Int J Clin Exp Med 2017;10(10):14803-14812
www.ijcem.com /ISSN:1940-5901/IJCEM0055962

Case Report

Primary angiosarcoma of inferior vena cava extending to right atrium: a case report

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Received January 19, 2017; Accepted September 10, 2017; Epub October 15, 2017; Published October 30, 2017

Abstract: Primary angiosarcomas of the inferior vena cava are exceedingly rare. We report a case of a 32-year-old Chinese female, who presented with progressive debilitation and dyspnea. Color Doppler vascular ultrasonography showed a solid irregular space-occupying lesion in the right atrium. Postoperative gross observation indicated that the tumor infiltrated and surrounded the inferior vena cava, also extended into the pericardium, right ventricle and cardiac facies diaphragmatica. Furthermore, histology revealed that the tumor had a scattered spindle-cell morphology, and immunohistochemistry for CD31, CD34, and Vimentin was positive for the tumor cells. Additionally, MDM2 amplification was absent as detected by FISH, which supported the diagnosis of angiosarcoma. The patient was treated with AI regimen (doxorubicin + ifosfamide) in combination with Endostatin for six cycles. She achieved complete response in the ninth month post operation.

Keywords: Angiosarcoma, AI regimen, endostatin

Introduction

Primary cardiac neoplasms are extremely rare, most of which are benign. However, primary malignant tumors account for nearly 25% of the cardiac neoplasm, among which the majority are sarcomas arising from transformed cells of mesenchymal origin including cartilaginous, cancellous bony, adipose, hematopoietic, muscular or vascular tissues [1-6]. Of these cardiac sarcomas, angiosarcoma usually originate in the right atrium and are related to a poor prognosis due to the aggressiveness and diagnosis in advanced stage [7, 8]. But Primary angiosarcoma of the inferior vena cava have been only occasionally reported.

Herein, we report a case of primary angiosarcoma of the inferior vena cava extending into the right atrium. To the best of our knowledge, this case is specific in that the tumor was originated from the inferior vena cava and was sensitive to the treatment of Endostatin, which serves as an anti-angiogenic agent.

Case report

A 32-year-old female was sent to our hospital with progressive debilitation and dyspnea for two months. Laboratory examination showed that CA125 was 176.70 U/ml in the serum (normal range: 0-35 U/ml). Computed tomography (CT, **Figure 1A**) and color Doppler echocardiography indicated extensive pleural effusion in both sides, as well as effusion in pericardial and abdominal cavity effusion. CA125 was 1443.00 U/ml in the hydrothorax and 1315.00 U/ml in the ascites (normal range: 0-35 U/ml). Post the effective drainage, both CT (**Figure 1B**) and color Doppler echocardiography (**Figure 1C**) revealed a solid irregular space-occupying lesion in the right atrium with the size of 38 mm × 21 mm, as well as slight pericardial effusion and pericardial thickening of the pericardium. The cardiac magnetic resonance (MRI) also displayed that the tumor extended into the pericardium, pericardial cavity and wall of the right atrium (**Figure 1D**). Then, the cardiac tumor enucleation was performed and the surgical exploration revealed that tumor tissues surrounded the inferior vena cava. No clear boarder of the tumor could be found and the tumor extended into the pericardium, right ventricle and cardiac facies diaphragmatica. Furthermore, histology demonstrated that the tumor had a scattered spindle-cell morphology (**Figure 2A-D**). And immunohistochemistry for CD31,

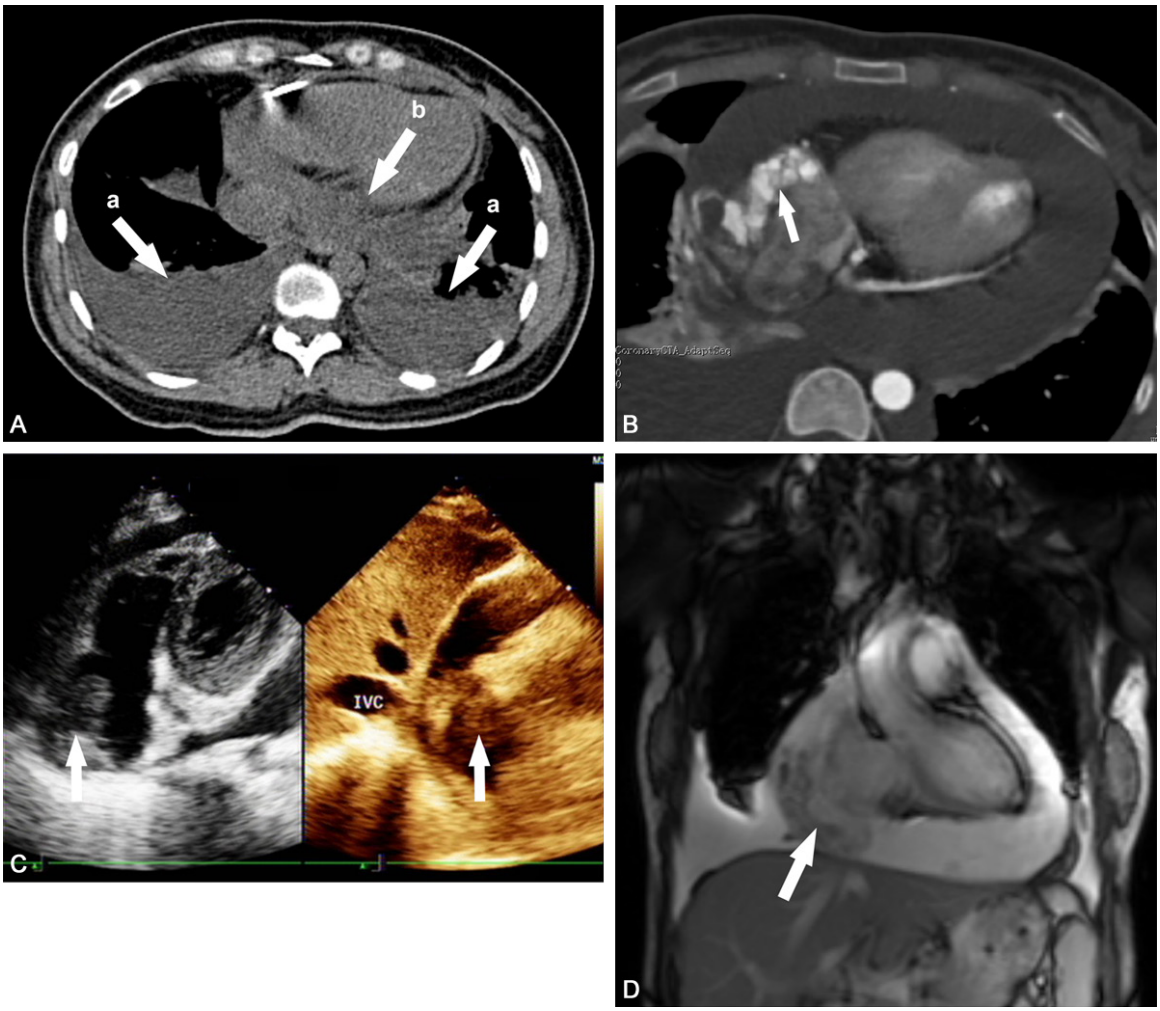

Figure 1. Radiological findings of the current patient by computed tomography (CT) and Color Doppler echocardiography before operation. (A) Pleural effusion in both sides (arrow a), as well as effusion in pericardial cavity effusion could be observed (arrow b) by CT. (B) After the effective drainage was performed, a solid irregular space-occupying lesion in the right atrium could be shown (arrow) by CT. Color Doppler echocardiography (C) and cardiac magnetic resonance (MRI) (D) both revealed a solid irregular space-occupying lesion in the right atrium with the size of 38 mm × 21 mm (arrow).

CD34, and Vimentin was strongly positive for the tumor cells, Ki-67 showed moderately proliferative activity (**Figure 3A-H**), while negative for Actin, Calretinin, CD56 (**Figure 4A-F**), CD99, CK, Desmin, EMA, LCA (**Figure 5A-H**), MC, MyoD1, NSE (**Figure 6A-F**), Myogenin, P63, S-100 (**Figure 7A-D**), SMA and TTF-1, which could help exclude the possibility of the origination from mesothelial tissue, epithelial tissue, striated muscle, nervous tissues or lymphoid hematopoietic tissues. Additionally, MDM2 amplification was absent as detected by FISH, which supported the diagnosis of primary angiosarcoma of the inferior vena cava extending to the right atrium (**Figure 8**). Post-operationally, the patient was treated with AI regimen in combination with Endostatin (pegylated liposomal doxorubicin 20 mg/m^2, days 1 + ifosfamide 1.5 g/m^2, days 1 through 4 + Endostatin 30 mg days 1 through 7) for six cycles. She achieved complete response in the ninth month after operation (**Figure 9**). The follow-up is still on-going.

Discussion

Primary cardiac angiosarcoma remains the most frequent primary sarcoma in adults ranged from 30 to 40 years old. Approximately 90% of angiosarcomas occur in the right atrium and most of them are asymptomatic, which are

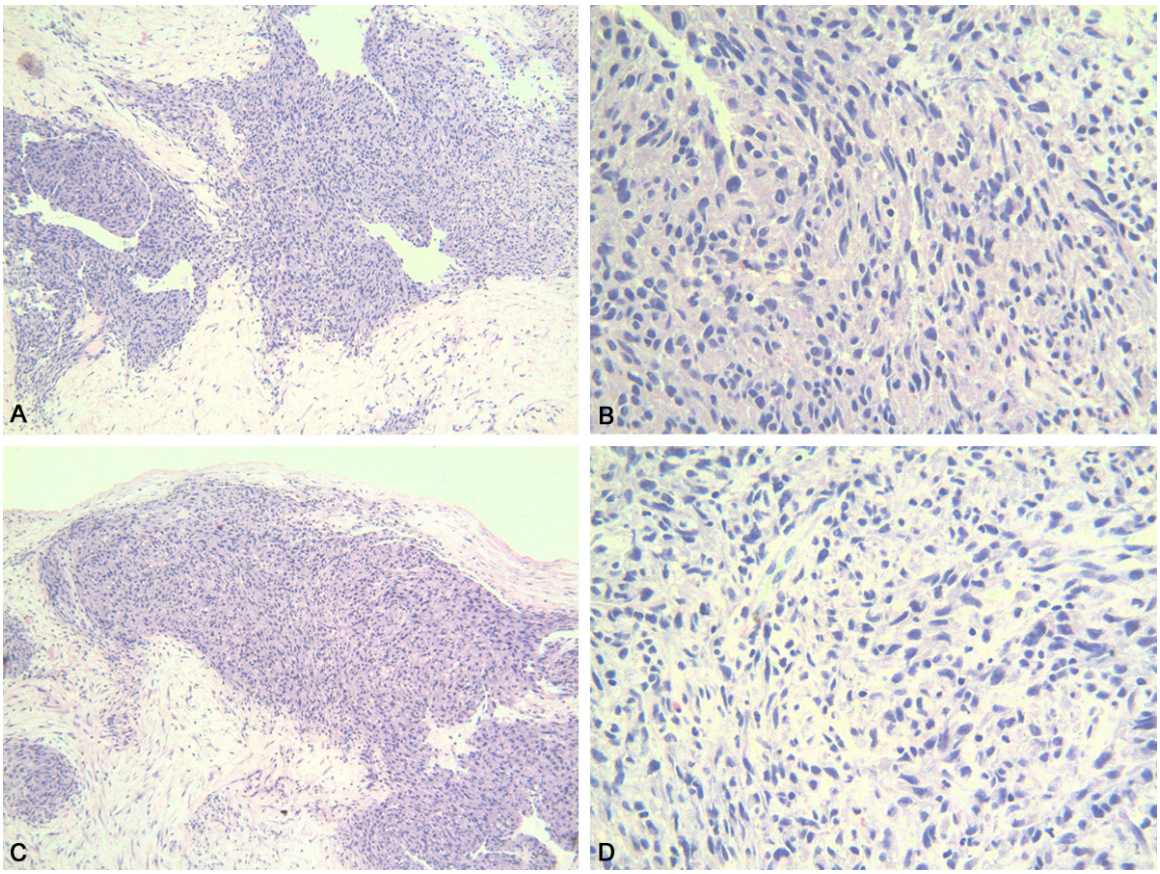

Figure 2. Histology examination of the cardiac angiosarcoma with HE staining. A scattered spindle-cell morphology was shown (A, C × 100, B, D × 400, HE staining).

often diagnosed in the advanced stage [9-13]. The patient reported in the current paper had a right atrial angiosarcoma arising from the region of the inferior vena cava, which has been particularly rarely reported previously [14]. To the best of our knowledge, only one case described the involvement of the inferior vena cava by an angiosarcoma from literatures with the searching keywords of "angiosarcoma" AND "inferior vena cava" in various databases, including PubMed, Web of Science, EMBASE, Science Direct, Wiley Online Library, Ovid, Cochrane Central Register of Controlled Trials, LILACs and Google Scholar, and the Chinese CNKI, VIP, CBM and WanFang databases. This was an angiosarcoma of the inferior vena cava with extension into the right atrium and right renal vein, which had the presenting symptom of hematuria reported by Lang EK et al [14] (**Table 1**). However, the right atrial angiosarcoma arising from the region of the inferior vena cava has not been available in the literatures.

Most of cardiac angiosarcomas were once found only at postmortem examination. Recently, modern echocardiography and high resolution tomographic imaging including CT and magnetic resonance tomography have enhanced the diagnostic abilities for cardiac angiosarcomas. However, most of the cases will miss the early diagnosis, which may lead to a poor prognosis of this highly aggressive malignant neoplasm [15, 16]. As the current case showed, echocardiography might be particularly valuable in describing the size, morphology, and origin of a cardiac tumor. However, the patient had already extensive metastases to the pericardium, right ventricle and cardiac facies diaphragmatica when CT and color Doppler echocardiography were performed.

The CT and echocardiography could assist the finding of a cardiac tumor; even so, the final confirmation of an angiosarcoma relies on pathology analysis. Histologically, the tumor cells in the current case were pleomorphic, spindle

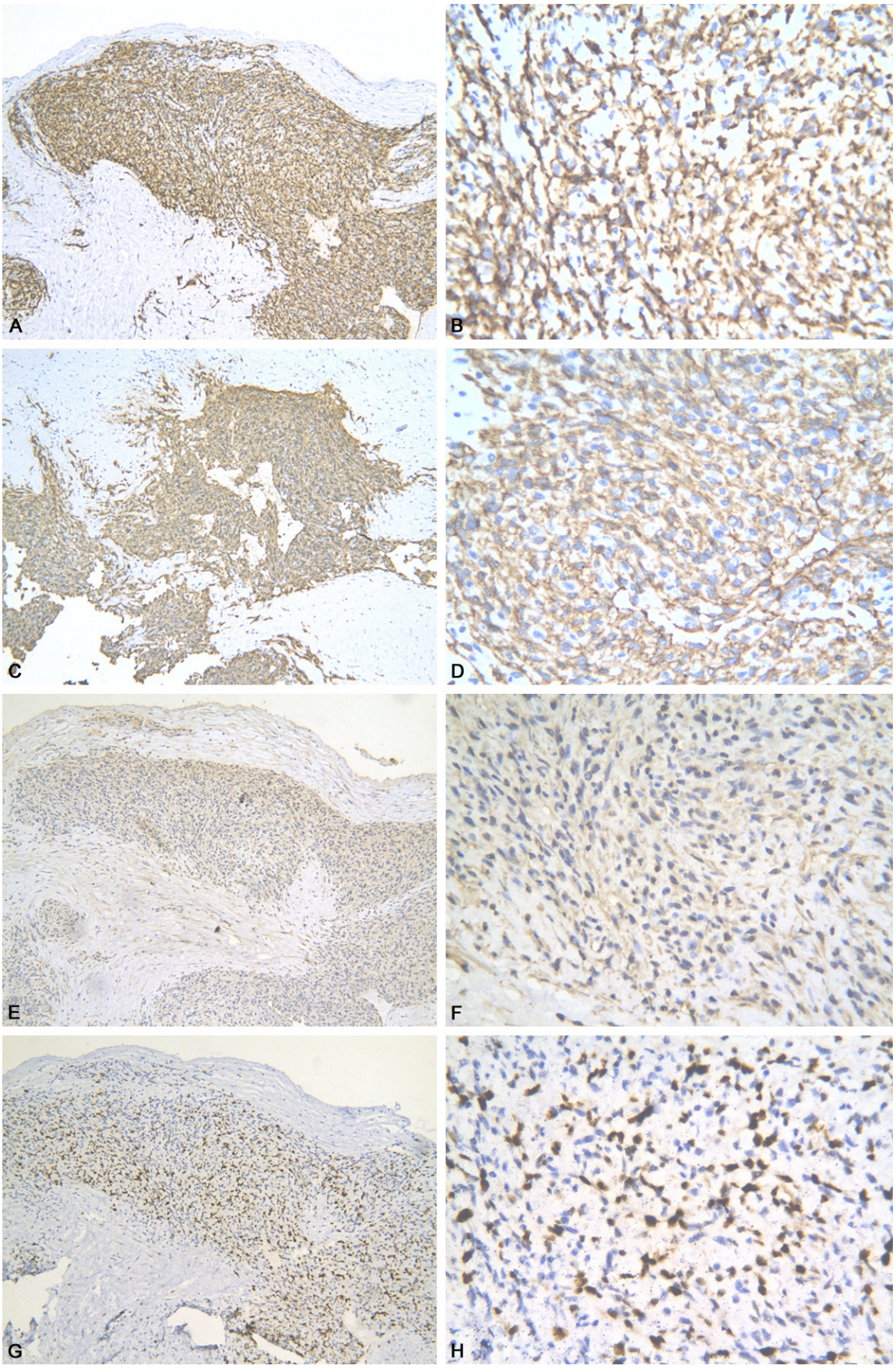
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Figure 3. Immunohistochemical examination of the cardiac angiosarcoma. Positive immunohistochemistry staining was presented for CD31 (A × 100, B × 400), CD34 (C × 100, D × 400), Vimentin (E × 100, F × 400) and Ki-67 (G × 100, H × 400).

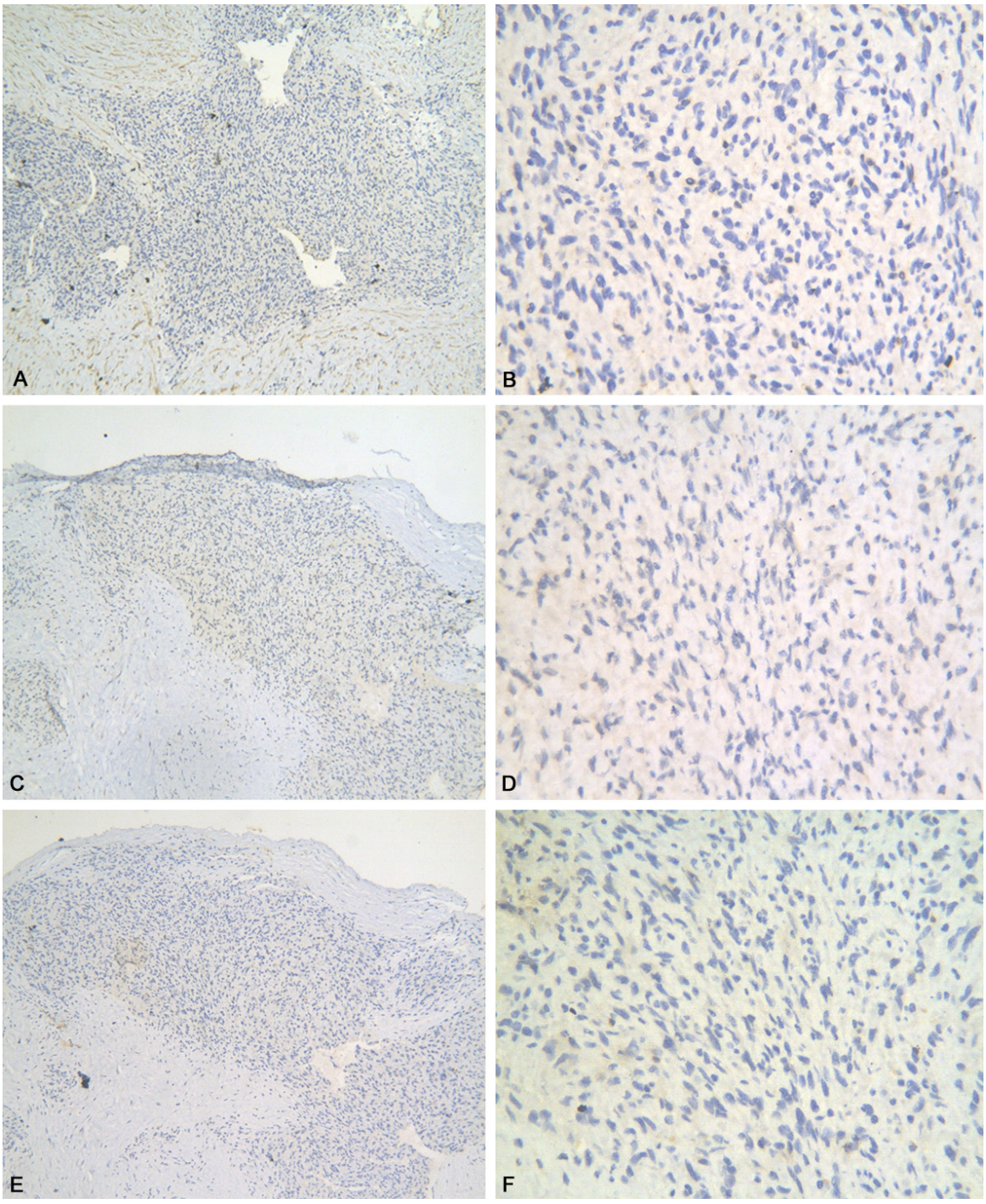

Figure 4. Immunohistochemical examination of the cardiac angiosarcoma. Negative immunohistochemistry staining was presented for Actin (A × 100, B × 400), Calretinin (C × 100, D × 400) and CD56 (E × 100, F × 400).

shaped and poorly differentiated. The negativity of a series of immunohistochemical biomarkers could exclude carcinoma, lymphoma, neuroendocrine neoplasm, and mesothelial sarco-

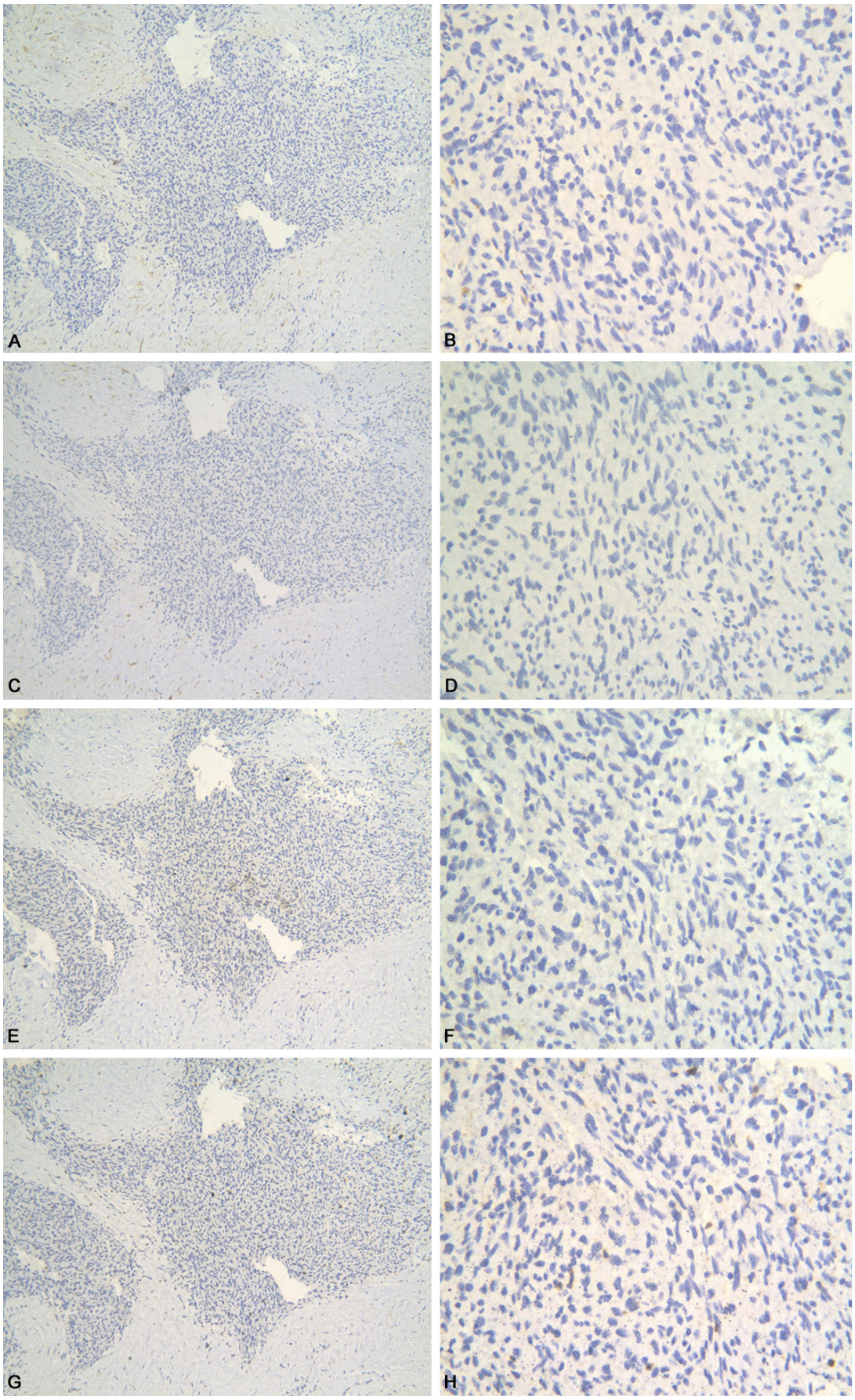
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Figure 5. Immunohistochemical examination of the cardiac angiosarcoma. Negative immunohistochemistry staining was presented for CK (A × 100, B × 400), Desmin (C × 100, D × 400), EMA (E × 100, F × 400) and LCA (G × 100, H × 400).

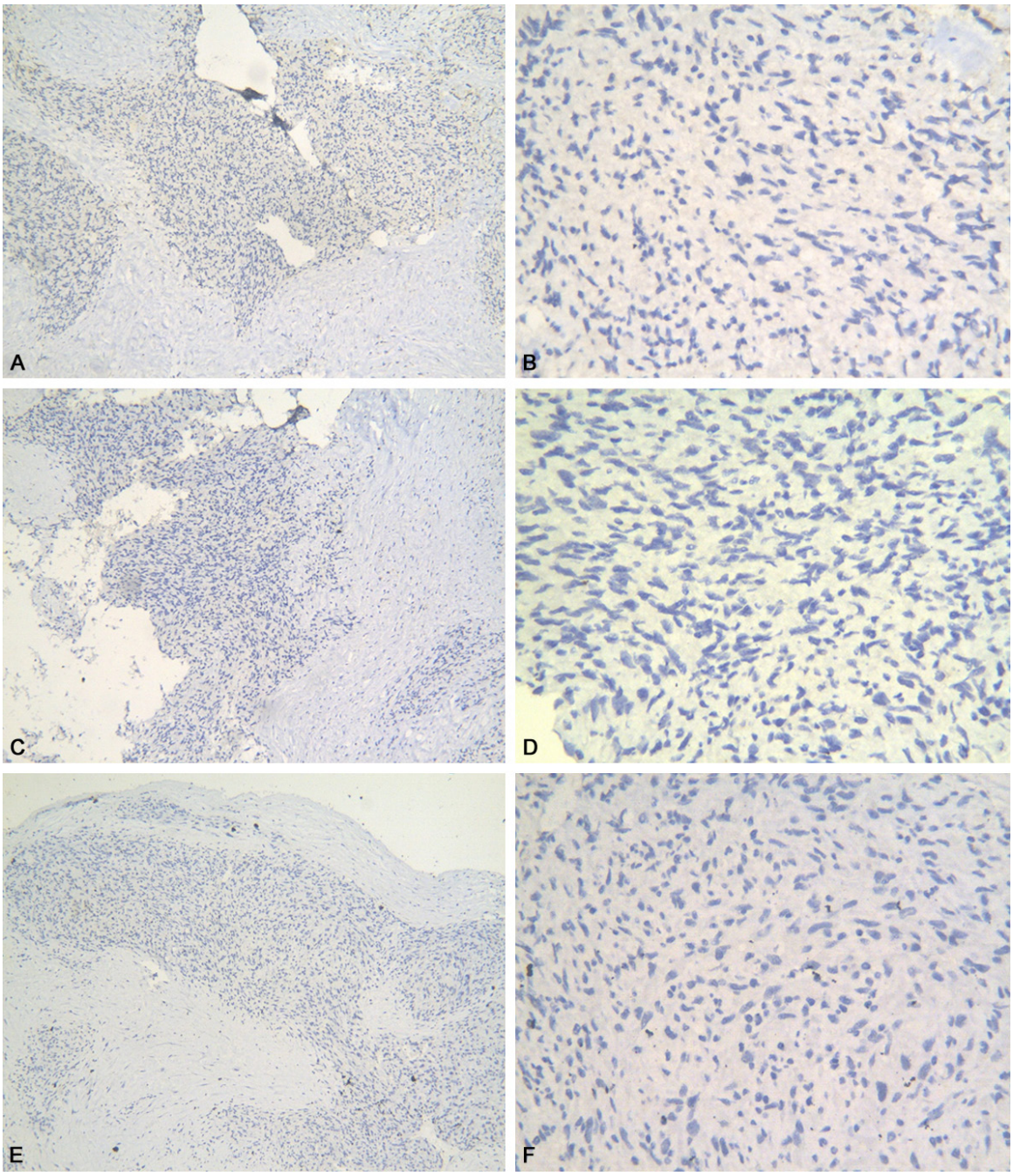

Figure 6. Immunohistochemical examination of the cardiac angiosarcoma. Negative immunohistochemistry staining was presented for MC (A × 100, B × 400), MyoD1 (C × 100, D × 400) and NSE (E × 100, F × 400).

ma, synoviosarcoma, rhabdomyosarcoma and leiomyosarcoma. The positivity of CD31, CD34, and Vimentin of the tumor cells provided a hint that this tumor was originated from vascular tissues. Since molecular cytogenetic analysis of intimal sarcomas shows amplification of MDM2 [17]. The absence of amplification of MDM2 in the current case detected by FISH

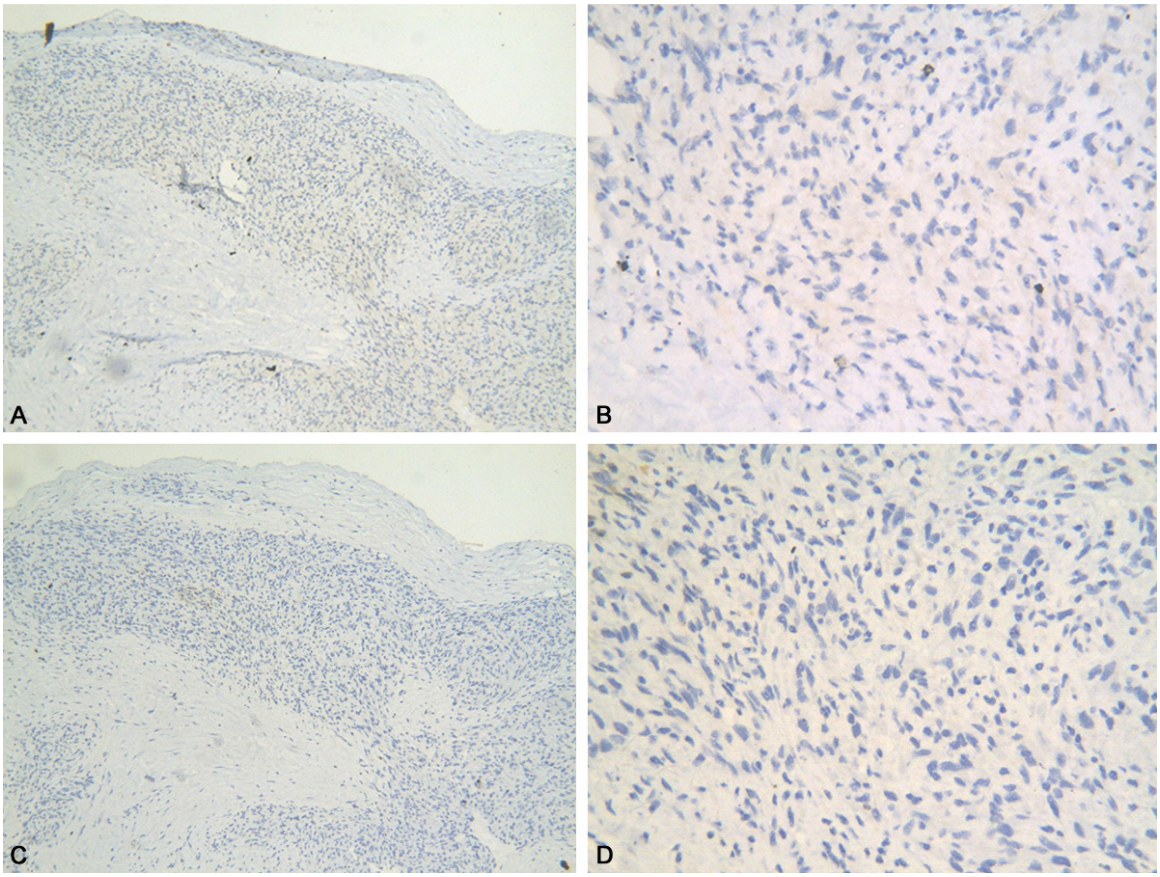

Figure 7. Immunohistochemical examination of the cardiac angiosarcoma. Negative immunohistochemistry staining was presented for P63 (A × 100, B × 400) and S-100 (C × 100, D × 400).

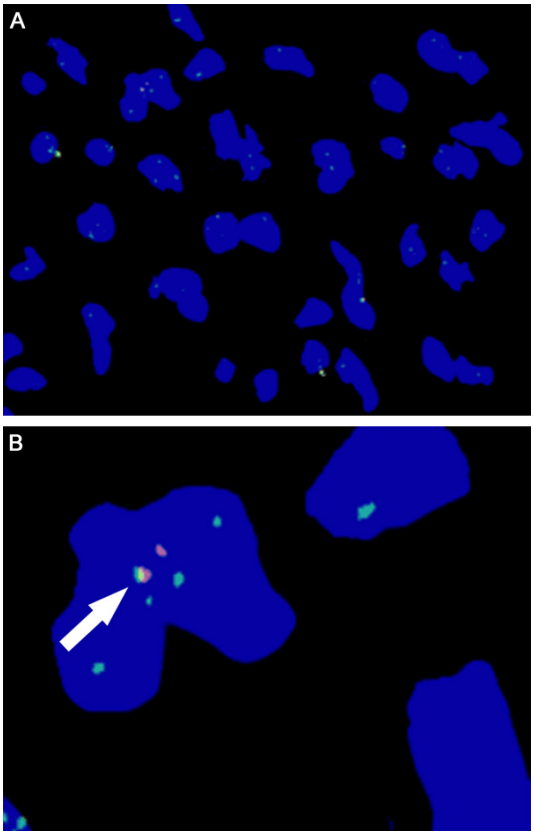

Figure 8. MDM2 amplification of the cardiac angiosarcoma in both low (A) and high (B) magnification. MDM2 amplification of the sarcoma tissues detected by FISH was negative.

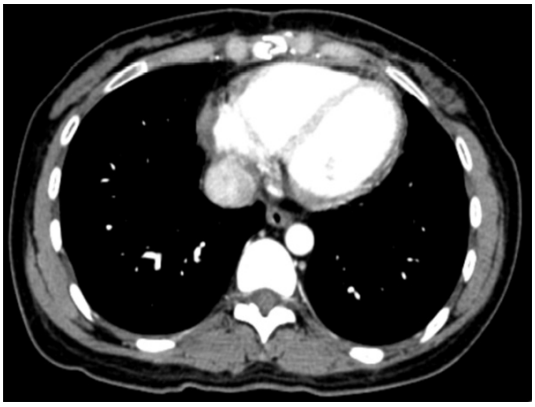

Figure 9. Radiological findings of the current patient after treatment. Computed tomography (CT) showed that no cardiac abnormal strengthening signals could be detected and the patient achieved complete response in the ninth month after operation.

supports the final diagnosis of an angiosarcoma.

Table 1. Summary of angiosarcoma of inferior vena from literatures

Title	PMID	Diagnose	Age	Sex	Treatment	Outcome
Primary angiosarcoma of inferior vena cava extending to right atrium: A case report	Current study	Primary angiosarcoma of inferior vena cava extending to right atrium	32	Female	Surgery, AI regimen in combination with Endostatin	The patient achieved complete response in the ninth month post operation. The follow-up is still on-going.
Hematuria: the presenting symptom of an angiosarcoma of the inferior vena cava	19765748	The angiosarcoma of the inferior vena cava with extension into the right atrium and right renal vein	41	Male	Not mentioned	Not mentioned

The prognosis of cardiac angiosarcoma is generally poor, with the survival time ranging from 6 to 12 months after being diagnosed [18-21]. Endostatin, which is a C-terminal proteolytic fragment of collagen XVIII with the length of 20-kDa, acts as an endogenous suppressor of angiogenesis. Thus, Endostatin plays a pivotal role of the extracellular matrix in inhibition of neoangiogenesis. Furthermore, Endostatin hinders angiogenesis via several signaling pathways influencing both cell growth and migration. Endostatin also restrains genes related to cell cycle control and anti-apoptosis in proliferating endothelial cells, therefore causing eventual cell death [22-26]. Endostatin combined with chemotherapy has scarcely been applied in the treatment of angiosarcoma, except the study of Cui, et al [27]. Herein, the current case received Endostatin with AI regimen for six cycles and achieved complete response for nine months. However, new clinical study and investigation of the molecular mechanism of Endostatin on angiosarcoma is required in the future.

Conclusion

We report a rare case underlining a cardiac tumor, namely, primary angiosarcoma of the inferior vena cava extending to the right atrium. MDM2 amplification helps differentiate it from intimal sarcoma and treatment of Endostatin combined with chemotherapy will open a new perspective for the clinical setting of cardiac angiosarcomas.

Disclosure of conflict of interest

None.

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