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Case Report

Progression and brain metastasis of adult-type fibrosarcoma with surgical intervention only: case report

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Abstract: Adult-type fibrosarcoma (AFS) is a malignant tumor derived from soft tissue fibroblasts. Herein, we report a case of AFS transformed solitary fibrous tumor (SFT) that metastasized into the brain. The patient, a 29 years-old male, received four surgical treatments without chemo-radiotherapy or other intervention. This case provides a rare opportunity to investigate and report the progression of a benign tumor in the soft tissue of the scalp and study the effect of surgical intervention. By studying this patient's clinical records, computed tomography (CT), magnetic resonance imaging (MRI), immunohistochemistry (IHC) biomarker analysis, and pathological report, we originally diagnosed the tumor as SFT. As the tumor progressed, it then transformed to AFS, with high levels of Ki67, Vimentin and CD34 positive cells. Ultimately the tumor metastasized into the brain. The initial data from this case demonstrates that SFT is capable of transforming into malignant AFS, which then metastasized into central nervous system, which then became a serious health threat. Unfortunately, no additional data were collected, as the patient decided to discontinue treatment and preserve his privacy. This suggests that surgical intervention is not effective enough by itself to control such a malignant AFS, and therefore, a combination of surgery and chemo-radiotherapy is strongly recommended for patients with AFS.

Keywords: Adult-type fibrosarcoma, head and neck cancer, intracerebral, metastasis

Introduction

Adult-type fibrosarcoma (AFS) is a rare type of malignant fibroblast/myofibroblast tumor found in adults that can be triggered by a number of different factors, including oxidative stress, pollution, chemicals and high fat diet [6-8]. AFS is more common in males than females, and usually presents between the ages of 30-55 years of age [1, 2]. According to the WHO report in 2013, AFS represents 1-3% of total sarcoma cases in the world and has an average tumor burden of about 3.5 years [2]. This type of tumor tends to occur mainly in the deep soft tissue of the trunk, neck, upper arms and legs, especially in areas surrounding bones; however, it is rarely reported in the head. Symptoms and patient prognosis are determined by the size and location of the tumor; AFS tumors localized proximal to the central nervous system (CNS) would likely cause more severe health threats than those in other regions of the body [3-5]. Standard clinical treatments of AFS include surgical removal of the tumor following chemoradiotherapy. Despite of advances in clinical technology and therapies in recent decades, AFS still has a high recurrence rate [2, 3]. AFS tumors usually grow relatively slowly as compared with other types of malignant tumors, but tend to be highly metastatic, which makes it a challenge to monitor and treat AFS recurrence and metastasis. In this case report, we describe a rare case of AFS that originally derived from SFT after four surgical removals and recurrences. This case provides an unique opportunity to investigate the biological nature of tumor progression and brain metastasis.

Case report

We report a case of malignant AFS found in a patient's head area of a 29 year old male. The medical record described that the first wound left a 1 cm × 2 cm size cavity on the vertex, between the coronal suture and lambdoid suture with a small hard nodule inside (**Figure**

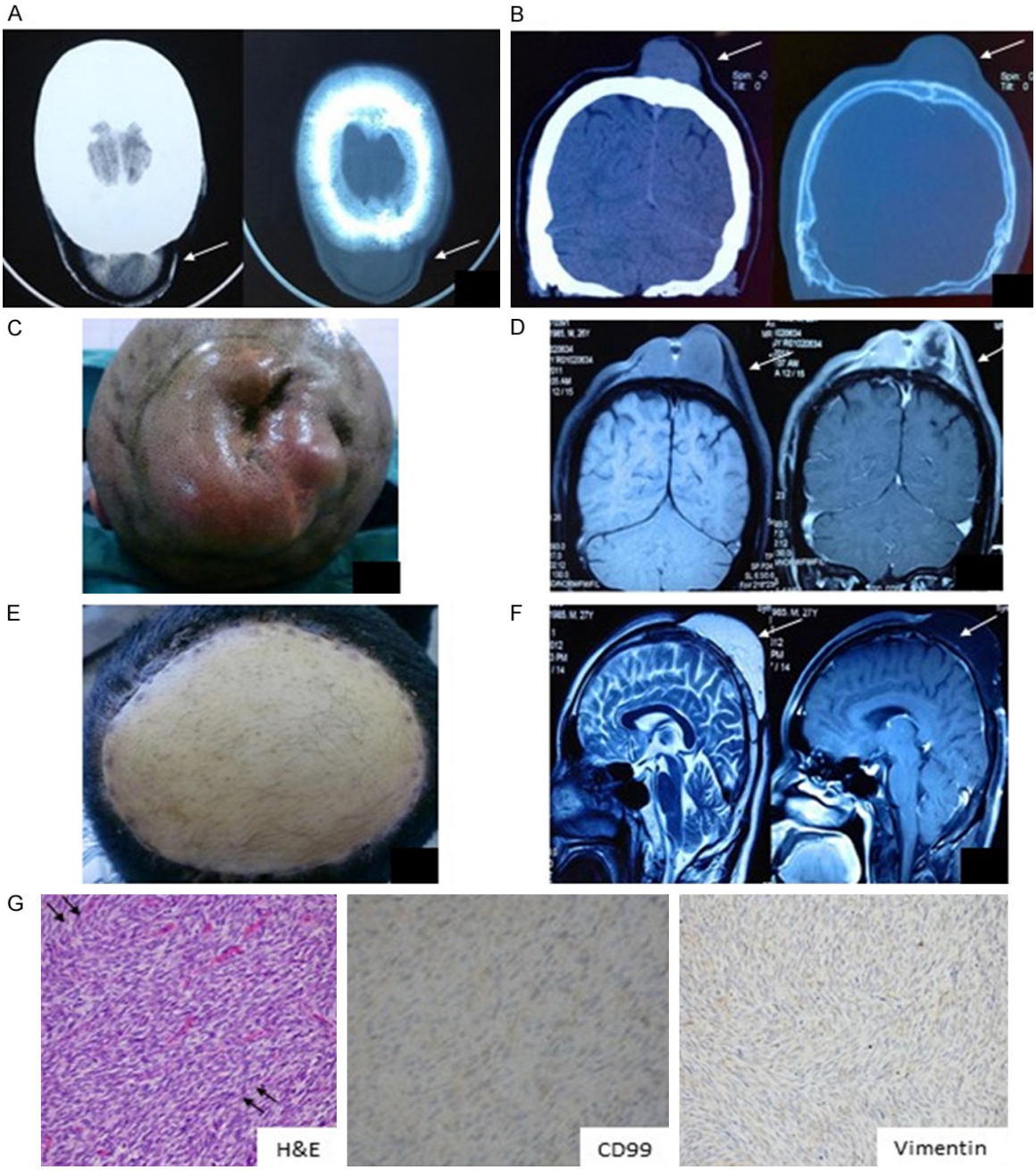

Figure 1. A. CT image before the first surgery: a visible 5 cm × 3 cm × 2 cm soft tissue benign vertex scalp (arrows). No detection of bone penetration or damage. B. CT image before the second surgery: a visible 3 cm × 2 cm × 2 cm soft tissue benign vertex scalp (arrows). No detection of bone penetration or damage. C. Photograph of the top of the patient's head before the third surgery with a visible 12 cm × 7 cm × 3.5 cm swollen tissue benign vertex scalp. Patient's scalp shows an uneven and rough surface with a clear border. D. MRI scan before the third surgery: detectable weak T1WI signal (left panel) and modest contrast with Gd-DTPA (right panel). E. Photograph of the top of the patient's head shows skin graft healing. F. MRI scan after the third surgery recovery: high level of T2WI without detectable contrast (arrows). G. Immunohistochemistry of the tumor sample: arrows in H&E staining point to herringbone pattern of spindle cells. Tumor sections IHC staining with CD99 (Fujian Maixin Biotech.) and Vimentin (Beijing Zhongshan Golden Bridge Biotech.) at 200 × magnification power.

1). He did not receive any treatment initially; his first treatment came in 2010 after visiting the clinic after multiple injuries. External observation found a soft and enlarged nodule, with

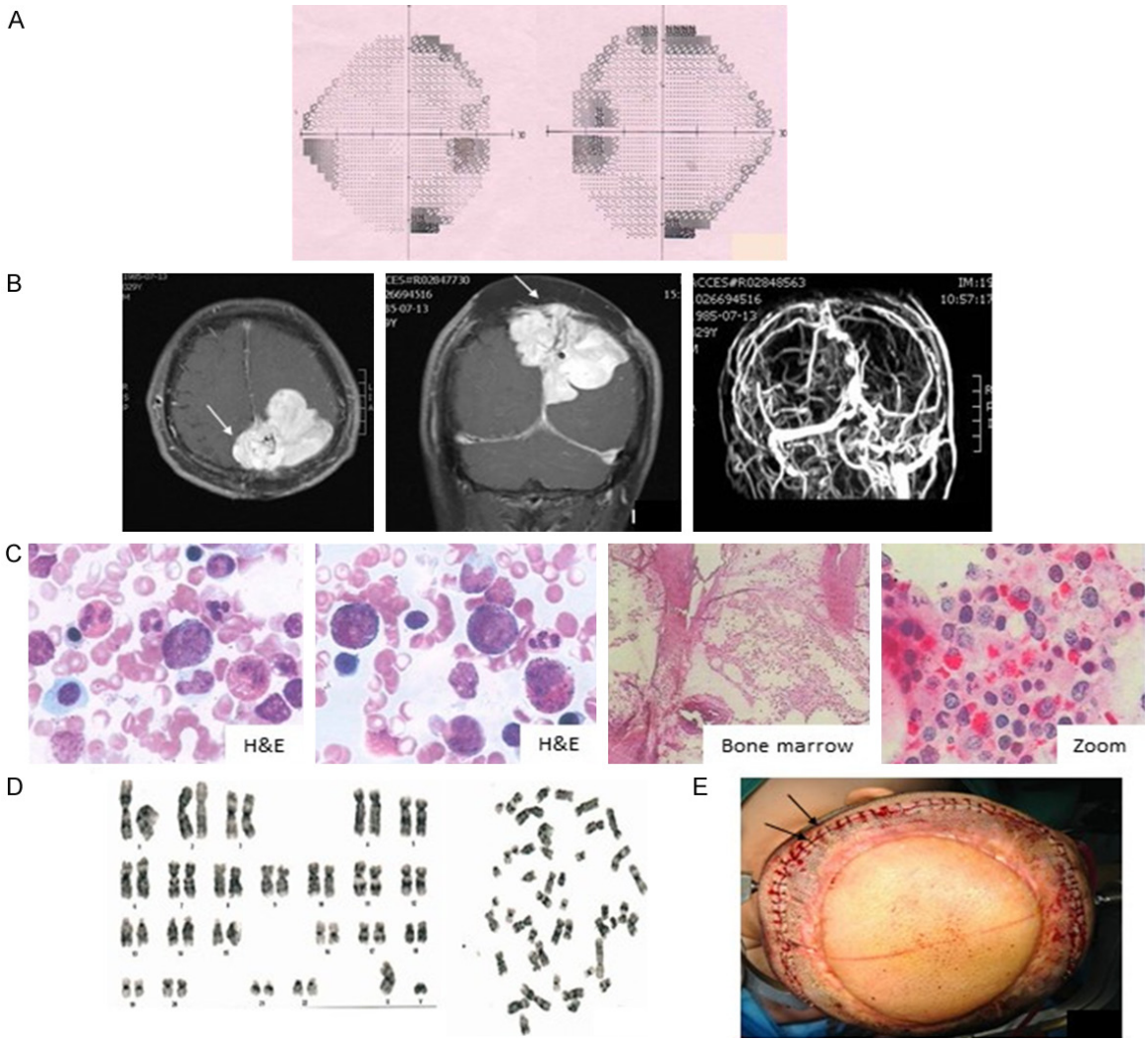

Figure 2. A. Patient's perimetry results before the fourth surgery demonstrates partial vision loss of both eyes (grey and dark area); B. MRI scan of patient's brain shows intracerebral tumor with visible skull penetration (arrow, middle panel). Strong contrast areas include the cisterna magna in the left hemisphere of cerebellum (arrow, left panel). Right panel shows hemorrhaging and tortuous veins in the sagittal sinus evident after the tumor mass expanded. C. H&E staining of bone marrow shows normal nucleated cell count with a higher level of eosinophils. D. Chromosome analysis shows normal chromosome morphology and 10 mitotic cells at high magnification. E. Photograph of the top of the patient's head after the fourth surgery. Arrows indicate incision position.

swelling in the surrounding soft tissues and skin inflammation. A computed tomography (CT) scan with bone window detected a sphere-shaped neoplastic region, 5 cm × 3 cm × 2 cm in size, with a clear border in sharp contrast; no parietal bone fracture or penetration was detected (**Figure 1A**). The initial biopsy diagnosed the lesion as solitary fibrous tumor (SFT). Surgery was performed to remove the primary tumor. After the first surgery, the patient had 5 additional contusions localized in this same region over a five year period (2010-2014) from work related injuries. The tumor relapsed twice: once at six months, with the tumor being 3 cm × 2 cm × 2 cm in size, and again at 9 months, with the tumor being 12 cm × 7 cm × 3.5 cm in size, as determined by MRI (**Figure 1B** and **1D**, respectively). After the third surgery, the pathology lab analyzed the tumor sample for histological markers, which found that the tumor consisted of solid areas with spindle and pleomorphic cells forming the AFS hallmark V-shape bundle formation and herringbone pattern. At this time, the tumor was diagnosed as malignant AFS. Low level of T1-weighted-image (T1WI) and strong contrast of Gd-DTPA images

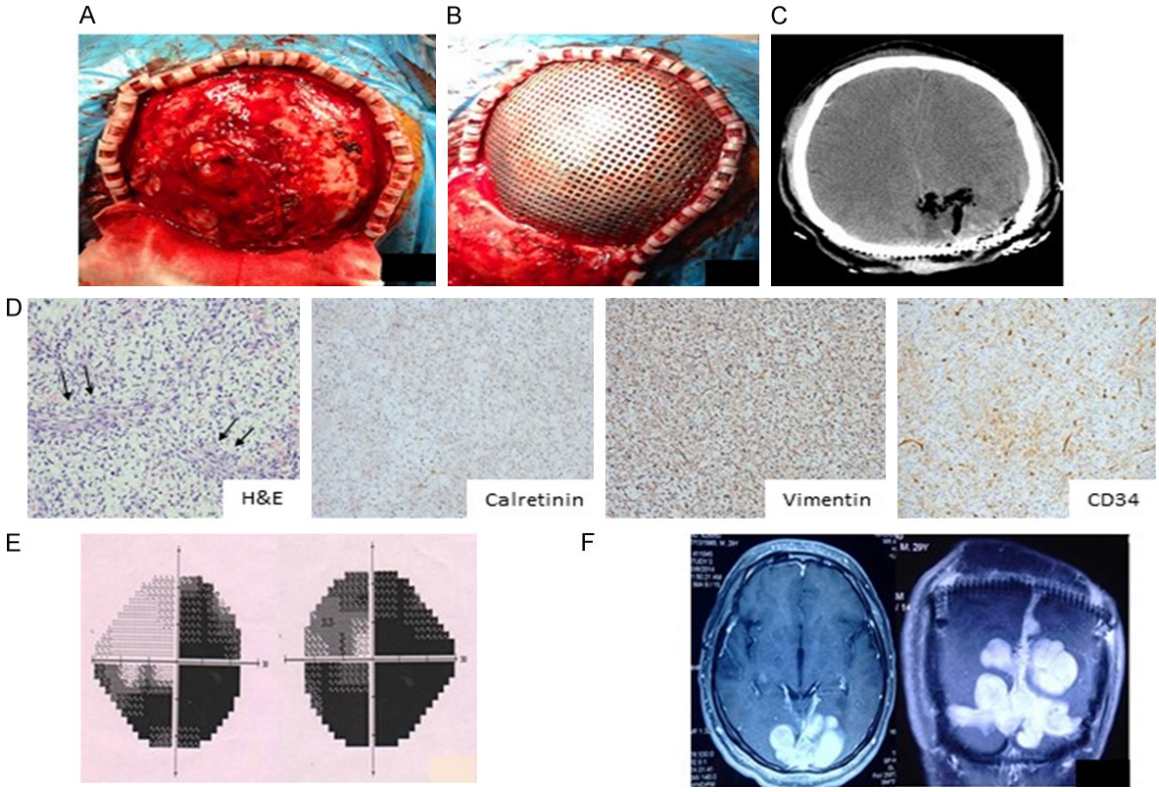

Figure 3. A. Photograph of the top of the patient's head during the operation shows bleeding and hemorrhages. B. Photograph of the top of the patient's head shows artificial meninges and pre-molded titanium mesh. C. CT imaging after the fourth surgery: a visible cavity after tumor mass removal with visible titanium mesh. D. IHC analysis of the tumor sections with 200 × magnification power. E. Final perimetry exam indicates extensive loss of vision (grey and dark area). F. Final MRI scan shows recurrence of tumor in patient's brain with strong contrast and 7.3 cm × 9.5 cm × 4.5 cm in size.

show the tumor has a rough surface and with a clearly defined border underneath the scalp (**Figure 1C**). The tumor mass was surgically removed with successful skin graft as shown in **Figure 1E**. At the patient's request, he did not receive radiation therapy after the surgery radiation; however, the patient has been monitored for three years without symptoms.

Due to the sample limitation, samples from the first and second surgery were not obtained for immunohistochemistry (IHC). IHC results from the third biopsy of the tumor lesion found the tumor to be Ki67 >50%, S-100 (-), CD99 (+), Vimentin (+), CD34 (-), Desmin (-), SMA (-), EMA (-), Bcl-2 (-), and Calponin (-). High levels of Ki67 and Vimentin suggest that the tumor is highly proliferative and metastatic (**Figure 1G**).

Five years after of the first diagnosis, the patient started experiencing more severe symptoms, including dizziness, numb muscles, feeling disorientated, a loss of mobility and decreasing vision (right eye: 0.4, left eye: 0.15). Perimetry tests suggested increasing visual field loss in both eyes (**Figure 2A**). Brain MRI identified a large intracranial growth 7.9 cm × 6.2 cm in size, and destruction of the morphology in the left cerebral hemisphere (**Figure 2B**, left two panels). The original tumor had metastasized into the brain and caused a large area of hemorrhaging and the veins in the sagittal sinus to become tortuous as the tumor mass expanded (**Figure 2B**, right panel). Strikingly, bone damage was not detected in previous head CT and MRI scans (**Figure 1A**, **1B**, **1D** and **1F**). Additional CT scans did not detect a lung metastasis. Eosinophils were 5.65 × 10^9/L (0.02-0.52 × 10^9/L), 0.40% (0.004-0.08). Bone marrow biopsy was negative for Reticulin, but found increasing levels of monocytes and eosinopils (**Figure 2C**). Circulating tumor cells were not detected in either the blood or bone marrow; however, eosinophils are significant

higher than normal, suggesting increasing tumor malignancy. Chromosome analysis of the bone marrow found normal morphology and 10 mitotic nuclei evident at high magnification (**Figure 2D**). The cells were negative for the FIP1L1-PDGFRA gene fusion in 2q14-22 region using florescence *in situ* hybridization (FISH) (data not shown).

The forth surgical resection was performed immediately after pre-operation tests. In order to preserve the previous skin grafting, the incision started 3-4 cm away from the last suture, and was smaller than half the length of the perimeter (**Figure 2E**). We were careful to avoid damaging the vascular supply to skin graft, particularly the superficial temporal artery and occipital artery. The tumor was highly invasive and vascular, with damage to both the skull bone and the meninges. A large area of hemorrhages and vascular infiltration inside the tumor caused significant blood loss (~8000 mL) during the operation (**Figure 3A**). Because of the tight connection between tumor and major sinus, a small part of the tumor was difficult to separate using surgical tools; while the majority of the tumor mass was removed, some small portions of tumor remained and may cause a relapse. Artificial meninges and premolded titanium mesh with bone wax sealing were applied as shown in **Figure 3B**. In order to preserve the skin graft and avoid leakage of cerebrospinal fluid, we used medical auralencephalic glue to seal the edge of meninges, and completed the operation with low-tension suturing. Even with these extra measures, the skin graft became necrotic and effusive. Following treatment procedures, included debridement of necrotic tissue, low-tension suturing, skin flap drainage and lumbar subarachnoid drainage, the skin graft eventually healed. Post-surgery CT imaging indicated intracerebral cavities and a visible titanium mesh (**Figure 3C**). IHC shows the tumor was Ki67+30%, CD34 (+), p53+20%, Calretinin (+), Vimentin (+), CD1a (+), CD23 (+), S-100 (-), GFAP (-), EMA (-), LCA (-), CD68 (-), CD31 (-), CD21 (-), and CK (-). In contrast to the primary tumor, which was Ki67 and Vimentin positive, IHC of the brain metastasized tumor was positive for CD34, p53, Calretinin, CD1a, and CD23, which are high grade cancer markers. Representative IHC staining are shown in **Figure 3D**.

Without radiation therapy, the tumor relapsed two months after the last surgery. The patient became increasing more blind (**Figure 3E**). MRI scans display strong T1 and T2 signals as shown in **Figure 3F**. The tumor enlarged to 7.3 cm × 9.5 cm × 4.5 cm in size with clear contrast. At this time, the patient decided to discontinue further clinical treatment and requested his privacy.

Discussion

Little is known about the nature of intracerebral AFS metastasis, and every additional case provides more information regarding the biological behavior of this tumor. This case, in particular, is rare, and the unique treatment history of this case allowed us to observe SFT progressing to malignant AFS, which then invaded the brain. Previously, some groups reported that surgical implants and foreign bodies caused AFS [9]. Reports have also suggested that radiation therapy may enhance patient's risk to AFS [10]. The patient in this case, however, has no history of radiation exposure. We conclude that the tumor began as SFT and then transformed to AFS, which was mainly triggered by repeated head injury over a four year period.

Previous clinical reports indicate that AFS usually develops slowly from highly vascular tumors that are painless, have clear-borders, and are small in size (between 3-8 cm in diameter), with localized ulcer and hemorrhaging [11-13]. Our case suggests that the tumor was highly proliferative (Ki67 and P53+) and vascular (CD34+) in its late stage, which directly caused the recurrence frequency to increase from several years to several months. A poor prognosis is expected based on the malignancy indicators, including a hallmark morphology pattern seen under microscope and positive cancer biomarkers. MRI imaging of the tumor in late stages showed that the T1 signal is uneven and weaker than that of muscles and the T2 signal is elevated. CT imaging indicate that the tumor border is diffuse. With enhanced MRI, 90% of region had strong radial contrast without specific marker, consistent with a previous report [14]. Those stronger contrasts are mostly due to fibroblast arrangement in the tumor mass; necrosis, thrombosis and hemorrhaging usually show no contrast.

Histological analysis suggested the tumor is a typical AFS tumor, with V-shape bundle formation and herringbone pattern evident under a

microscope [15]. Our IHC results found the tumor was Vimentin positive at all stages examined, with CD34 and p53 positive only in the late stage. These markers indicate the aggressive nature of the tumor. Negative staining of brain astrocyte markers S-100 and GFAP in all tumor sections clearly demonstrate the tumor cells are from same origin and metastasized into brain. Our clincopathologic analysis is consistent with previous reports.

Interestingly, this tumor did not have a chromosome abnormality despite a high frequency of chromosome fusion and recombination commonly reported with AFS [17-22]. Using comparative genomic hybridization (CGH), Schmidt *et al.* found that 12q are frequently amplified in AFS [22]. Sheng *et al.* reported that 2q14-22 region COL1A1-PDGFB gene fusion in dermatofibrosarcoma protuberans (DFSP) transformed superficial fibrosarcoma [21-23]. However, our FISH result of FIP1L1-PDGFRA shows normal gene organization in 2q14-22 region. Although it was not analyzed in this tumor, COL1A1-PDGFB gene fusion would be worth investigating in future tests. We also believe that advance genetic analytic tools, such as next-generation sequencing and transcriptome analysis should be further explored in future studies.

Despite of recent advances in clinical treatment for head and neck cancers, surgical intervention followed by chemoradiotherapy is still the first option for cancer patients. Surgery advances in the head vertex area are needed to overcome anatomic complexity, which limits the resection size and location of tumors. Patients treated promptly with radiation therapy have better overall survival, although radiation exposure may enhance gene mutation incidence [12, 24]. However, as described in this article, the patient treated only with surgery has a very poor prognosis.

Metastasis is the major cause of death for AFS patients, with a five-year survival rate of 39-54.4% [25]. The three main organs AFS metastasizes to are the lung, bone and lymph systems, generally through blood vessels (17.8%) and the lymph system (2%) [26, 27]. In this case, we clearly demonstrate that AFS tumors can metastasize into the brain as the tumor became more aggressive, in this case after the third surgery. No skull bone damage was apparent in previous CT and MRI scans (**Figure 1A**, **1B**, **1D**, **1F**). Lung CT, blood test, and bone marrow test are all negative for tumor cells in this patient's pre-operation exam. Although the details still need to be further investigated, the elevating level of eosinophils in both blood and bone marrow indicate changes in the tumor's microenvironment. Although we maximized the surgical removal for the patient, without radiation therapy, the outcome is not favorable.

In conclusion, this rapid dissemination of this disease treated with surgical intervention only highlights the aggressive nature of AFS tumors, which have not been fully recognized in the literature. The present AFS tumor metastasized deeply into the brain. The tumor was composed of the V-shape spindle cells bundle formation and herringbone pattern and was positive for the biomarkers of adult fibroblasts, which supports the slow transformation of SFT into malignant AFS, which eventually metastasized. Total surgical removal of aggressive AFS in the brain is limited with the current technology; however, the progression of tumor malignancy was demonstrated with multiple advanced clinical analytic tools. Those results provide more valuable information to define the biological and clinical characters of AFS. We believe that this case contributes useful knowledge to help find a cure for AFS, however, more has to be learned to find curative therapy for AFS in the future.

Disclosure of conflict of interest

None.

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