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A Case of Undifferentiated Sarcoma in the Superior Vena Cava and Bilateral Cervical Veins

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 76
Final Diagnosis: Undifferentiated sarcoma in the great veins
Symptoms: Superior vena cava syndrome
Medication: —
Clinical Procedure: —
Specialty: Cardiology

Objective: Rare disease

Background: Intimal sarcoma (IS) is a malignant mesenchymal tumor with predominantly intraluminal growth in large vessels and the heart. Due to the rarity of cases it often poses diagnostic problems in clinical and pathological settings. Although the classification of IS is still controversial, undifferentiated type of IS has recently been found to show immunohistochemical positivity with MDM2, CDK4, or PDGFRA and amplification of *MDM2/CDK4* and *PDGFRA*.

Case Report: The patient was a 76 years-old Japanese man who presented with superior vena cava (SVC) syndrome. CT identified a tumor or thrombi in the SVC, bilateral brachiocephalic, and jugular veins. The histology of the biopsy specimen revealed an undifferentiated tumor without immunohistochemical positivity for all antibodies available except vimentin and smooth muscle actin. He was treated conservatively and died of respiratory failure 2 months after presentation. At autopsy, the large veins were filled by a sausage-like tumor and the cut sections revealed hemorrhagic and necrotic tumor. The tumor cells were negative with MDM2, CDK4, and PDGFRA by immunohistochemistry. Amplification of *MDM2* and *PDGFRA* was not identified by fluorescence *in-situ* hybridization.

Conclusions: We concluded that the case was an undifferentiated sarcoma (IS without any specific phenotype) arising in the SVC, bilateral brachiocephalic, and jugular veins. We propose a way of subtyping sarcomas with predominantly intraluminal growth in large vessels and the heart based on immunohistochemistry and amplification of *MDM2* and *PDGFRA*. However, proper subtyping of these sarcomas requires further study.

MeSH Keywords: Blood Vessels • Hemangiosarcoma • Immunohistochemistry • *In Situ* Hybridization, Fluorescence • Jugular Veins • Vena Cava, Superior

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Background

Sarcomas that arise in large blood vessels are rare. Intimal sarcoma (IS) is the most frequent of sarcomas with predominantly intraluminal growth involving large arteries of systemic and pulmonary circulation and the heart, and it is believed to derive from the intima [1,2]. Leiomyosarcoma (LMS) is the most frequent of sarcomas with predominantly extraluminal growth involving large veins of systemic and pulmonary circulation, and it is thought to arise in the smooth muscle layer [3,4]. Sarcomas with predominantly intraluminal growth in the venous system are extremely rare and often pose diagnostic problems [5–7].

The classification of IS is still controversial due to the paucity of cases and histology of the miscellaneous poorly differentiated tumors [8–10]. The WHO classification (2012) does not seem to accept angiosarcoma with immunohistochemical positivity for endothelial markers in the category, while the AFIP in 2015 states that "intimal" sarcoma just represents the site of origin rather than the tumor cell differentiation [1,11]. Recently, IS without the endothelial markers has been reported to frequently show immunohistochemical positivity for MDM2, CDK4, or PDGFRA, as well as amplification of *MDM2/CDK4* and *PDFGRA* [12–15].

Case Report

The patient was a 76-year-old man. He became aware of bilateral neck swelling and sought medical attention. On CT, massive thrombi were suspected in the SVC, and bilateral brachiocephalic and jugular veins (Figure 1A, 1B). Although he underwent anticoagulation therapy, his conditions did not improve. SVC syndrome due to a tumor was suspected.

Aspiration cytology of the cervical lesion showed many atypical cells, which were 2–3 times larger than the small lymphocytes, and there was scarce cytoplasm, and round or focally indented nuclei with 1 or 2 small nucleoli and a slightly thickened nuclear membrane. The cells formed several discohesive clusters and most of them were scattered individually (Figure 2). The cytological diagnosis was suspicious for undifferentiated carcinoma or malignant lymphoma. Immunohistochemistry was not performed because it was not possible to make a cell block specimen. There were no enlarged lymph nodes and no suspected primary sites except for bilateral tumors of the thyroid gland. Specific tumor markers were not detected. Radiologic studies did not support the thyroid gland as the primary site for the tumor because the tumor of the right lobe was small in size and that of the left lobe was encapsulated (Figure 1A, 1B). CT of the lungs showed neither tumors nor thrombi. The patient did not undergo PET/CT scan to identify the tumor origin because it was not available at our hospital.

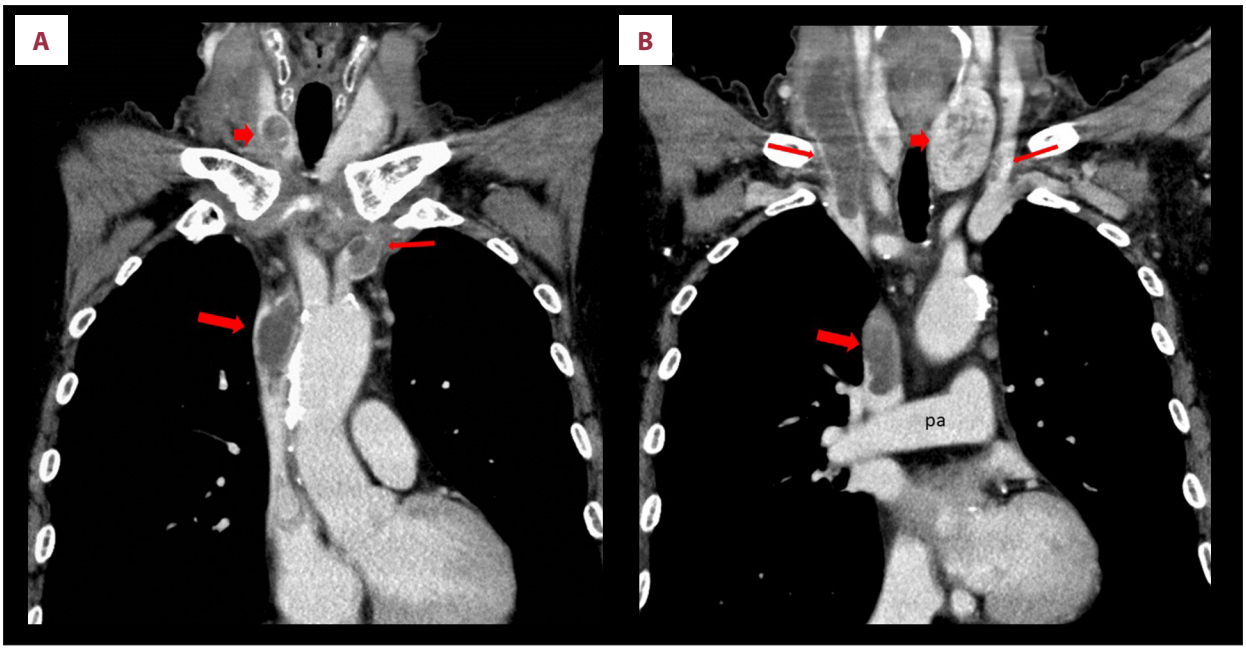

Figure 1. (**A**) Coronal section of contrast-enhanced CT of the thorax. There were filling defects in the superior vena cava (thick arrow) and left brachiocephalic veins (thin arrow). A focally calcified 2-m tumor was seen in the right thyroid gland (arrow head). (**B**) Coronal section of contrast-enhanced CT of the thorax. The filling defects were observed in the superior vena cava (thick arrow) and in bilateral internal jugular veins (thin arrows). The pulmonary artery (pa) was free of disease. An encapsulated, 2×4 cm tumor was also seen in the left thyroid gland (arrow head).

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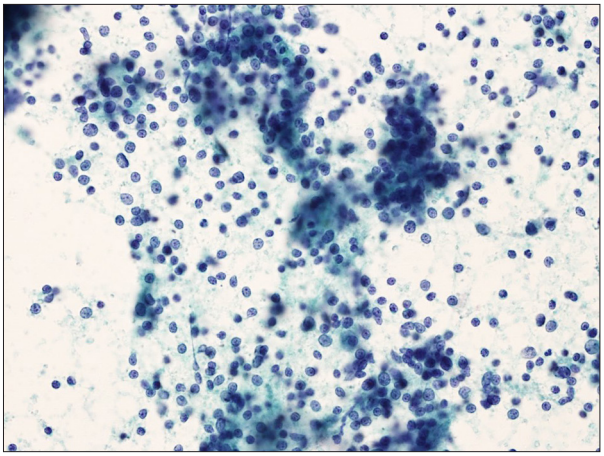

Figure 2. Fine-needle aspiration specimen taken from the cervical tumor revealed scattered atypical cells with scarce cytoplasm, and round nuclei with 1 or 2 small nucleoli. Several discohesive cell clusters were also found. Papanicolaou stain. ×400.

A cutaneous metastasis of the anterior chest appeared. The histologic specimen revealed a mass in the surrounding fibroadipose tissue (Figure 3A). The mass appeared to be colonizing or arising from a large vessel, as highlighted by Elastica-VanGieson special stain (Figure 3B). The tumor was composed of sheets and short fascicles of epithelioid and spindled cells with uniformly round nuclei, vesicular chromatin, small nucleoli, and a moderate amount of pink cytoplasm. Mitotic activity was brisk (more than 20/10HPF) (Figure 3C) The lesional cells were immunohistochemically negative for all antibodies tested, including several cytokeratins, desmin, h-caldesmon, myogenin, MyoD-1, S-100, HMB45, CD31, CD34, ERG, CD20, CD3, CD79a, and bcl-2, but vimentin and smooth muscle actin were positive (Figure 3D–3F). Therefore, the diagnosis of undifferentiated IS was possible if the lesion originated from the great vessels.

A metastasis to the thoracic spine forced the patient to be bedridden and he suffered from severe pain treated with morphine. His condition deteriorated and he died of respiratory failure 2 months after presentation.

Autopsy findings

An autopsy was performed to elucidate the precise diagnosis and primary site of origin of the tumor. The venous system from SVC to bilateral brachiocephalic and jugular veins showed an elastic, soft, sausage-like tumor and the cut sections were hemorrhagic and necrotic and up to 2.3×1.8 cm tumors, which macroscopically could not be differentiated from thrombi. The tumor seemed to be confined to the vascular lumina without any invasion or destruction of the vascular walls (Figure 4A, 4B). The thyroid gland contained a 1.7×2 cm partially calcified tumor of the right lobe and a 2×3.6 cm encapsulated tumor of the left lobe. Two hemorrhagic tumors (1.3 cm and 1.0 cm) of subcutaneous adipose tissue of the anterior chest and a 2.8×1.9 cm necrotic tumor of the thoracic vertebrae were observed. Cut sections of both lungs (left 245 g, right 371 g) demonstrated several intravascular nodules up to 0.5 cm in size in the pulmonary artery. No tumors were found at any other sites, including the heart, aorta, inferior vena cava, and the other visceral organs. The lungs showed moderate emphysema. The kidneys (left 156 g, right 145 g) revealed moderate arteriosclerotic change and the liver (927 g) demonstrated moderate acute congestion and senile atrophy.

Histology of the tumor in the veins was similar to that of the biopsy specimen, with a malignant undifferentiated tumor showing medullary proliferation of the cells in a patterenless pattern. The tumor showed massive necrosis with a small to moderate amount of fibrin thrombi and it partially invaded into the vascular wall but did not extend beyond it. We performed immunohistochemistry on the autopsy specimens using antibodies that had not been available for the biopsy specimen. The antibodies included CDK4 (mc, DSC-31, 1/100; Invitrogen), MDM2 (mc, IB10, 1/10; Novocastra), and PDGFRA (mc, D13C6, 1/300: Cell Signaling). All of them were negative in the tumor cells. We also conducted fluorescence *in-situ* hybridization (FISH) analysis for *MDM2* and *PDGFRA,* as one of the authors described previously [16]. Amplification of *MDM2* and *PDGFRA* were not identified (Figure 5A, 5B). The *SS18-SSX* fusion gene was not detected by reverse transcription-polymerase chain reaction (RT-PCR).

The tumor in the right lobe of the thyroid gland demonstrated the same histology as the tumors in the veins, and no findings of papillary carcinoma. Immunohistochemistry was negative for TTF-1, PAX-8, several cytokeratins, CEA, thyroglobulin, and p53. The encapsulated tumor of the thyroid gland was found to be a follicular adenoma. The bilateral nodules in the pulmonary artery and the tumor in the thoracic vertebrae also showed the same histology as the tumor in the veins. There were no other metastases identified at autopsy. The final diagnosis was UDS arising in SVC or the large cervical veins.

Discussion

The statistical incidence of sarcomas in large arteries and veins of systemic and pulmonary circulation is not reliable because of the very low incidence and the serious diagnostic challenges associated with these tumors [9,10,17]. However, IS is the most frequent sarcoma in the arterial system and usually shows predominantly intraluminal growth. About 200 total cases and at least 70 cases of IS have been reported in the English language literature in the pulmonary artery and the aorta, respectively [1,2]. The histological subtypes are believed

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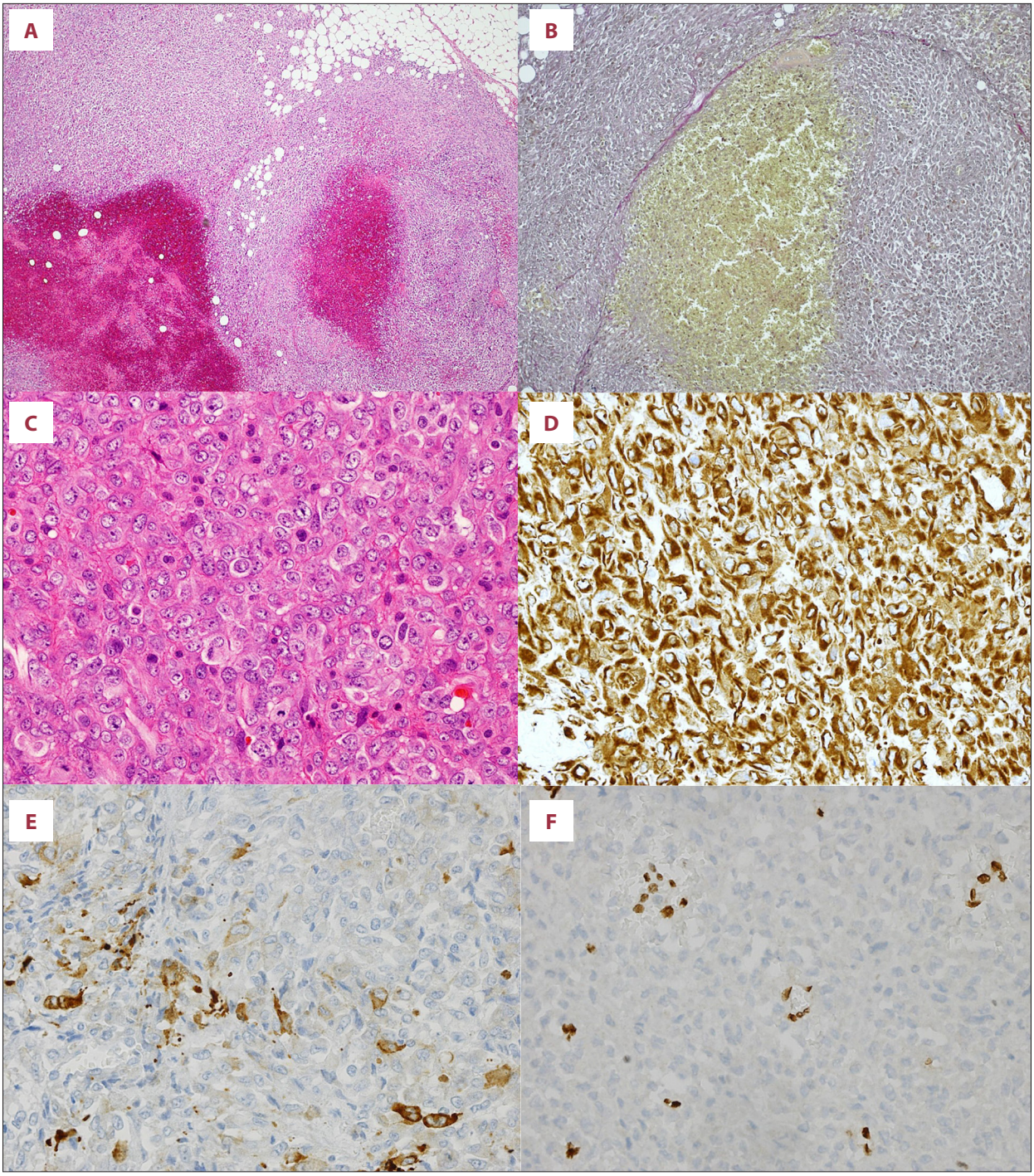

Figure 3. (**A**) Histologic specimen of the cutaneous metastasis of the anterior chest revealed a mass centered within fibroadipose tissue. H&E. ×40. (**B**) The metastatic mass appeared to colonize or arise from a large blood vessel. Elastica-van Gieson stain. ×100. (**C**) The tumor was composed of sheets and short fascicles of epithelioid and spindled cells with uniformly round nuclei, vesicular chromatin, small nucleoli, and a moderate amount of pink cytoplasm. H&E. ×400. (**D**) The tumor cells were diffusely positive in the cytoplasm with vimentin. ×400. (**E**) The tumor cells were focally positive with smooth muscle actin. ×400. (**F**) The tumor cells were negative with ERG while the nuclei of the capillary endothelial cells were positive for it. ×400.

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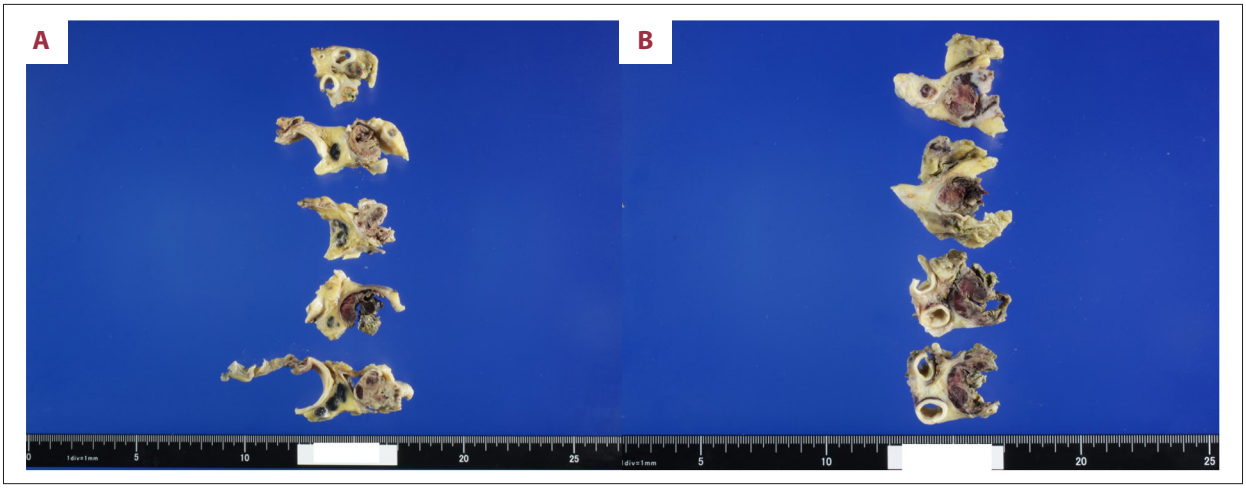

Figure 4. (**A**) Cut sections of the tumor in the superior vena cava, right brachiocephalic, and jugular veins. (**B**) Cut sections of the tumor in the left brachiocephalic and jugular veins. Both figures show hemorrhagic and necrotic tumor which macroscopically could not be differentiated from thrombi in the veins.

to include angiosarcoma (AS), undifferentiated IS, and other sarcomas such as osteosarcoma, synovial sarcoma (SS), and rhabdomyosarcoma (RMS), among others [1,8,17]. Tumors of the heart and great vessels in the AFIP atlas described that AS with immunohistochemical positivity for endothelial markers was the most frequent subtype of the aortic IS followed by undifferentiated IS without immunohistochemical positivity for the markers [1]. It also described that over half are pleomorphic sarcomas in the pulmonary artery IS. Other subtypes of pulmonary artery IS include osteosarcoma, chondrosarcoma, myxofibrosarcoma, myogenic sarcoma, and fibrosarcoma [1]. AS seems to occur much less frequently in the pulmonary artery than in the aorta [17–19].

On the other hand, LMS is the most frequent sarcoma in the large veins and usually demonstrates predominantly extraluminal growth. Over 300 cases of LMS were described in English papers in the inferior vena cava [3]. Over 20 cases of LMS were also reported in the pulmonary vein and over a dozen cases in the SVC and/or large cervical veins [4,20,21]. Meanwhile, sarcomas with predominantly intraluminal growth in the venous system are extremely rare, as only a few sporadic cases of the sarcomas have been reported in the English literature in systemic veins [6,7]. Two cases of IS [5,22], 5 cases of AS [7,23–26], and 2 cases of SS [7,27] have been reported in SVC and/or large cervical veins. We could not find a case of UDS other than IS involving these vessels in a search of PubMed.

Since UDS of our case grew predominantly intraluminally in the large veins, it had to be differentiated from undifferentiated IS, AS, and other miscellaneous sarcomas such as LMS, RMS, and SS. We also believed that undifferentiated (anaplastic) carcinoma of the thyroid gland (ACT) had to be discriminated from UDS since ACT sometimes mimics UDS on histology. Firstly, we thought that immunohistochemistry enabled us to differentiate UDS from LMS, RMS, and SS because of its lack of immunoohistochemical reactivity with desmin, h-caldesmon, myogenin, MyoD1, and several cytokeratin markers. SS was even less likely due to absence of the *SYT-SSX* fusion gene. Our case did not have the histological features of osteosarcoma, chondrosarcoma, or myxofibrosarcoma.

Regarding the distinction between UDS and ACT, ACT most frequently grows rapidly to form a huge tumor extending beyond the gland at diagnosis [28]. Although histologically ACT may sometimes mimic UDS, it is usually positive for cytokeratins, PAX 8, and p53 [28–30]. Considering these features of ACT, we concluded that the tumor in the thyroid gland was not ACT, but instead represented retrograde metastasis of UDS into the thyroid gland from the vein.

Due to the rarity of IS, its classification is unclear, and is defined as a malignant mesenchymal tumor with a defining feature of predominantly intravascular growth. Sebenik et al. suggested more than a decade ago that IS could be considered a form of "intravascular angiosarcoma/hemangioendothelioma" because of immunohistochemical positivity of the tumor cells for endothelial markers (CD31 and FLi-1) [8]. However, the WHO classification (2012) indicated that in typical case of IS, endothelial markers were negative [11]. The AFIP defined in 2015 that "intimal" sarcoma denoted the site of origin rather than the tumor cell differentiation [1]. According to this definition, several subtypes of sarcoma can be included in this category.

Bode-Lesniewska et al. first reported that IS frequently shows a high rate of overexpression and amplification of *MDM2* in 8 cases of IS in the pulmonary artery [12]. Neuville et al. showed that all the cases (42 cases) of IS, 5 of 26 cases of AS, and 6 of

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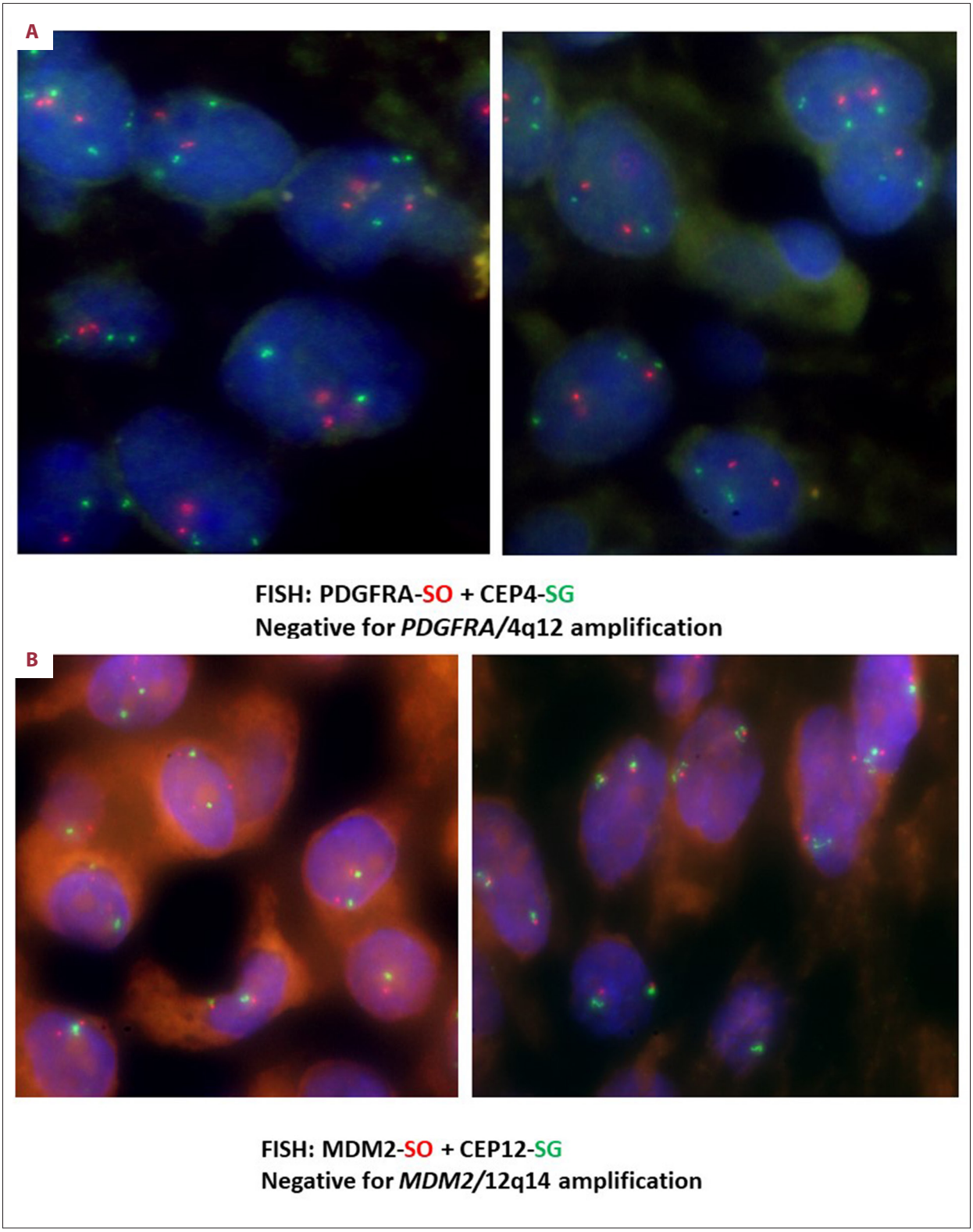

Figure 5. (**A**) Dual-color interphase FISH on paraffin sections of the tumor by co-hybridization of BAC's DNA *PDGFRA*/RP11-24O10 (red signals) and chromosome 4 centromere (green signals) probes disclosed lack of *PDGFRA*/4q12 amplification. (**B**) Dual-color interphase FISH performed using commercially available *MDM2* (SO)/SE12 (SG) [12q15/SE12, Kreatech, The Netherlands] probes, showed lack of *MDM2*/12q15 amplification.

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22 cases of UDS in the heart were positive for MDM2, while amplification of *MDM2* was observed in all the cases of IS but none of the cases of AS and UDS [13]. They also found that CDK4 was negative in all the cases of AS and UDS and was positive in 70% of the cases of IS. Dewaele et al. and Van Dievel et al. independently demonstrated high frequency of amplification of *PDGFRA* as well as *MDM2* in over a dozen cases of IS in the pulmonary artery, several arteries, and heart [14,15]. Although immunohistochemical and molecular examination of MDM2 and PDGFRA have not been reported in aortic IS, Tajima reported overexpression of MDM2, CDK4, and PDGFRA and amplification of *PDGFRA* in a case of aortic IS [31]. They also suggested that overexpression of PDGFRA can become a surrogate marker of amplification of *PDGFRA* [31].

Considering all the above results, we believe that immunohistochemical staining with endothelial markers of CD31 and ERG or Fli-1, and frequently positive markers of IS, MDM2, and CDK4 or PDGFRA, should be performed in the differential diagnosis of sarcomas with predominantly intraluminal growth involving the large vessels. If the tumor is clearly positive for endothelial markers and negative for the IS markers, the tumor should be diagnosed as AS or IS with endothelial phenotype. If the result of these markers is the opposite, the diagnosis should be IS or IS with common phenotype. If immunohistochemical results are ambiguous or negative for the markers, molecular examination for amplification of *MDM2* and *PDGFRA* should be performed. If amplification is identified, the tumor can be classified as IS or IS with common phenotype. If amplification is not identified, a diagnosis of UDS or IS without any specific phenotype is warranted. Sarcomas that exhibit definite differentiation should be classified as RMS or osteosarcoma. Whether this algorithm can properly classify sarcomas with predominantly intraluminal growth in great vessels requires further study.

Conclusions

We presented an autopsy case of undifferentiated sarcoma arising in SVC, bilateral brachiocephalic veins, and jugular veins. Sarcomas with predominantly intraluminal growth in the great vessels of the arterial and venous system are very rare and the classification is still controversial. We propose a classification of these sarcomas based on immunohistochemistry and amplification of *MDM2* and *PDGFRA*.

Acknowledgements

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Conflict of Interest

None.

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