. This scheme will yield:

$$\ln\left(\frac{p}{1-p}\right) = -0.046\,(\text{age}) - 0.990\,(\text{surgery division}) - 1.165\,(\text{community and long-term care}) - 1.723\,(\text{psychiatry}) + 0.196\,(\text{perceived susceptibility to HPV-related diseases}) + 0.656\,(\text{perceived benefits of HPV vaccination}) - 0.623\,(\text{perceived barriers to HPV vaccination}) + 0.458\,(\text{self-efficacy of disease prevention}) - 0.563\,(\text{have never received any self-financed vaccine}) - 2.311\,(\text{have never received HPV vaccination}) - 0.518\,(\text{no family members who have received HPV vaccination})$$

Where p is the rate of self-financed HPV vaccination intention.

received free vaccination had lesser intention to receive free HPV vaccination. The results are similar to the factors that affect self-financed HPV vaccination intention.

In conclusion, the clinical practice and professional education of nurses can be improved to increase HPV-related knowledge among nurses and the public. In future research, the scope of data collection should be expanded and other medical personnel should be investigated to further examine the factors that affect their HPV vaccination intention, which will help increase the rate of HPV vaccination.

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探討護理人員接種人類乳突病毒疫苗意向之相關因素

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摘要

背景：人類乳突病毒是一種雙股 DNA 的濾過性病毒，使人類之肛門、生殖器黏膜造成感染及病變，隨著新型 Gardasil 9 人類乳突病毒疫苗的研發上市，臨床護理人員在推薦民眾及預防疾病上扮演著重要的角色。

目的：探討台灣中部護理人員接種人類乳突病毒疫苗之意向及相關因素。

方法：採量性橫斷面研究設計，以健康信念模式為理論架構，自填 QR code 線上問卷進行調查，採叢聚隨機取樣台灣中部一所醫學中心、四所區域教學醫院，年滿 20 歲以上共 701 位在職臨床護理人員，採 SPSS22.0 統計軟體，以描述性統計和二元羅吉斯迴歸，探討護理人員接種人類乳突病毒疫苗接種意向及相關因素。

結果：護理人員 HPV 相關知識認知不足；有意願免費接種 HPV 疫苗高於自費接種 HPV 疫苗、平均可負擔價格為 6,400 元新台幣；影響自費接種 HPV 疫苗相關因素：年齡、服務科別為綜合科、對於預防接種行為的相關健康信念；影響免費接種 HPV 疫苗相關因素：年齡、家庭平均月收入、沒有照顧過子宮頸癌的病人、沒有親友罹患過人類乳突病毒的感染、有親友罹患過人類乳突病毒的感染、沒有親友罹患過子宮頸癌、沒有聽說過人類乳突病毒或是 HPV 、HPV 疫苗相關知識、對於預防接種行為的相關健康信念。

討論：可提供學校及醫療相關單位，了解影響護理人員接種人類乳突病毒疫苗之相關因素以利排除，並鼓勵提供 HPV 相關知識及訊息，有助於推廣民眾接種人類乳突病毒疫苗意願提升。

關鍵詞：護理人員、人類乳突病毒疫苗、健康信念模式

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Case Report

Spinal Epidural Abscess after Epidural Anesthesia: A Case Report and Literature Review

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Abstract

We report a case of a patient with spinal epidural abscess (SEA) after an epidural catheter placement for analgesia during a cesarean section. The parturient was healthy and did not present any risk factors for SEA. Four days postoperatively, worsened back pain and erythema with pus discharge over the epidural insertion site accompanied by sensory deficits in the lower extremities were noted. Magnetic resonance imaging revealed SEA with adjacent inflammation of the paravertebral soft tissue. Emergency laminectomy and SEA removal were performed, followed by a 6-week antibiotic therapy course with vancomycin. The parturient completely recovered from her neurologic deficiencies. In addition, several research articles on SEA were reviewed and discussed in this study.

Key words: spinal epidural abscess, epidural anesthesia

Introduction

Spinal epidural abscess (SEA) postspinal or epidural anesthesia is a rare complication in healthy parturient without septicemia or infective disease. A delay of treatment may cause permanent neurologic deficits or even death. Opportune surgical decompression and antibiotics are the major therapy strategies recommended. Therefore, we highlight the necessity for high alertness toward the clinical manifestation of symptoms.

Case Report

A 27-year-old healthy parturient, 160-cm tall and weighing 65 kg with breech presentation, was scheduled to undergo a cesarean section at 39 weeks of gestation. Preoperative survey and anesthetic consultation were arranged, and epidural anesthesia was performed. His blood pressure and heart rate were monitored, and pulse oximetry and electrocardiography were performed during the anesthesia induction and surgery. Her baseline blood pressure and heart rate were 132/66 mmHg and 82/min, respectively. Her SpO_2 was 99% while breathing room air. The parturient was placed in the left lateral decubitus position, and 2% chlorhexidine gluconate was used for skin preparation carefully. The anesthesiologist wear mask and sterile gloves. Then, epidural anesthesia was induced using a midline approach with the placement of an epidural catheter, using a 17-G Tuohy needle, positioned between L2 and L3. Epidural puncture and catheter insertion were performed easy in first attempt, and no spinal fluid or blood was detected. The parturient was administered 400 mg of total lidocaine in 20 mL (2% w/v) with 1 mEq of sodium bicarbonate and 100 mcg of epinephrine. The anesthetic block manifested within 5 min without side effects. Because the sensory block

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was sufficiently high (T6) for a cesarean section, the operation was started after 15 min. Blood pressure remained stable for the entire duration of surgery and during the postoperative period. No evidence of perioperative complications was observed, and the patient did not complain any pain symptoms. Single-dose cefazolin (1g) was administered for infection prophylaxis. After the delivery of the baby, for postoperative analgesia, 1 mg of morphine and 60 mg of lidocaine were injected into the epidural space through the catheter for postoperative pain relief. The parturient was kept under observation for 1 h. Before being transferred to the ward, her catheter was removed.

Three days postoperatively, the parturient complained of moderate low-back pain, and the epidural insertion site revealed erythema tenderness. On the following day, the parturient experienced progressively severe back pain, and the epidural insertion site revealed erythema with pus discharge. At that time, the white blood cell count was 14.3×10^3/mL, and the C-reactive protein level had increased to 9.69 mg/dL. Due to sensory deficits in the lower extremities, the anesthesia team was alerted to the development of an epidural abscess with the spinal cord compression. Emergency magnetic resonance imaging (MRI) was performed and revealed a posteriorly placed epidural abscess extending from L2 to L3 on T1-proton density and T2-weighted images. MRI also revealed subcutaneous soft tissue enhancement in the back that extends along the spinous process due to infection (Fig. 1). A neurosurgery consultation was conducted, and emergency decompressive L2 to L3 laminectomy with abscess evacuation was performed. The intraoperative site exhibited a partially organized and epidural abscess, and the pus culture revealed oxacillin-resistant *Staphylococcus aureus*. Postoperatively, a 6-week antibiotic treatment with vancomycin was administered and the parturient completely recovered from her neurologic deficiencies. The parturient was discharged 7 weeks postoperatively.

Discussion

SEA is a rare condition but can cause severe neurological damage[1]. The overall incidence rate in the general population is 0.2–2.8/10,000. Risk factors include immunocompromised states, alcoholism, diabetes mellitus, intravenous drug use, cancer, spinal trauma, and spinal procedure[2]. Epidural catheter placement is a major risk factor for SEA, and the reported incidence following this procedure ranges from 0.5% to 3%[3]. SEA may occur due to cather insertion, catheter track contamination, or contaminated syringe or local anesthetic solution[4]. The most common causative organism in 60%–90% of patients with iatrogenic SEA is S. aureus, followed by S. epidermidis[5].

The classic clinical triad of SEA includes back pain, fever, and neurologic deficits[6]. However, few patients exhibit this triad of symptoms. Neurological symptoms include irradiation pain (47%), bladder dysfunction (30%), loss of sensations (23%), and paraplegia (21%)[6,7]. Leukocytosis may be the only abnormal laboratory finding. The presentation of symptoms may also begin only after the hospital discharge, or a superficial infection may be treated with antibiotics enabling the progression of the underlying abscess[4,8].

Gadolinium-enhanced MRI is the imaging technique of choice to diagnose SEA due to its high sensitivity (>90%) [2]. Computed tomography (CT) myelography is reported to be as sensitive as MRI, but is an invasive procedure associated with the risk of additional contamination of the subarachnoid space. Therefore, CT myelography should be performed only when MRI is unavailable. A CT scan without

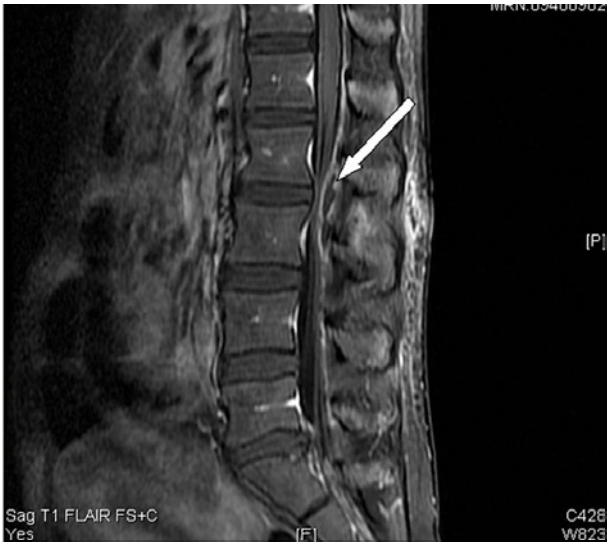

Fig. 1 Abnormal enhancement is shown notably at L2–L3 with 50% cord compression due to a posterior enhancing fluid collection in the epidural space (arrow). Moreover, subcutaneous soft tissue enhancement in the back and extended along the spinous process was caused by an infectious process.

myelography dose not provide essential information for the SEA diagnosis; it is not recommended[9].

Conservative management is possible for patients presenting no neurological symptoms[10]. In patients with neurological signs, the degree of the cal sac compression correlates with permanent neurological damage. Therefore, urgent surgical decompression is the first choice of treatment when neurological symptoms occur. Darouiche[7] suggested that early surgical decompression and prolonged (6–12 weeks) antibiotic treatment are the mainstay management. Several factors are associated with poor outcomes, such as older age, high degree of thecal sac compression, sepsis, and long duration of symptoms. The main predictor of neurologic outcomes is the patient's preoperative neurologic status[7]. Except in case of perioperative complications, the final neurologic outcome in patients with adequate decompression is usually as good as or better than the preoperative condition.

Anesthetists should pay attention to reducing the risk of contamination during epidural an catheter insertion. Rigid aseptic techniques include hand washing and wearing sterile gloves, caps, and masks. The skin should be disinfected with antiseptic agents before an epidural insertion. In addition, cholorhexidine may be a better choice than iodine[11]. Another possible source of infection is epidural solution contamination. Using a closed delivery system and solution prepared by the pharmacy reduce the possibilities of contamination. Injecting epidural solutions through bacterial filters may further decrease the risk of contamination. The practice of epidural catheter insertion used on our patient had followed the suggested guideline carefully. According to the erythema with pus discharge on the epidural insertion site and the infection of subcutaneous soft tissue shown by MRI, SEA may have spread along the catheter track via a subsequent skin contamination.

In summary, epidural catheter placement is a major risk factor for SEA. Anesthetists should do their best to reduce the risk of contamination during an epidural catheter insertion. Being alert to SEA symptoms and signs is a key for its diagnosis. Superficial infection at the catheter insertion site should be monitored in patients with pain, redness, or purulent drainage at the site, as well as with unexplained new neurologic findings. The catheter should be removed and sent for culture. A pain solution unlikely inducing paralysis is helpful for the early diagnosis. Opioids and other additives enable the reduction of the local anesthetic concentration, particularly in patients with controlled epidural analgesia. As epidural abscess may occur after hospital discharge, patients must be instructed to pay attention to the possible symptoms and signs of epidural abscess. If an epidural abscess is suspected, an MRI scan should be performed without delay. In patients with neurological signs, timely surgical decompression is the treatment of choice.

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硬脊膜外麻醉後併發脊髓硬脊膜外膿瘍病例報告與文獻回顧

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摘要

我們在此報告一個病例。患者施行剖腹產，採用硬膜外導管置入麻醉，術後發生脊髓硬膜外膿腫。患者是一位健康的年輕女性，沒有任何風險因素。術後 4 天，患者背部疼痛，伴隨注意到硬膜外針入的部位，有紅腫和膿液排出現象，同時合併下肢感覺缺損。緊急對患者安排核磁共振成像，報告顯示脊髓硬膜外膿腫伴有椎旁軟組織的相鄰炎症。於是進行了緊急椎板切除術和切除脊髓硬膜外膿腫。隨後輔以萬古黴素，進行為期六週的抗生素治療。然後患者完全恢復並沒有遺留任何的神經缺損。此外，我們還回顧了幾篇關於脊髓硬膜外膿腫的研究文章，並在此進行討論。

關鍵詞：脊髓硬膜外膿腫、硬脊膜麻醉

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Case Report

Aorto-esophageal Fistula: Case Report and Review of the Literature

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Abstract

Aorto-esophageal fistula is a rare cause of upper gastrointestinal (GI) bleeding. The mortality rate is high if it is not diagnosed early. Hence, physicians should consider this condition, particularly in patients with unexplained or uncontrolled GI bleeding. In most cases, computed tomography angiogram is effective in detecting this condition, and emergent endovascular repair with aortic stent implantation can control the bleeding and can save the patient's life. Herein, we present a male patient with aorto-esophageal fistula bleeding; he was timely diagnosed but still died of massive gastrointestinal bleeding.

Key words: aorto-esophageal fistula, gastrointestinal bleeding, hypovolemic shock, upper gastrointestinal endoscopy

Introduction

Aorto-enteric fistula is an abnormal anatomical communication between the aorta and the gastrointestinal tract. Aorto-esophageal fistula (AE fistula) is a special type of fistula. Acute upper gastrointestinal bleeding caused by AE fistula might be fatal. Further, diagnosis is considered challenging due to the rarity of the condition. Thus, a timely diagnosis is critical in saving a patient's life.

Case Report

A 78-year-old male patient had a previous history of atrial fibrillation with slow ventricular response status post permanent pacemaker implantation, hypertensive cardiovascular disease, and type2 diabetes mellitus (DM). The patient experienced vomiting of fresh blood early in the morning and chest tightness for 30 min on the day of admission. He presented to the emergency department of our institution. His vital signs were as follows: body temperature, 35.9°C; pulse rate, 91 beats/min; respiratory rate, 24 breaths/min; and blood pressure, 60/49 mmHg. The laboratory test results included the following: hemoglobin level, 8.5 (baseline: 13.5) g/dL; troponin-I level, <0.04 ug/L (within normal limit); creatine phosphokinase level, 133 U/L (within normal limit); creatine kinase-MB level, 3.3 ng/mL (within normal limit); prothrombin time, 11s; and activated partial thromboplastin time, 23s (within normal limit). He was admitted to the intensive care unit due to hypovolemic shock.

The patient's blood pressure normalized with intravenous fluid resuscitation and blood transfusions. Upper gastrointestinal (GI) endoscopy was performed and revealed much fresh blood and blood clot in the gastric lumen, particularly in the gastric fundus (Fig. 1A); in addition, a bulging submucosal tumor-like lesion was found in the mid-esophagus (30cm from the mouth), with an adherent blood clot and a nipple sign (Fig. 1B). However, there was no active bleeding during the examination.

To assess the cause of upper GI bleeding, we performed chest and abdominal dynamic computed

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tomography (CT) scan. Results revealed atherosclerosis of the aorta, a1.1-cm penetrating aortic ulcer in the medial aspect of the descending thoracic aorta (Fig. 2A), and a 3.5-cm hematoma compressing the mid-esophagus just outside the penetrating aortic ulcer (Fig. 2B). Bleeding caused by AE fistula was suspected.

After discussing with the patient's family, percutaneous thoracic endovascular aortic repair (TEVAR) with aortic stent placement was performed. However, another episode of massive hematemesis (>200cc of fresh blood) occurred just before surgery, followed by severe hypotension and pulseless electrical activity. Emergent endotracheal intubation and cardiopulmonary resuscitation were performed for about 30 min. However, the patient died of cardiopulmonary collapse despite aggressive treatment. Discussion

In 1818, Dubrueil first described AE fistula after a French soldier ingested a beef rib, which led to massive hematemesis[1]. In 1914, Chiari described the typical triad of AE fistula, which include chest pain, herald hemorrhage, and fatal hematemesis[2]. There may be intermittent gastrointestinal hemorrhage before fatal hematemesis. The time between herald hemorrhage and fatal hematemesis may last from hours to days.

Primary AE fistula is defined as the spontaneous erosion of the aortic wall into the esophagus, and secondary AE fistula as a complication of surgeries, endoscopic procedures, or aortic stent implantation. Owing to improvements in minimally invasive procedure and the increasing number of aortic interventions, secondary AE fistula was found to be 10 times more common than the primary. The incidence of

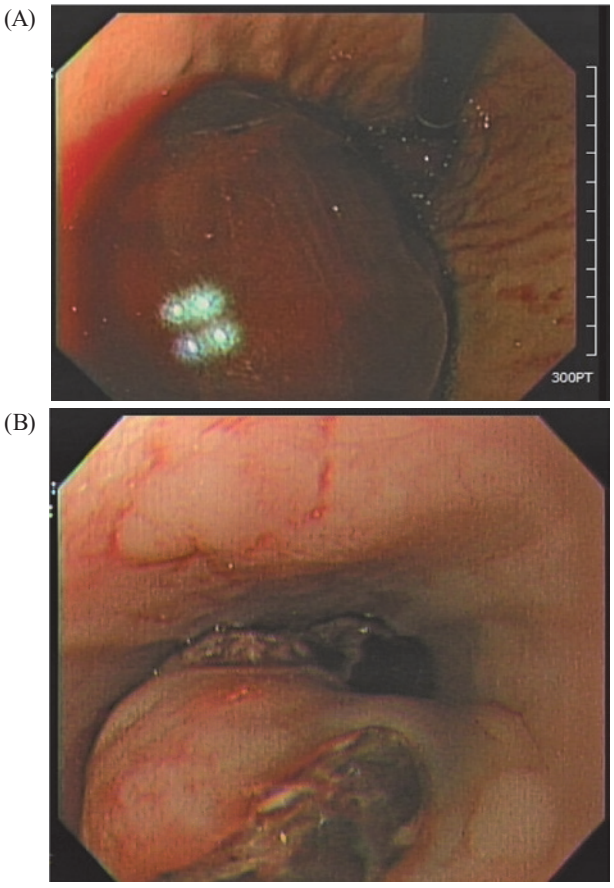

Fig. 1 (A) (left). Fresh blood and blood clot in the gastric lumen, particularly in the gastric fundus (which cannot be removed). (B) (right).A bulging submucosal tumor-like lesion was found in the mid-esophagus (30cm from the mouth), with one adherent blood clot and a nipple sign.

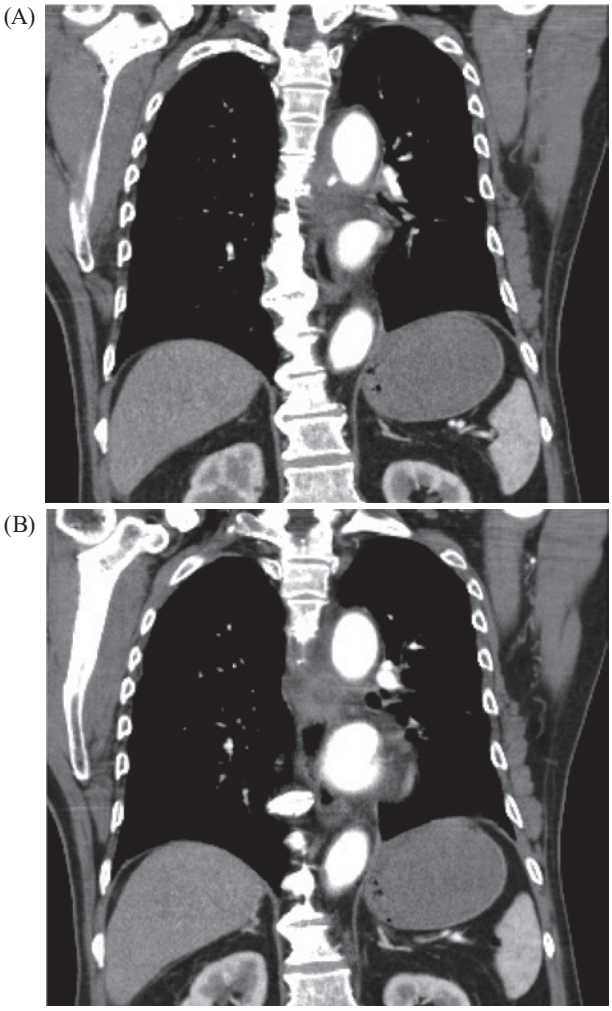

Fig. 2 (A) (left). A1.1-cm penetrating aortic ulcer in the medial aspect of the descending thoracic aorta. (B) (right). A 3.5-cm hematoma compressing the mid-esophagus just outside the penetrating aortic ulcer.

AE fistula after TEVAR is about 0.5%–1.7% [3]. Aortic aneurysm accounts for more than half of the primary cases[4]. The other etiologies include foreign body ingestion, esophageal malignancy, reflux esophagitis, trauma, caustic ingestion, esophageal biopsies, mycotic aneurysm, and aortitis due to infections such as tuberculosis and syphilis[4,5].

The initial management of upper gastrointestinal bleeding comprises assessment and stabilization with volume resuscitation. Patients with hematemesis, hemodynamic instability, coagulopathy, renal failure, old age, and multiple comorbidities are considered at high risk; thus, they require more intensive monitoring. In most cases, upper GI endoscopy is effective in the diagnosis and treatment of upper GI bleeding. In AE fistula, a submucosal tumor-like protrusion or an extrinsic compression is the most common finding on upper GI endoscopy[6]. Other possible findings include pulsatile mass, bluish discoloration, esophageal varicose-like lesions, ulcerative lesion, or, simply, blood clot in the esophagus. In some cases, the examination findings are negative, with sensitivity ranging from 50% to <10% [6,7]. AE fistula should be considered if there is massive hematemesis but only fresh blood is found on endoscopy and if the source cannot be identified[4].

CT arteriogram is the common diagnostic method for AE fistula. The diagnosis of this condition is supported by leakage of contrast medium into the periaortic space or extravasation of contrast medium into the esophagus[8,9]. Other findings indicative of AE fistula on CT arteriogram include ectopic gas adjacent to or within the aorta, discontinuity of the aortic wall, loss of fat plane, hematoma, tethering of the bowel wall toward the aorta, and mediastinal gas or expanding perigraft fluid after TEVAR[8,9]. An esophagogram can visualize an extravasated contrast medium arising from the esophageal side of the fistula, which is also considered a definite sign[10].

The mortality rate of acute upper GI bleeding is about 8.2%[11]. Bleeding caused by AE fistula has a higher mortality rate , a generally fatal condition. Percutaneous TEVAR with aortic stent placement can control the initial bleeding and can save the patient's life. Compared with open surgical repair for AE fistula, TEVAR had several advantages. That is, the procedure is well tolerated by high-risk patients. Moreover, it can reduce the risk of cardiovascular disease and mortality and can be performed under sedation and local anesthesia, and is a rapid method for decreasing the volume of blood loss even in unstable patients[12]. In some case reports, the Sengstaken–Blakemore tube was used to control bleeding temporarily[13]. Broad-spectrum antibiotics should be used for infection control. If the bleeding is controlled, complex aortic and esophageal reconstruction is performed in multiple stages.

In the current case, the submucosal tumor-like protruding lesion in the esophagus on endoscopy was the compressing effect of the hematoma found on chest CT scan. Hematoma was the coagulated blood clot of the bleeding aortic ulcer. There was much fresh blood in the stomach and an endoscopic nipple sign was found in the esophagus; hence, we concluded that the GI bleeding was caused by an AE fistula. The patient had no previous history of esophageal malignancy, reflux esophagitis, trauma, caustic ingestion, or esophageal biopsy. Moreover, he did not present with signs and symptoms of infection such as fever, tachycardia, fatigue, or poor appetite before the current admission. Hence, mycotic aneurysm/aortitis was unlikely. In this case, the risk factors associated with the development of atherosclerosis and aortic aneurysm were old age, history of hypertension, and type2 diabetes mellitus. However, there was no evident aneurysmal formation in the aorta; there was only a small penetrating aortic ulcer in the thoracic part. Thus, AE fistula was attributed to the penetrating aortic ulcer, which has the same risk factor of aortic aneurysm, mainly atherosclerosis. The cause is rare, and there are only two case reports about penetrating aortic ulcer causing AE fistula in the literature[14,15].

Summary

AE fistula is a rare cause of upper GI bleeding. The mortality rate is high if it is not diagnosed early. Hence, physicians should consider this condition, particularly in patients with unexplained massive gastrointestinal bleeding. In most cases, computed tomography angiogram can detect the condition, and emergent endovascular repair with aortic stent implantation can control the bleeding and save the patient's life.

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主動脈 - 食管瘺管，病例報告及文獻回顧

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摘要

主動脈 - 食管瘺管是上消化道出血的罕見原因。如果沒有及早診斷，死亡率很高。醫生應該對這種情況持高度警覺，特別是對於原因不明或大量的胃腸道出血患者。電腦斷層掃描之血管造影可以檢測大多數病例，主動脈支架植入的緊急血管內修復可以控制出血並挽救患者的生命。我們提出了一個及時診斷但仍然死於大量胃腸道出血的病例。

關鍵詞：瘺管、主動脈 - 食管瘺管、胃腸道出血、低血容性休克、上消化道內視鏡

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Case Report

Life-Extending Chemotherapy by Vincristine Plus Irinotecan in a Young Adult With Refractory Ewing Sarcoma in Terminal Stage

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Abstract

A combined regimen of vincristine plus irinotecan (i.e., VI regimen) was chosen during the search for an effective and affordable treatment for terminal Ewing sarcoma. We report our experience of prescribing four courses of VI for a 21-year-old man diagnosed with refractory Ewing sarcoma of the right sacrum with multiple metastases. In addition to dramatically reducing his tumor fever and systemic inflammation, his life was extended for five months longer than expected. Based on this case, we suggest considering using VI regimens in Ewing sarcoma not only for life-extending purposes but also as a first-line therapy for newly diagnosed high-risk patients.

Key words: chemotherapy, Ewing sarcoma, irinotecan, relapsed, vincristine

Introduction

Ewing sarcoma is a rare malignant bone tumor typically found in children and adolescents[1]. However, the prognosis for treated patients with distant metastasis and multiple relapses is dismal, with a five-year overall survival rate of only 10%–30%[2,3]. The current standard-of-care regimens used as the first-line chemotherapy for Ewing sarcoma include vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VAC/IE)[4]. Irinotecan with or without temozolomide has been used as the second-line chemotherapy treatment of choice for relapsed, refractory, or metastatic Ewing sarcoma[5,6]. However, the use of combined irinotecan plus temozolomide is more expensive than irinotecan alone, which limits its clinical use. In this case report, we describe our experience of prescribing four courses of vincristine plus irinotecan (VI regimen; irinotecan given daily for five consecutive days [d × 5]) to a young adult with relapsed/metastatic Ewing sarcoma. A previous randomized trial compared two different schedules of irinotecan to treat relapsed or progressive rhabdomyosarcoma [a d × 5 or a d × 5 × 2 schedule (given for five consecutive days, two weeks in a row)][7], and importantly, there was no significant difference in efficacy. In an attempt to control our patient's tumor fever and cancer pain with a life-extending purpose, we administered VI on a d × 5 schedule because this shorter schedule is less expensive and more convenient.

Case Report

Our patient was a 21-year-old man diagnosed with Ewing sarcoma of the right sacrum with

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pulmonary metastasis in October 2015. He underwent concurrent chemoradiotherapy without definitive surgery at a local hospital. His disease displayed a partial response to therapy, and no evidence of disease progression was noted until February 2017. Acute paraplegia occurred as a result of spinal cord compression from extradural metastasis of the tumor over the thoracic spine, and he was referred to our institute for spinal decompression surgery. His lower limb muscle power partially improved after a laminectomy of the sixth to eighth thoracic vertebrae. Adjuvant chemotherapy with vincristine, dactinomycin (Actinomycin-D), and cyclophosphamide alternating with IE was prescribed. However, the patient's disease progressed with multiple new metastases at the lung, rib, and spine, as identified by chest computed tomography and a Tc-99 m methylene diphosphonate whole-body bone scan (WBBS).

On September 6, 2017, the patient was admitted to our hospital with a spiking fever and pain radiating from the low back to the lower extremities. Elevated C-reactive protein (CRP; 30.74 mg/dL) and lactate dehydrogenase (LDH; 1717 U/L) levels were noted, and piperacillin/tazobactam and isepamicin were administered because of suspicion of a possible infection. However, chest X-ray, routine urine tests, and blood culture yielded negative findings. The clinical impression was tumor fever based on clinical evidence of progressive disease without other symptoms/signs of infection. We stopped antibiotics after informing the patient and his family of his poor prognosis and suggested subsequent chemotherapy on a palliative basis. Instead, a new regimen was commenced with a single dose of 2 mg of vincristine on day 0 and 50 mg/m^2 of irinotecan for five consecutive days on days 0–4 (the VI regimen was given intravenously). Subsequently, the patient's fever subsided dramatically, accompanied by excessive sweating during the first three days of administration. Moreover, his CRP levels measured on the fifth day had decreased to 2.85 mg/dL, and his LDH levels had decreased to within the normal range (303 U/L) (Fig. 1). The patient's low back pain subsided and could be controlled with 10 mg of oral oxycodone at night. The patient experienced no significant side effects associated with irinotecan, except for diarrhea (Common Terminology Criteria for Adverse Events grade 3), which could be controlled by administering loperamide. The patient was

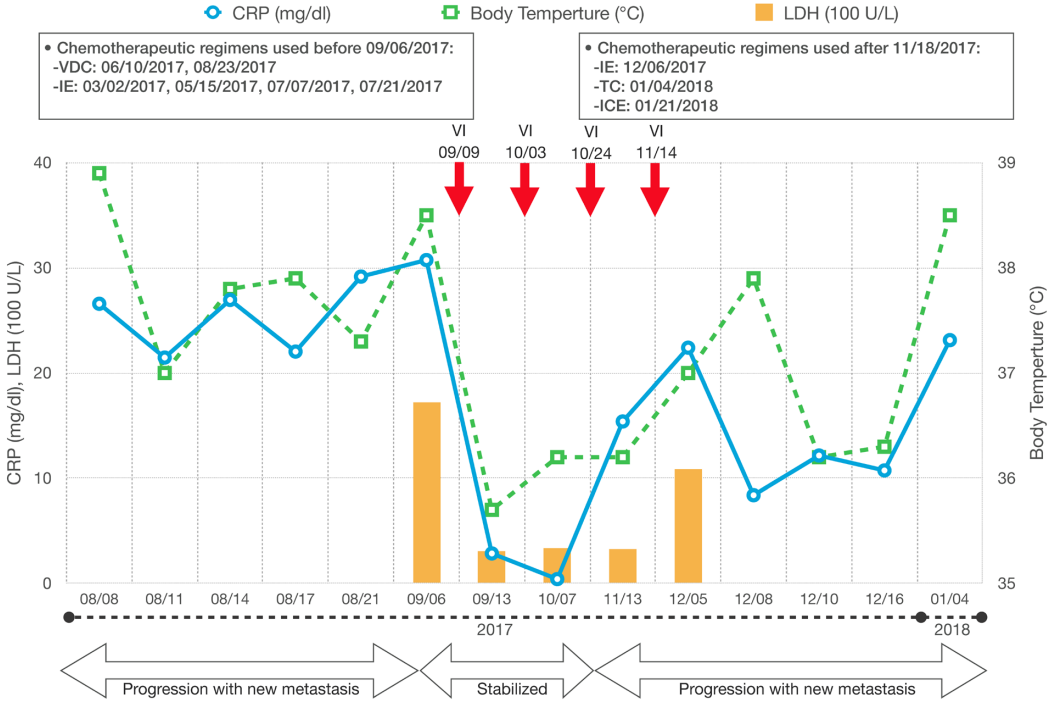

Fig. 1 Clinical and laboratory response to irinotecan plus vincristine (VI) in a patient with refractory Ewing sarcoma at the terminal stage, including a dramatic decline of fever and significant decreases in C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels. ICE, ifosfamide, carboplatin, and etoposide; IE, ifosfamide and etoposide; TC, topotecan and cyclophosphamide; VDC, vincristine, dactinomycin, and cyclophosphamide.

discharged to home on the fifth day of VI therapy.

After discharge, the patient was in stable condition and afebrile. Only tolerable pain at the rib metastasis over the left chest wall was noted, which could be relieved by a pain-relieving patch and an ice pack. The second course of VI was prescribed on October 3, 2017. The patient tolerated this course of therapy smoothly, and only mild anorexia and diarrhea were noted. After this course of VI, the patient's rib pain improved, his CRP levels declined to within the normal range (0.41 mg/dL), and his LDH levels remained within the normal range (334 U/L).

On October 24, 2017, the patient had a fever that peaked at 38.3°C without any signs of active infection. The clinical impression was tumor fever, and a third course of VI was prescribed the next day. The patient's fever subsided immediately, but his CRP levels increased to 15.4 mg/dL; his LDH remained within the normal range (329 U/L). Moreover, spinal magnetic resonance imaging revealed a new metastasis at the lumbar spine. A fourth course of VI was commenced on November 14, 2017, as scheduled, but subsequently, the patient's CRP and LDH increased even further (22.41 mg/dL and 1083 U/L, respectively). Additionally, a WBBS on November 20, 2017, identified a new metastasis at the right fourth rib. Because of the high cost of irinotecan and the disease progression, we suggested to the patient that VI treatment be stopped.

Thereafter, we prescribed an IE regimen on December 6, 2017; topotecan and cyclophosphamide on January 4, 2018; and ifosfamide, carboplatin, and etoposide on January 21, 2018. However, the patient's disease progressed with evidence of tumor fever becoming increasingly difficult to control together with increasing CRP and LDH levels. On February 21, 2018, the patient was admitted to our hospital with progressive dyspnea. A chest X-ray revealed massive pleural effusion over the right lung. The patient underwent thoracocentesis and insertion of a pigtail catheter, but his symptoms were relieved for only a few days. His condition deteriorated gradually, and he died on March 2, 2018.

Discussion

Vincristine has been included as part of the standard-of-care regimens (e.g., VAC/IE regimen) in the first-line systemic therapy for Ewing sarcoma. The efficacy of irinotecan and temozolomide has previously been reported for treating relapsed or progressive Ewing sarcoma[5,6]. The VI regimen, which has mostly demonstrated its efficacy in recurrent rhabdomyosarcoma[7,8], was adopted to treat our patient because it is less expensive than irinotecan plus temozolomide. Because vincristine and irinotecan have both been shown to be effective against Ewing sarcoma, either as first-line or second-line therapy, it was reasonable to combine the use of these two drugs, particularly on a palliative basis, for this patient. In fact, the clinical and laboratory responses of this patient, including the dramatic decline of fever and CRP and LDH levels, were encouraging, particularly after the first course of VI. Although the efficacy of VI in relapsed Ewing sarcoma has not been widely reported in the literature, this regimen has been added to the Bone Cancer section in the National Comprehensive Cancer Network® guidelines (version 2.2018)[9] for treating relapsed/refractory or metastatic Ewing sarcoma, based on lower-level evidence. This case report can serve as evidence supporting VI intervention in cases of high-risk Ewing sarcoma.

Evidence from previously published reports has shown that Ewing sarcoma can induce systemic inflammatory responses and that the clinical symptoms/signs and laboratory data can mimic those of bacterial infections, which often leads to misdiagnosis, such as osteomyelitis[10]. In our patient with progressive Ewing sarcoma, CRP was considered a laboratory indicator demonstrating tumor activity, in addition to LDH[11]; the elevation of these levels in conjunction with the cancer pain/tumor fever before the first course of VI and their dramatic decline thereafter support their role as indicators. Because there is no specific diagnostic test for tumor fever, physicians usually make an effort to exclude the possibility of infection first in patients with tumor fever and underlying cancer progression, or they "treat" for a possible infection even if there is no evidence of infection before prescribing tumor-specific chemotherapy. In our patient's case, spiking high fever and elevated CRP levels were found before the first VI infusion, and the possibility of occult bacteremia could not be excluded at that time. Therefore, a sepsis workup was performed, and intravenous antibiotics were prescribed. However, this diagnostic process can potentially lead to the delayed treatment of progressive cancer. In brief, physicians should be

aware of the possibility of tumor fever with undiagnosed malignancies (e.g., Ewing sarcoma) in children and young adults who have fever combined with bony lesions or extraskeletal masses. Chemotherapy should be commenced as soon as possible once no evidence of infection is found in patients with known underlying progressive cancer.

In conclusion, our patient with terminal stage Ewing sarcoma lived for five months longer than expected with the use of the VI regimen. This regimen had shown its efficacy in Ewing sarcoma by controlling cancer pain, tumor fever, and reducing CRP/LDH levels. Further clinical trials are desirable to compare the efficacy of VI with that of irinotecan plus temozolomide in relapsed/progressive Ewing sarcoma or to compare the efficacy of this regimen with that of other standard-of-care regimens in first-line therapy for patients with newly diagnosed high-risk Ewing sarcoma.

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Vincristine 加上 Irinotecan 能延長頑固依汶氏肉瘤年輕成人之末期生命

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摘要

在兼顧治療效益與經濟成本的考量之下，我們選擇 vincristine 加上 irinotecan 的組合方案（VI 組合）治療一位依汶氏肉瘤的末期病人。一名 21 歲男性罹患右薦椎的頑固型依汶氏肉瘤，合併多重轉移，我們處方了四次 VI 組合的療程，除了戲劇化的成功緩解腫瘤熱和系統性發炎外，他的壽命更比預期延長了五個月。基於在這個案例的發現，我們認為在新診斷的高風險依汶氏肉瘤病人身上，VI 組合可以被考慮使用於一線治療，而非只是擔任延長生命的角色。

關鍵詞：化學治療、依汶氏肉瘤、irinotecan 、復發、vincristine

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Case Report

Brown-Sequard Syndrome after Airbag Explosion – Case Report

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Abstract

In the event of a car crash, airbags can be a lifesaver. However, airbags can sometimes explode when deployed and send shrapnel into the drivers and passengers, causing injury or death. Here we report a patient struck by shrapnel from an exploding airbag. The penetrating fragment damaged the T1 paravertebral area, leading to the Brown-Sequard syndrome and left subclavian artery disruption. After emergent operation for foreign-body removal and aggressive rehabilitation for 6 months, the patient recovered from motor and sensory loss almost completely.

Key words: airbag explosion, spinal cord injury, Brown-Sequard Syndrome, subclavian artery disruption

Introduction

Brown-Sequard syndrome (BSS), a rare neurological condition, is caused by damage to one half of the spinal cord. The clinical features of BSS include weakness or paralysis ipsilaterally and loss of pain sensation contralaterally[1]. BSS may be caused by neoplasms, disk herniation, demyelination, infective or inflammatory lesions, and epidural hematomas with penetrating trauma[2]. BSS is an incomplete spinal cord injury with a potential for significant recovery[3].

Here, we report a case of BSS caused by a traffic accident. The release of shrapnel during airbag explosion damaged the thoracic spinal cord of the patient, leading to BSS, which was not initially detected. The patient almost completely recovered from motor and sensory deficits after 6 months of rehabilitation.

Case report

A 30-year-old man without comorbidity was trapped in a car crash. While driving his 2008 Honda Civic, he crashed into the sidewalk, resulting in the deployment of the bilateral front airbag. At the accident scene, the emergency medical technician found him unconscious with an open wound on the left upper chest wall (Fig. 1A). He was sent to the hospital immediately where he was intubated with ventilator support. A chest X-ray revealed a fracture to the left clavicle head and a circular foreign body, 2.6 cm in diameter, located at the left sternoclavicular joint (Fig. 1B). He was transferred to our emergency room after being adequately resuscitated.

Upon arrival, his consciousness levels were E2VeM5. An ill-marginated circular penetrating wound was present over the left upper chest wall without active bleeding. The left radial pulse was weak and the extremity was warm. Chest computed tomography (CT) revealed the presence of a metallic-foreign body penetrating from the left anterior apical thorax to the left T1 paravertebral area, resulting in a comminuted fracture of the left proximal clavicle and fractures of the left anterior first rib and left T1 pedicle (Fig. 2A). Additionally, the CT scan revealed left superior hemomediastinum, left upper lobe pulmonary hemorrhage, and mild hemothorax on the left. The left proximal jugular vein and left subclavian

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artery showed no contrast opacification (Fig. 2B), suggesting vessel dissection. An emergent operation was needed.

During wound exploration, we discovered a fragmentary airbag shrapnel, which was flat and firm, with a sharp and irregular margin (Fig. 1C and 1D), lodged into the left aspect of the T1 vertebral body, and retrieved it from his chest cavity. However, we could not ascertain whether his left proximal jugular vein and left subclavian artery were damaged because numerous bone fragments distorted the normal structure of the muscles, bones, and vessels. No further surgical intervention was needed due to no active bleeding and warm left upper limb. The wound was irrigated and approximated with a wet dressing.

The next day, his left lower limb showed complete paralysis with preserved pain and touch sensation after endotracheal tube extubation. An experienced neurologist was requested for the patient. He

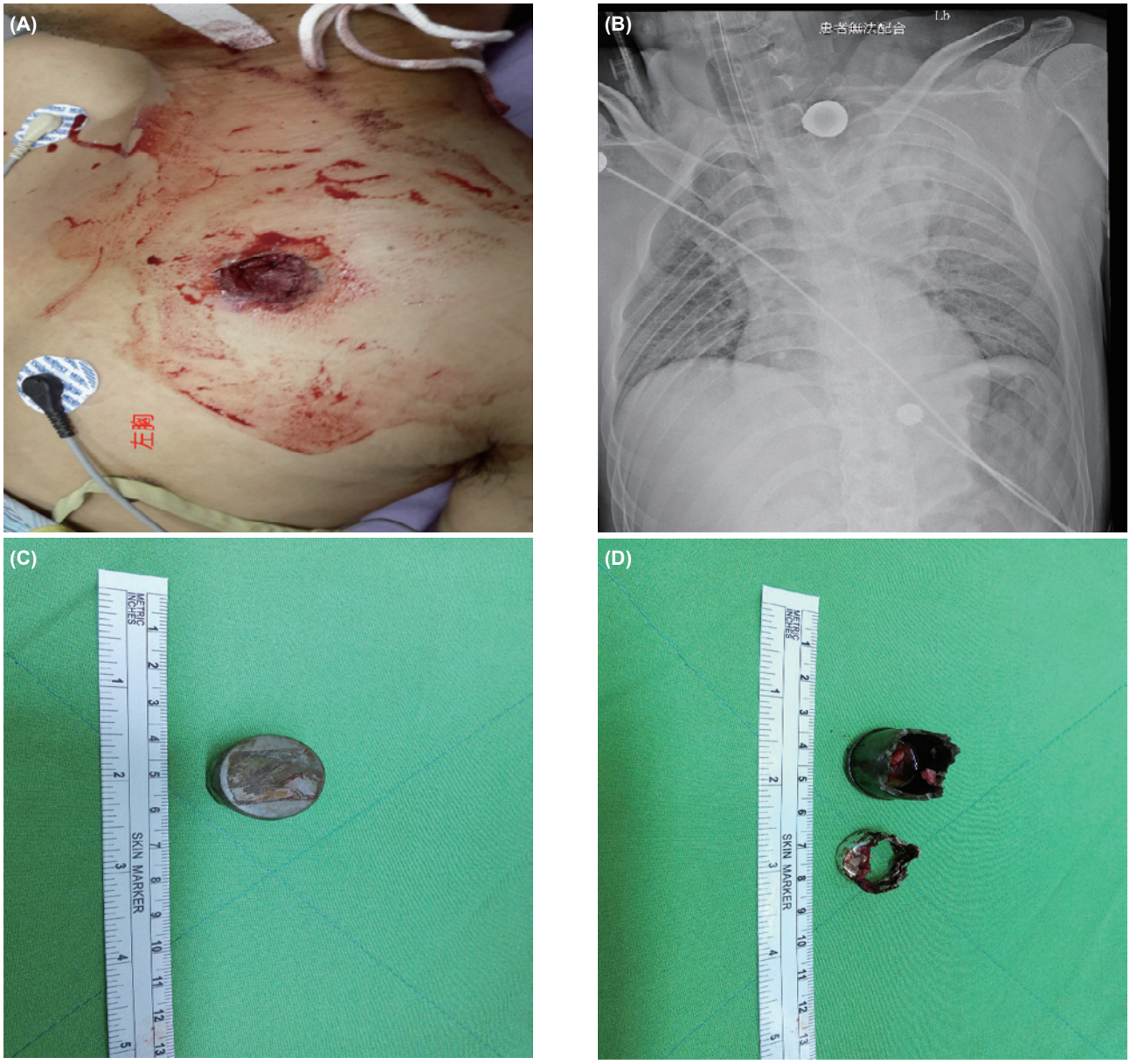

Fig. 1 (A) One ill-marginated circular penetrating wound over the left upper chest wall without active bleeding. (B) One circular foreign body, 2.6 cm in diameter, over the left sternoclavicular joint. (C) The airbag shrapnel was a metallic fragment with a flat and blunt-headed end. (D) The rear side of the shrapnel was sharp with irregular margins and contained a smaller fragment.

had diminished deep tendon reflex over the left lower limb. His pinprick and crude touch sensation over the right trunk and right lower limb were impaired with poorly defined levels of sensory loss. Spinal magnetic resonance imaging (MRI) revealed effaced normal fat marrow signal in the left half of the T1 vertebral body and adjacent left posterior elements and spinal cord edema with ill-defined margins at C7–T2 level (Fig. 3A and 3B). His clinical presentations and imaging findings suggested BSS of the upper thoracic-spine.

For incomplete spinal cord injury, rehabilitation counseling was provided as soon as the general

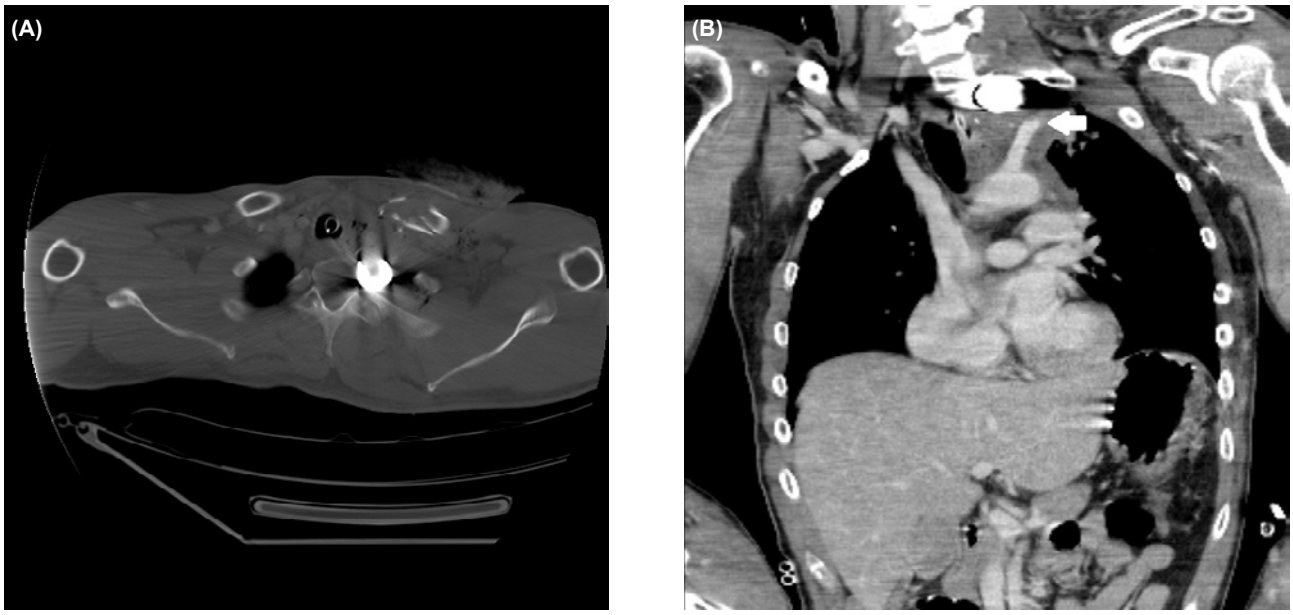

Fig. 2 (A) Chest computed tomography showing a metallic foreign-body penetrating from the left anterior apical thorax to left T1 paravertebral area, causing a comminuted fracture of the left proximal clavicle and fractures of the left anterior first rib and T1 vertebra pedicle. (B) Interruption of contrast over the left subclavian artery (arrow) with upper mediastinal hematoma suggesting subclavian artery injury.

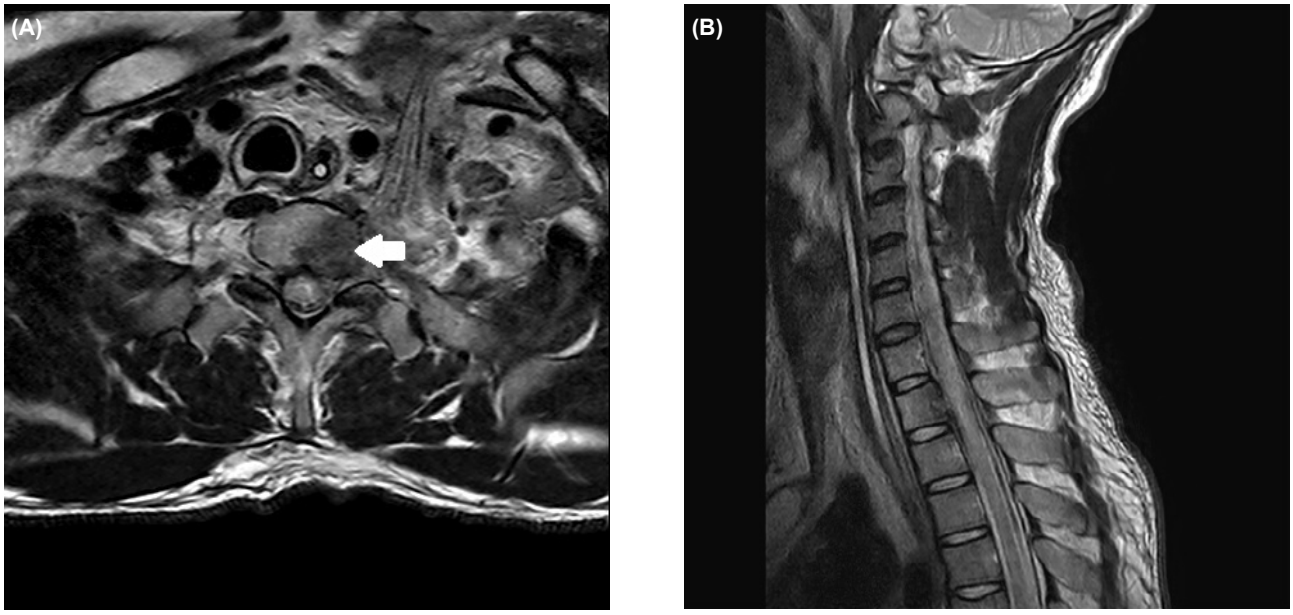

Fig. 3 (A) Spine magnetic resonance imaging revealed effaced normal fat marrow signal in the left half of the T1 vertebral body (arrow) and adjacent left posterior elements. (B) Spinal cord edema with ill-defined margin at the level of C7–T2.

condition stabilized. Physical therapy rehabilitation included left lower limb passive range of motion and electrical stimulation. Bed mobility and transfers were also useful for this patient. In addition, a tilt table was introduced for upright position tolerance and orthostatic hypotension. With the aid of rehabilitation five days a week, the muscle power of the left lower limb recovered to grade 3 (movement against gravity but not resistance) approximately 2 months after trauma at discharge. Six months after the spinal cord injury, he walked to our outpatient department instead of being in the wheelchair. Moreover, he recovered sensation completely.

Discussion

The airbag is an important safety equipment when driving a car. Ideally, a carefully controlled explosion will fire an airbag out from the dashboard, quickly and powerfully, cushioning the impact and reducing the damage to the head and other parts of the body. Unfortunately, airbag explosion can sometimes hurt drivers and passengers. At least 24 people were killed due to faulty Takata airbags, leading to the largest recall in history that has affected nearly every automaker[4].

In 1849, Charles-Édouard Brown-Sequard described a rare spinal cord injury, which came to be known as Brown-Sequard syndrome (BSS)[5]. BSS is a rare disorder that affects men and women equally, with an incident rate of 4% of traumatic spinal cord injuries[6]. BSS caused by penetrating insults, resulting in the physiological hemisection of the spinal cord, are much more common than blunt trauma or other spinal diseases, including hematoma, neoplasms, myelitis, demyelinating disease, and disk herniation[7]. In our case, the shrapnel released from the airbag penetrated the left upper chest wall with force, leading to fracture of the left clavicle head and left T1 pedicle. The contusion impact to left T1 vertebral body also caused hemisection of the upper thoracic spinal cord.

The distinct neurologic findings in BSS are due to disruption of three separate neural pathways[8]. Damage to fibers in the descending lateral corticospinal tract and the ascending dorsal column-medial lemniscal pathway, both decussate in the medulla, results in ipsilateral hemiplegia and ipsilateral loss of proprioception, respectively. Disruption of fibers running in the ascending lateral spinothalamic tract, which decussate within three levels of the dorsal root entrance, results in the contralateral loss of pain and temperature sensation.

The diagnosis of BSS is established based on findings of neurological examination and MRI. No specific treatment for patients with BSS exists; instead, treatment focuses on the cause of the disorder. Operations are reserved for patients with spinal instability, spinal cord compression, or progressive deterioration[9]. Management is conservative with aggressive early rehabilitation[10]. The physical therapy protocol for the paralytic limb includes passive range of motion to prevent contracture and electrical stimulation to avoid rapid muscle wasting. A tilt table is introduced for upright position tolerance, early weight-bearing, and orthostatic hypotension. Moreover, bed mobility and transfers are central components of early spinal cord injury rehabilitation[11]. For patients in a comprehensive rehabilitation program, BSS has a relatively good prognosis. Most patients regain functional walking ability within 6 months of the injury.

Conclusion

Because the patient was injured by a high-velocity shrapnel from airbag explosion, spinal cord injury should be considered if the penetrated item contacted the vertebra. A detailed neurological examination to identify if spinal cord injury is needed as soon as the patient responds to instructions. First-line clinicians should manage patients with BSS according to the causative pathology. The patient's neurological status and clinicoradiological findings are crucial factors for operation. Surgical intervention is strongly recommended in post-traumatic BSS if the presence of foreign objects, cerebrospinal fluid leakage, infection, or signs of extrinsic spinal cord compression is detected.

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安全氣囊爆炸導致布朗斯夸症候群：病例報告

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摘要

當我們發生汽車車禍時，安全氣囊可以保護我們。但是，安全氣囊的引爆有時反而會傷害司機和乘客。在這篇病例報告當中，我們提出了一名被安全氣囊爆炸後彈出碎片傷害的病人。穿透性的碎片擊中第一節胸椎旁的區域並導致布朗斯夸症候群及左鎖骨下動脈破裂。經緊急異物取出手術及六個月的積極復健後，病人的運動和感覺喪失幾乎完全恢復。

關鍵詞：安全氣囊爆炸、脊髓損傷、布朗斯夸症候群、鎖骨下動脈破裂

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Image

Tc-99m ECD Brain Perfusion SPECT in the Logopenic Variant of Primary Progressive Aphasia

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Abstract

We report the case of a 75-year-old woman who presented with gradually progressive speech disorders and memory impairment. Brain magnetic resonance imaging revealed no significant finding. Technetium-99m ethyl cysteinate dimer brain perfusion single photon emission computed tomography (SPECT) with semiquantitative analysis revealed hypoperfusion in the left hemisphere, predominant on the posterior temporal lobe extending to the posterior parietal lobe. After considering the clinical presentation and SPECT findings, we established a diagnosis of logopenic variant of primary progressive aphasia.

Key words: logopenic variant, primary progressive aphasia, SPECT

Primary progressive aphasia (PPA) is a slowly progressing language disorder resulting from neurodegenerative diseases. Based on the criteria published in 2011[1], PPA is divided into the following three categories: non-fluent variant (nfvPPA) with agrammatism or apraxia of speech, semantic variant (svPPA) with anomia and single-word comprehension deficits, and logopenic variant (lvPPA) with frequent word-finding pauses and word retrieval and sentence repetition deficits. Clinical findings of specific variants are associated with relatively distinct neuroimaging patterns of either atrophy on magnetic resonance imaging (MRI) or hypoperfusion/hypometabolism on single photon emission computed tomography (SPECT) or positron emission tomography. Majority of the nfvPPA cases present with left posterior frontoinsular atrophy or hypoperfusion/hypometabolism, while svPPA cases present with bilateral anterior temporal lobe atrophy or hypoperfusion/hypometabolism. In contrast, majority of the lvPPA cases present with left posterior perisylvian or parietal atrophy or hypoperfusion/hypometabolism beyond the frontotemporal region. Notably, nfvPPA and svPPA are associated with frontotemporal lobar degeneration, whereas lvPPA is primarily associated with Alzheimer's disease (AD). Interestingly, majority of the reported lvPPA cases presented with AD pathology at autopsy or received amyloid-binding ligands such as Pittsburgh compound B[2-4]. Therefore, lvPPA is considered an atypical presentation of AD. Here, we report a case of lvPPA wherein the diagnosis was supported by the findings of brain perfusion SPECT.

A 75-year-old uneducated homemaker complained of progressive aphasia and memory impairment since 3 years. She presented prominent progression of word-finding difficulties during the past 2 years. Neurological examination revealed mild disorientation in time and space and difficulty in single-word retrieval during spontaneous speech and when naming objects. Word comprehension and object knowledge were better preserved. The motor aspects of speech and grammar were unaffected. Serial Mini-Mental State Examinations showed progressive impairment of naming objects and persistent impairment of short-term memory. Serum vitamin B12, rapid plasma reagin, thyroid stimulating

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hormone, free thyroxine, and cortisol levels were within normal limits. Based on the aphasia profile and short-term memory impairment, her clinical findings were suggestive of lvPPA. Brain MRI performed at 74 years of age revealed a senile change of the brain without asymmetrical atrophy (Fig. 1). Technetium-99m ethyl cysteinate dimer (Tc-99m ECD) brain perfusion SPECT performed at 75 years of age revealed cortical hypoperfusion on the left temporal, frontal, and parietal lobes (Fig. 2). Semiquantitative analysis of SPECT images with dedicated statistical parametric mapping software (eZIS) was performed. The eZIS software involves spatial normalization of the images to a standardized stereotactic (Talairach and Tournoux) 3-dimensional space, followed by isotropic 12-mm smoothing and comparison against a sex- and age-matched group of control subjects, thus allowing the objective demonstration of the extent and magnitude of regional cerebral blood flow changes[5]. The results confirmed unilateral cortical hypoperfusion of the left hemisphere that was predominant on the posterior temporal lobe and extended to the posterior parietal lobe (Fig. 3). After considering the clinical presentation and SPECT findings, lvPPA was diagnosed. Five months following the lvPPA diagnosis, the patient developed complete impairment of naming objects.

According to the diagnostic criteria for lvPPA[1], word retrieval and sentence repetition deficits are the core features—both essential for diagnosis. Other diagnostic features include phonologic paraphasias, relative sparing of single-word comprehension, object knowledge and motor speech, and nonfrank agrammatism. In our case, the language-related symptoms satisfied the lvPPA criteria except the sentence repetition deficit. That might be explained by a relatively early stage of the disease. Meanwhile, the patient presented a typical clinical feature of AD, including the persistent impairment of short-term memory and age. Hence, differentiating lvPPA and typical AD based on the initial clinical presentation was difficult in this patient. However, based on the serial neurological examinations, a predominantly language-related symptom of word-finding difficulty was suggestive of lvPPA.

In lvPPA, the clinical finding suggests impairment in the phonological loop functions, portrayed as atrophy or decreased blood flow on the left posterior perisylvian and the parietal cortex on neuroimaging. Although the pattern of temporoparietal involvement

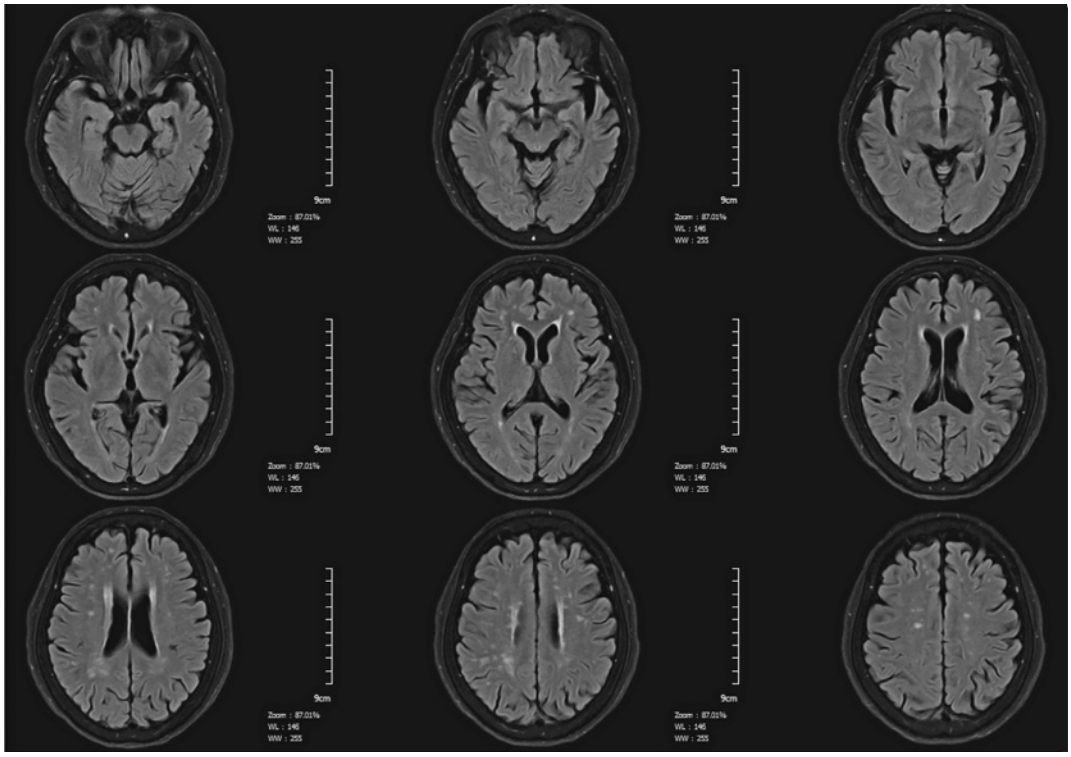

Fig. 1 Fluid attenuation inversion recovery (FLAIR) MRI shows senile change of the brain with symmetrical widening sulci and fissures and punctate leukoaraiosis in periventricular and subcortical white matter.

in lvPPA is similar to that in typical AD, there is a preferably asymmetrical pattern showing greater involvement of the left temporal cortex in lvPPA[4]. In our case, SPECT findings of unilateral cortical hypoperfusion of the left posterior temporal lobe extending to the left parietal lobe supported lvPPA diagnosis.

Although MRI provides accurate localization, earlier perfusion abnormalities may precede the atrophy and allow SPECT for early PPA variant classification. Previous studies have shown that the quantitative analysis of hypoperfusion abnormalities revealed by SPECT appears to be advantageous over

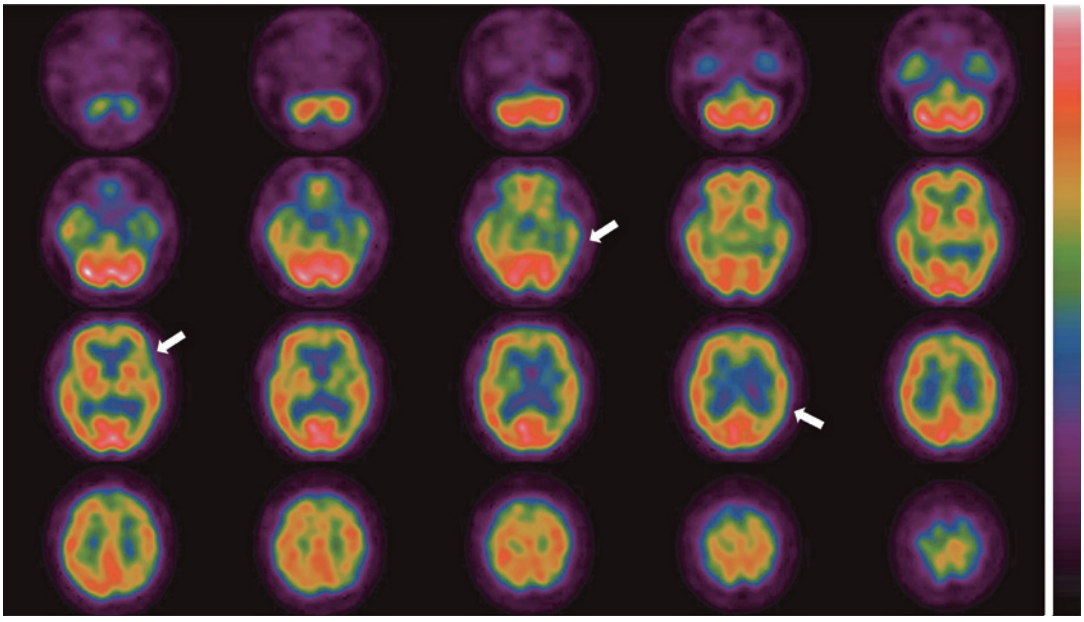

Fig. 2 The technetium-99m ethyl cysteinate dimer (Tc-99m ECD) brain perfusion SPECT reveals cortical hypoperfusion of the left temporal, frontal and parietal lobes (arrows).

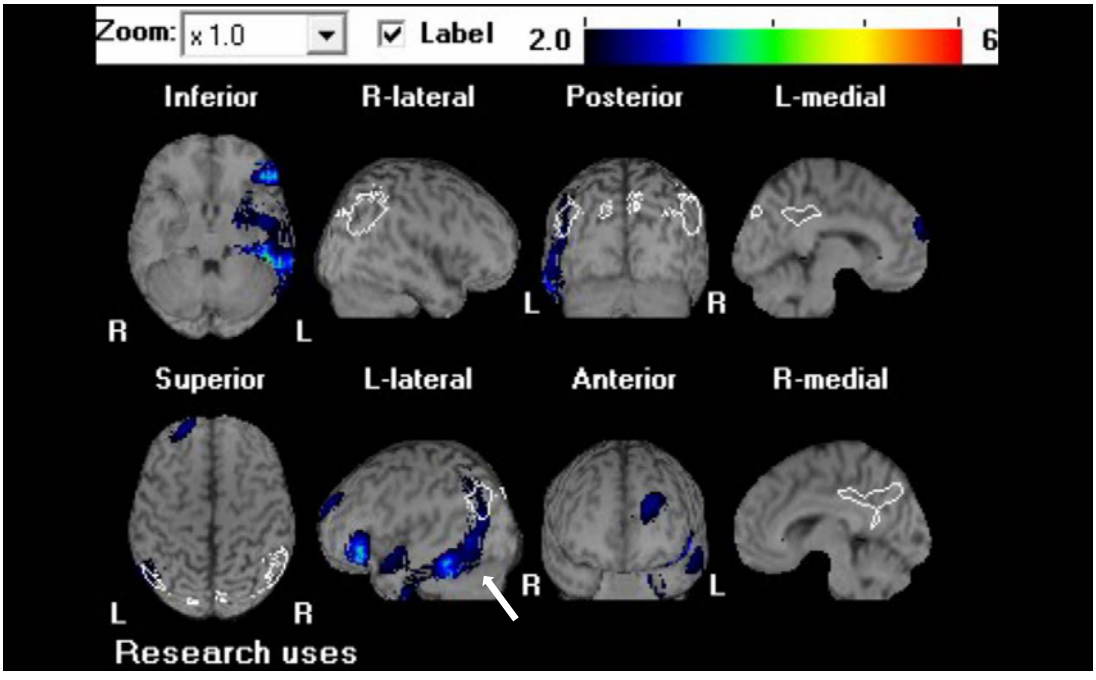

Fig. 3 Semiquantitative analysis of brain perfusion SPECT with dedicated statistical parametric mapping software (eZIS) reveals unilateral cortical hypoperfusion of the left hemisphere that is predominant on the posterior temporal lobe and extends to the posterior parietal lobe (arrow).

purely qualitative visual MRI in the differential diagnosis of PPA variants[6]. This case highlights the significance of brain perfusion SPECT with quantitative analysis for imaging-supported PPA variant diagnosis.

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鍀 -99m 雙半胱乙酯腦血流灌注單光子射出電腦斷層掃描於缺詞型原發漸進性失語症

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摘要

我們報告一位 75 歲女性案例，其表現為緩慢進行之言語與記憶障礙。腦部磁振造影並無顯著發現。鍀 -99m 雙半胱乙酯腦血流灌注單光子射出電腦斷層掃描（Tc-99m ECD brain perfusion SPECT）搭配半定量分析顯示左側大腦半球血流灌注下降，主要是在顳葉後部並延伸至頂葉後部。考慮病人的臨床表現以及 SPECT 發現後，我們建立了缺詞型原發漸進性失語症的診斷。

關鍵詞：缺詞型、原發漸進性失語症、單光子射出電腦斷層掃描

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Review Articles	≦300	≦3500	≦60	≦6
Brief Communications	≦150	≦750	≦7	≦1
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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。

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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）

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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.

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影像判讀

104　　鍀-99m 雙半胱乙酯腦血流灌注單光子射出電腦斷層掃描於缺詞型原發漸進性失語症

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