Initial Misdiagnosis and Subsequent Disastrous Events in an Adult with Neurofibromatosis Type I Complicated by Vascular Involvement

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Case Report

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Abstract

Background: Neurofibromatosis type 1(NF1) is a hereditary neurocutaneous syndrome caused by the mutation in NF1 gene with a very low incidence. Neurofibroma, Café-au-lait spot and osseous deformity are the most common clinical findings, however, uncommon vascular involvement in NF1 is the second most common cause of mortality following after malignancy.

Case presentation: We report a patient with NF1 who suffered a rupture of his internal thoracic artery aneurysm and subclavian artery branch aneurysm in the setting of an intact extracranial vertebral artery aneurysm, which was ever mistaken for neurofibroma and subsequently underwent right brachial plexus nerve bundle separation due to conspicuous pain of his right upper arm and hand.

Conclusions: This case highlights synchronous multiple aneurysms of NF1 presenting with life-threatening aneurysm rupture after surgery. Contrast-enhanced CT precisely defines its location and anatomic relationship with adjacent organs. Additionally, endovascular treatment has become the mainstay for vascular lesions or aneurysm rupture in those patients with NF1.

Introduction

Also known as Von Recklinghausen's disease, neurofibromatosis type 1 (NF1) is a hereditary neurocutaneous syndrome caused by the mutation in NF1 gene with a very low incidence rate of approximately 1 in 2500 to 1 in 3000[1]. It is characterized by neuroectodermal or mesodermal tumor growths like neurofibromas, optic gliomas, hamartomas and their associated complications. Cardiovascular involvements are frequently underestimated because a diagnosis could be made only in patients with specific clinical symptoms. Vascular anomalies described within the framework of NF1 include stenoses, aneurysms, and arteriovenous malformations. Arterial system shows a strong predilection than venous system in NF1[2]. Those vessels such as the aorta, and intercostal, subclavian, brachial, radial, and vertebral arteries can be involved by aneurysmal dilatations. Patients with NF1 can have aneurysm, but the synchronous involvement of two different circulatory regions is rarely documented[3]. Clinicians must be aware of its diverse clinical features, particularly with vascular complications. The propensity for malignant transformation in any organ also leads to increased morbidity and mortality in sufferers of this disease[4, 5]. Here, we report such a patient with NF1 who suffered multiple aneurysms rupture and an intact extracranial vertebral aneurysm synchronously.

Case Report

A 43-year-old male with a one-month history of right upper arm and hand pain was admitted to our hospital on August 22, 2018. Neurofibromatosis type 1(NF1) associated with the right brachial plexus injury was diagnosed in March 2015 in our hospital. There was no obvious abnormality reported on cervical magnetic resonance imaging (MRI) (Fig. 1A) at that time. The patient denied a family history of neurofibromatosis. Physical examination on this admission indicated that pigmented, flat, well-

demarcated lesions of the skin in many sites of the body, which primarily distributed in the trunk but scarcely in the extremities(Fig.1B). Picking sensation was decreased in the right outer upper arm, the right outer forearm, the right radial palm, the thumb, the forefinger, and the middle finger. Extension strength in right shoulder was weak. There was no mass or vascular bruit on the whole body. Although genetic testing was strongly suggested, the patient refused to perform. Blood routine test indicated a normal red blood cell count 3.75×10^{12}/L(4.3-5.8$\times10^{12}$/L) and a slightly elevated platelet count of 472×10^{12}/L(125-350$\times10^{12}$/L). Coagulation screening, hepatic and renal functions were within the normal limit. The value of routine tumor-related marker was not elevated. MRI scan of brachial plexus showed an abnormal oval signal intensity at the right level of cervical 6-7 vertebra (Fig. 1C), measuring 1.8cm×2.8cm in size and closely abutting the right brachial plexus on August 21, 2018. Based on his medical history and MRI data above, neurofibroma was firstly suspected. On August 24, 2018, the patient underwent right brachial plexus nerve bundle exploration and separation under general anesthesia. The C6 nerve trunk and epineurium were found thickening, and each nerve bunch was evenly thick and tough. Nerve decompression was performed separately, and no tumor tissue was seen (Fig. 1D). Pain in the right upper arm was significantly improved after surgery. The lesion shown by preoperative MRI was not associated with neurofibroma based on intraoperative findings, and this gradual enlarged lesion was finally confirmed to be veteral arterial aneurysm followed by later angiography. The patient experienced the sudden onset of precordial pain on the right side of his chest in the early morning of August 26, 2018, followed by two episodes of intermittent attack. Echocardiography showed reduced left ventricular diastolic function, but electrocardiogram lacked the evidence of myocardial ischemia and serum troponin was not elevated. Emergent non-enhanced lung CT suggested mediastinal hematoma, right massive hemothorax and passive partial atelectasis of the right lung (Fig. 2A). Urgent thoracoscopic exploration and thoracic drainage were performed, only visualizing the hematoma with an approximate size of 10.0cm×10.0cm×5.0cm in the right upper mediastinum. No obvious source of active hemorrhage was identified. However, the value of hemoglobin still continued to drop. Further contrast-enhanced CT scan revealed an aneurysm in the proximal portion of right internal thoracic artery close to the hematoma(Fig. 2B). There was no any pathologic sign of the thoracic aorta. Unfortunately contrast-enhanced CT of thorax was not performed to assess the status of thoracic great vessels, including the right internal artery aneurysm prior to the surgery. Meanwhile, two units of packed red blood cells and fresh frozen plasma were transfused. Digital subtraction angiography (DSA) was promptly initiated to control active bleeding via the puncture of the right femoral artery. Cystic aneurysm in the proximal internal mammary artery was identified, and the proximal right vertebral artery was irregularly dilated. Up to now, previous cervical MRI findings was identical to be the aneurysm of the right vertebral artery. This lesion failed to diagnose in 2015 owing to small size and was misdiagnosed as neurofibroma on this admission. Total embolization of the internal thoracic artery was performed using multiple coils from the distal to proximal portion of the aneurysm (Fig. 2C-D). The patient's blood pressure and hemodynamics stabilized immediately after the procedure. Then, the patient was transferred to the intensive care unit to monitor hemodynamics, and he kept a relatively stable condition only lasting for two days. On August 29, 2018, massive oozing of blood abruptly occurred in the incision site of his right shoulder and bloody fluid also went into drainage bottle through the inserted tube of the right neck. The rupture of the vertebral artery aneurysm was highly

suspected to be culprit for recurrent catastrophic event. The angiography of the right subclavian artery was conducted, which showed intact saccular aneurysm of the right vertebral artery, and thyrocervical aneurysm rupture with contrast extravasation(Fig.3A-B). Covered stent implantation at the origin of the vertebral and thyrocervical artery resulted in a complete exclusion for two vascular pathologies above, which was verified by subsequent DSA(Fig.3C). An angiogram of left vertebral artery demonstrated adequate perfusion of the basilar artery and its branches(Fig. 3D). No change in the patient's neurologic status was observed after the procedure. After a comprehensive medical care including blood transfusion, fluid infusion, intravenous feeding, prevention of infection, et al. His vital signs were persistently stable and then discharged from our hospital without any complication on September 18, 2018. On the postoperative follow-up of three-month interval, thoracic contrast-enhanced CT scan indicated that mediastinal hematoma and right pleural effusion were almost resolved, only leaving a minimal amount of encapsulated effusion in the right thorax. The right subclavian artery stent was well positioned and patent(Fig. 4A). The left vertebral artery was normally filled, while no contrast agent was present in the right vertebral artery(Fig. 4B). Meanwhile, the patient also led a normal life.

Discussion

Neurofibromatosis type1(NF1) can involve any organ, but connective and nerve tissues are predominantly affected[6]. Neurofibroma, Café-au-lait spot and osseous deformity are most common clinical findings. The real incidence of these abnormalities is indeed unknown because many lesions are undetected[2]. Vasculopathy in NF1 mainly includes stenosis, occlusion, aneurysm, and arteriovenous malformation. Incidental findings or complications secondary to rupture or bleeding are the most reported modality in most literatures. Arterial lesions may be located in the aorta or in renal, mesenteric, carotid-vertebral or intracranial arteries, et al[7–9]. The causes described in these cases are variable and generally can be divided into two categories: bleeding by vascularized tumors of mesenchymal origin, such as ganglioneuromas or neurofibromas, and bleeding caused by rupture of weak medium to large-caliber arteries[10–12]. Vascular complications are the second most common cause of mortality in NF1 following after malignancy[13]. The first report of vascular complications linked to neurofibromatosis was in 1945 when Reubi described changes in the renal artery of a patient with this disease. Right vertebral aneurysm in our case evolved with an extremely indolent growth over past three years. When the patient was firstly diagnosed as NF1, aneurysm of the right vertebral artery was neglected by MRI because of its small size. Three years later, the right-side lesion at C6 level was found and mistaken for neurofibroma because of the pain in the right upper limb. Intra-operative exploration demonstrated brachial plexus thickening, adhesion, interfascicular neurolysis, and no any evidence of neurofibroma. A series of radiculopathy in this patient, which possibly originated from the compression of the nerve bundle and aseptic inflammation by mass effect of vertebral aneurysm according to our speculation, was alleviated after the release of the nerve bundle. Therefore, establishing a diagnosis of neurofibroma must preclude the possibility of vascular lesion in those patients with NF1.

On the 3th day of post-surgery, the patient suffered rupture of the right internal thoracic artery aneurysm and subsequent mediastinal hematoma. This event was not related to recent surgery because aneurysm

was located within the thoracic cavity. The reason of spontaneous rupture may be related to the increased vascular fragility due to arterial mesoderm dysplasia and elevated blood pressure due to postoperative stress. Three days after embolization of the internal thoracic artery, recurrent bleeding happened at the incision site. Based on the results of the initial DSA angiography, the rupture of the vertebral aneurysm may contribute to this disastrous event. Contrary to our anticipation, the right vertebral aneurysm did not rupture on second angiography, while the small aneurysm of the branch of the subclavian artery ruptured. According to our re-consideration for operative field, surgical iatrogenic injury was responsible for its formation and subsequent rupture. Signs and symptoms of vascular involvement in those patients with NF1 manifest as a wide spectrum based on its nature, usually including ischemic symptoms or mass effects from the affected artery. Clinicians must learn about its diverse clinical features. Synchronous vascular involvement of two different circulatory regions was found, and rupture happened at the short interval in our patient.

Current management for vasculopathy in NF1 includes open surgery and endovascular treatment[3, 10]. Surgical repair is aggressive and complex, and vessel reconstruction is also limited due to the fragile nature of the vessel wall and surrounding tissue. Endovascular treatments, such as coil transarterial embolization or percutaneous stent graft placement, are often considered preferable when it is mandatory to maintain an efficient blood flow in the regions perfused by the targeted vessel, which are less invasive, low intra-operative and post-operative mortality[14]. In our patient, percutaneous arterial embolization was first utilized, then endovascular stent was implanted at the second time of bleeding from the incision site. Two procedures produced a satisfactory outcome. As literatures mentioned[3], endovascular treatment has currently become the preferred method and been shown to be an effective therapy in complicated circumstances. Surgical intervention should be reserved for use when minimal methods are not totally effective.

NF1-induced vasculopathy can occur anywhere in the human vascular system. Albeit with a low incidence, their possibility must be kept in mind when a patient with NF1 is examined even without obvious symptoms of vascular involvement. In the terms of diagnostic investigations, ultrasonography, CT angiography and MRI may help achieve early diagnosis of vascular involvement. Especially, vascular trees imaging monitored by one-stop CT angiography is easily available update[15]. A routine vessel evaluation is strongly recommended for those patients with NF1[3]. Combined with our experiences and lessons, it is vitally important to assess systemically great vessels in patients with NF1.

In conclusion, this case highlights synchronous multiple aneurysms of NF1 presenting with life-threatening aneurysm rupture after surgery. Contrast-enhanced CT precisely defines its location and anatomic relationship with adjacent organs. Additionally, endovascular treatment has become the mainstay for vascular lesions or aneurysm rupture in those patients with NF1.

Abbreviations

Neurofibromatosis type 1: NF1

magnetic resonance imaging: MRI

Digital subtraction angiography: DSA

Declarations

Ethics approval and consent to participate

All methods were performed in accordance with the Declaration of Helsinki. The study was approved by the Medical Ethics Committee of the First Hospital of Jilin University.

Consent for publication

The study was informed written consent was obtained from the patient for publication of this case report and accompanying images.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

RP was the major contributor in writing the manuscript, completing the collection and analysis of relevant literature and the writing of the first draft of the manuscript.

LD and XL participated in the analysis and collation of documents.

DC helped perform the analysis with constructive discussions.

All authors read and approved the final manuscript.

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Not applicable

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Figures

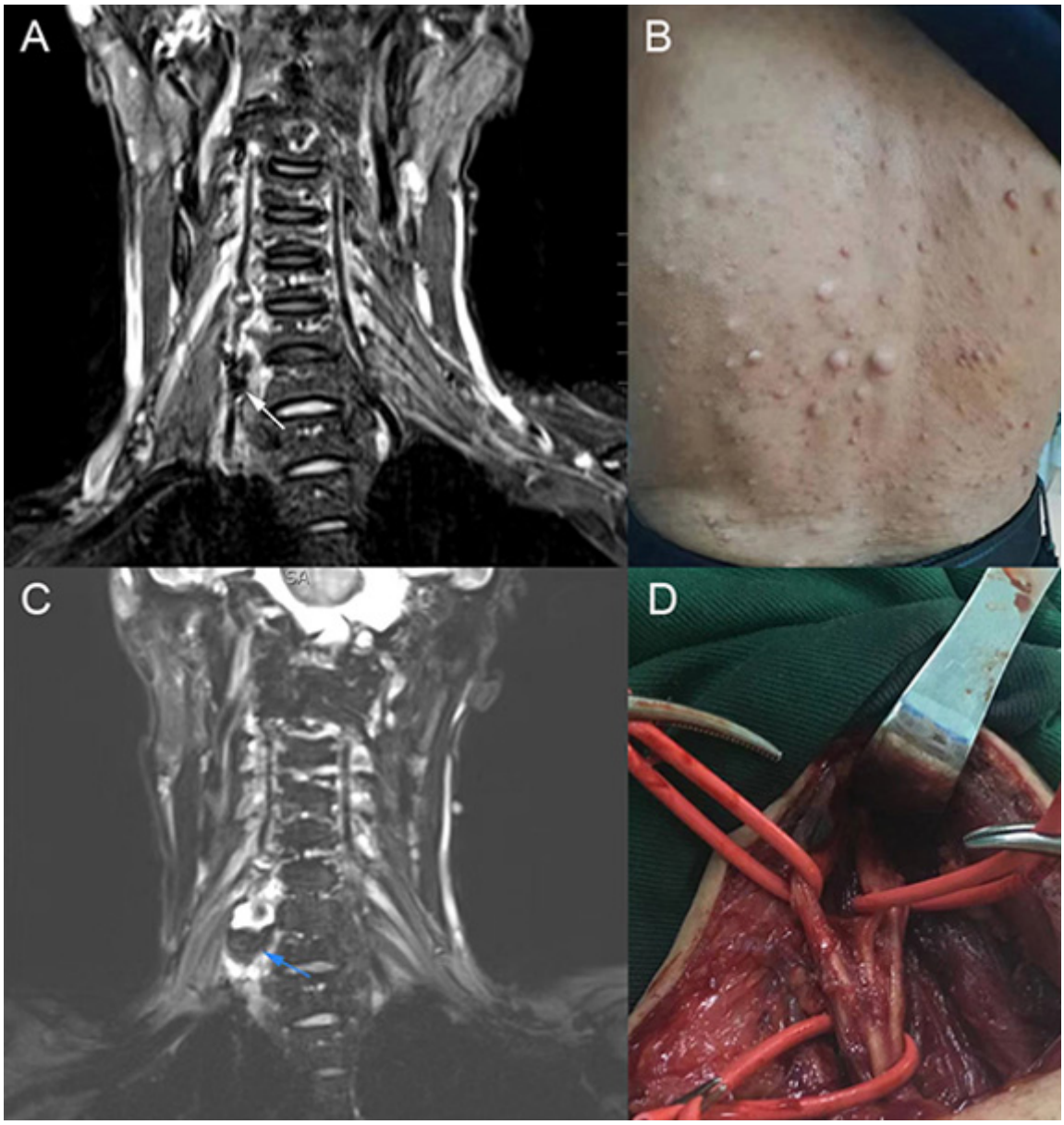

Figure 1

A: Coronary MRI in March 2015 showed the tortuous and slightly dilated course of proximal right vertebral artery with being neglected diagnosis.

B: Picture indicated that pigmented, flat, well-demarcated lesions of the skin distributed in the trunk.

C: Coronary MRI in August 2018 revealed an oval mass with flow void and high intensity at the right level of cervical 6-7 spine.

D Intraoperative picture showed the process of brachial plexus nerve bundle separation and no neurofibroma.

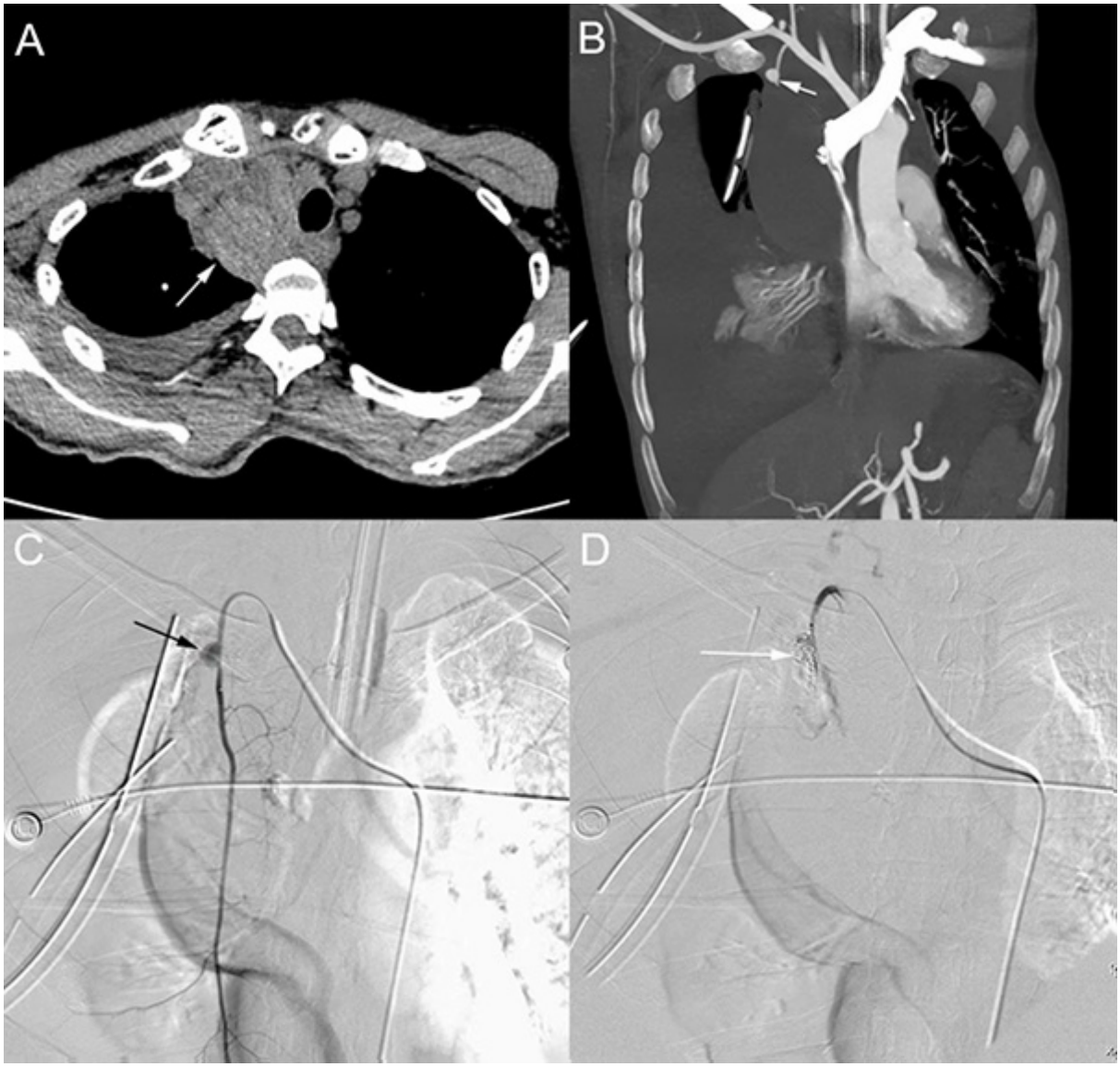

Figure 2

A: Axially unenhanced CT showed hematoma in the right upper mediastinum and pleural effusion in the right thoracic cavity.

B: Contrast-enhanced CT showed aneurysm of proximal right internal thoracic artery together with mediastinal hematoma and passive lung atelectasis secondary to massive pleural effusion.

C: Selective angiography indicated cystic aneurysm of proximal right internal thoracic artery.

D: Selective angiography showed the disappearance of cystic aneurysm after the deployment of multiple coils.

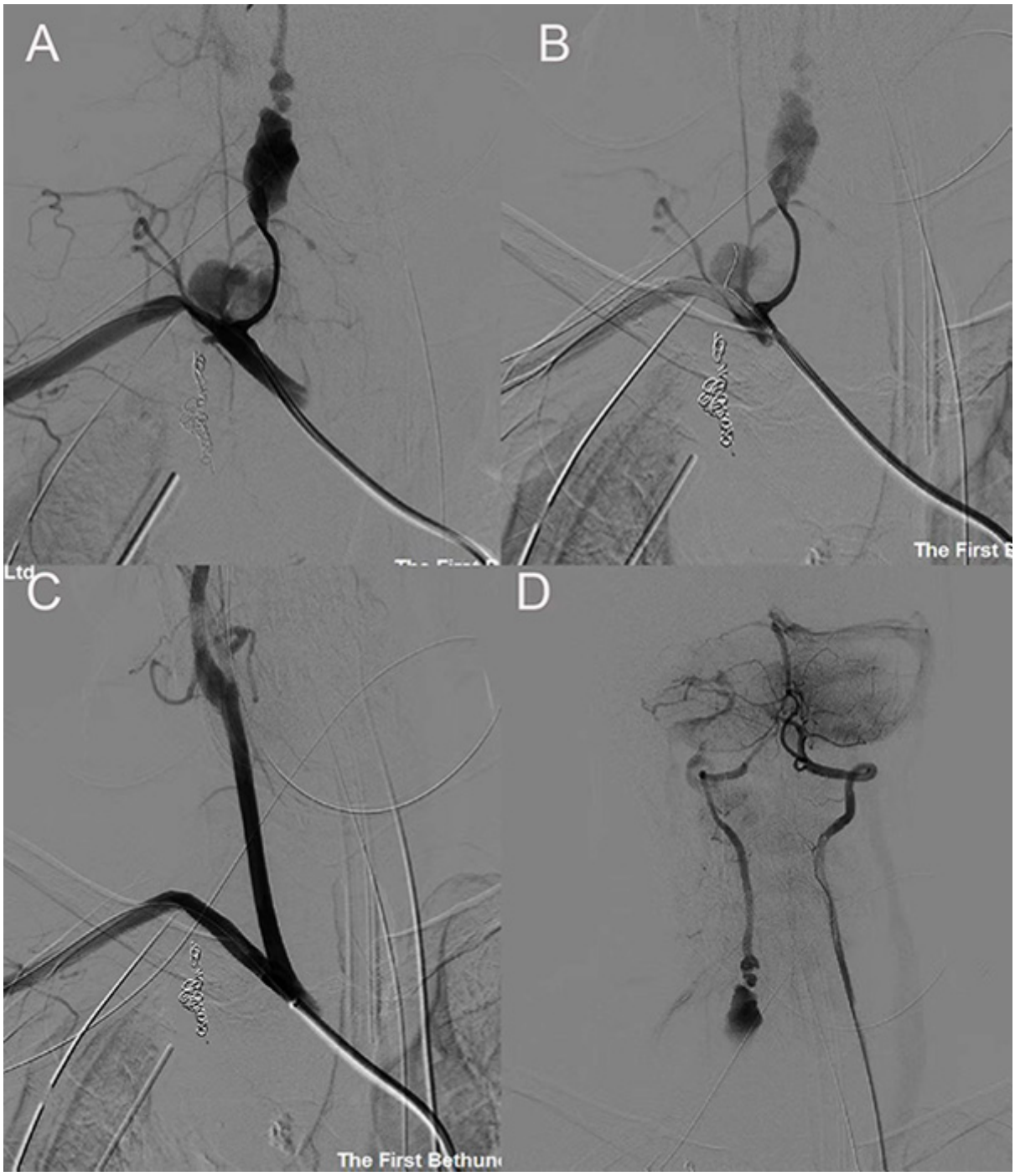

Figure 3

A-B: Right subclavian arterial angiography showed subclavian branch pseudoaneurysm rupture with contrast extravasation and intact right vertebral cystic aneurysm corresponding to the lesion of recent MRI finding.

C: Repeated angiography after covered stent implant showed a complete exclusion for vascular pathologies above.

D: Left vertebral artery angiography showed good collateral vessels of the posterior cerebral artery and faint retrograde filling of the distal portion of vertebral aneurysm.

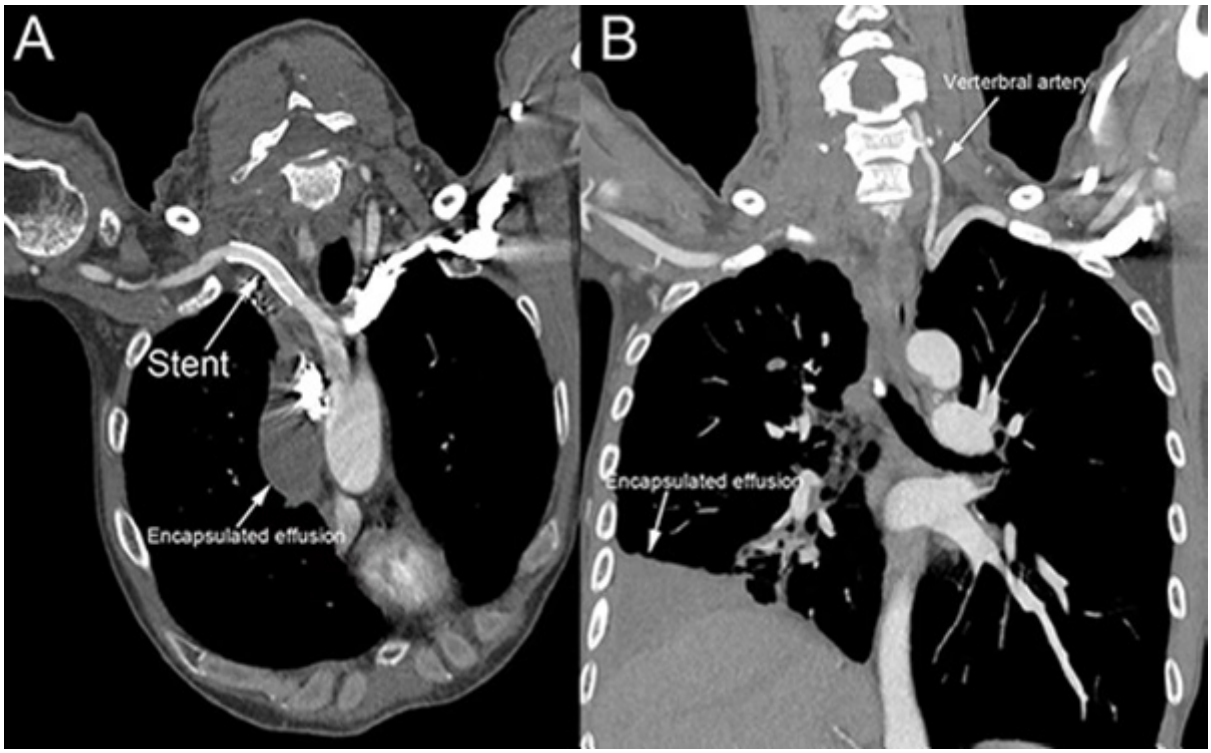

Figure 4

A-B: Contrast-enhanced CT scan showed the right subclavian artery stent patency, the absence of right vertebral artery and normal left vertebral artery at the postoperative follow-up of three months interval.