



# Uncommon case of brain metastasis in a patient with a history of heavy smoking

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## ABSTRACT

Primary sarcomas of the aorta are extremely uncommon. Depending on histomorphology and immunohistochemical pattern, intimal sarcomas can show angiosarcomatous differentiation. Here, we describe the case of a 60-year-old woman with a primary intimal sarcoma of the aortic arch and signs of cerebral metastatic disease as the initial manifestation.

After the patient experienced the onset of severe headaches, ataxia, and left-sided weakness, magnetic resonance imaging showed several brain lesions. Histologic assessment of a brain biopsy specimen revealed a malignant tumour composed of large pleomorphic cells that were positive for pan-cytokeratin and CD10. Radiation to the brain did not significantly improve the patient's symptoms, and cranial computed tomography (CT) imaging revealed several metastases, indicating lack of response. Because of the patient's smoking history, the presence of central nervous system and skeletal metastases on combined positron-emission tomography and CT imaging, and the focal pan-cytokeratin positivity of the tumour, carcinoma of the lung was favoured as the primary tumour.

Despite chemotherapy with cisplatin and etoposide, the patient's neurologic symptoms and general condition deteriorated rapidly, and she died within a few days. At autopsy, an undifferentiated intimal sarcoma of the aortic arch was diagnosed. The primary tumour in the aorta consisted of large pleomorphic cells. Immunohistochemical analysis of the aortic tumour and brain metastases demonstrated diffuse positivity for vimentin and p53 and focal S-100 staining.

In summary, we report a challenging case of advanced intimal sarcoma of the aortic arch with brain and bone metastases at initial presentation. Our report demonstrates the difficulties in diagnosing and treating this disease, and the need for multicentre studies to accrue more patients for investigations of optimal therapy.

## KEY WORDS

Sarcoma, angiosarcoma, brain metastasis

## 1. INTRODUCTION

Primary sarcomas of the aorta are extremely uncommon. Depending on histomorphology and immunohistochemical pattern, intimal sarcomas can show angiosarcomatous differentiation; however, they more commonly correspond to high-grade malignant mesenchymal neoplasias, with variable myofibroblastic differentiation and, sometimes, other heterologous elements (for example, osteosarcoma)<sup>1</sup>. Fewer than 140 cases of aortic sarcoma have been described in the literature, and about 40 of those were classified as intimal sarcoma<sup>1-6</sup>. These tumours are found mostly in the abdominal aorta, and their clinical presentation depends on the precise site of occurrence<sup>2,3,7-9</sup>. A definitive diagnosis is often made only after surgery or even autopsy.

Here, we describe the case of a 60-year-old woman with a primary intimal sarcoma of the aortic arch, in whom signs of cerebral metastatic disease were the initial manifestation.

## 2. CASE DESCRIPTION

A 60-year-old white woman living on a houseboat in Kuala Lumpur, Malaysia, suddenly developed severe headaches, ataxia, and left-sided weakness. She had stopped smoking 5 years before presentation with those complaints; her husband remained a heavy smoker.

Magnetic resonance imaging showed several brain lesions throughout the right cerebral hemisphere and cerebellum. Subsequent imaging by combined positron-emission tomography and computed tomography (PET-CT) revealed a lytic lesion measuring 2×1.5 cm in the right scapula, but no obvious primary tumour. Histologic assessment of a brain biopsy specimen revealed a malignant tumour composed

of large pleomorphic cells, which immunolabeling showed to be positive for pan-cytokeratin and CD10, and negative for S-100, CDX2, synaptophysin, desmin, renal cell carcinoma antigen, and thyroid transcription factor 1. The proliferation index was 60%–70%.

A dedifferentiated sarcomatoid carcinoma of lung, thyroid, or kidney was postulated, and the patient underwent palliative whole-brain radiotherapy, receiving a total dose of 30 Gy in 10 fractions.

Clinical examination after radiotherapy showed only a mild improvement in the patient's neurologic symptoms. Another PET-CT scan detected fluorodeoxyglucose (FDG)-positive lesions in the right palatine tonsil (diameter: 9 mm) and in several lymph nodes [to the right, behind the processus spinosus of the second vertebral body of the neck (diameter: 12 mm); to the left, at cervical level III (diameter: 6 mm); to the right, retroclavicularly (6 mm); and mediastinal above the aorta (diameter: 11 mm)]. The right column scapulae, the middle third of the left clavicle, the left pubic bone, the colon descendens, and the sigmoid colon also showed FDG-positive osteolytic lesions. Further, the multiple lesions already known to be present in the right half of the brain were again detected, indicating at least partial nonresponse to radiotherapy [Figure 1(A)]. A biopsy of the tonsil showed no malignant cells.

The patient's condition worsened again, with progressive dizziness and headache. Imaging of the brain by CT showed multiple lesions suggestive of metastases, with central necrosis and surrounding edema in the right hemisphere and cerebellum [Figure 1(B)]. Given the large number of brain metastases and the prior radiation, local treatment options were exhausted. High-dose steroids were started, and systemic treatment was initiated.

Because of the patient's smoking history, the presence of brain and bone metastases, the FDG-positive mediastinal and supradiaphragmatic lymph nodes, and the focal pan-cytokeratin positivity of the tumour, carcinoma of the lung was favoured as the primary tumour. Notably, no FDG-positive lesions were detected within the soft tissue or large vessels on PET-CT.

Chemotherapy with cisplatin and etoposide, accompanied by anti-edema treatment with dexamethasone and mannitol, was initiated. However, the patient's general condition deteriorated rapidly, and she died within a few days.

At autopsy, an undifferentiated intimal sarcoma of the aortic arch, composed of cells similar to those seen in the brain metastases, was diagnosed. Tumour cells lined the intimal surface of the aortic lumen and infiltrated the media, causing a mural thrombus with thrombosis of the brachiocephalic artery and stenosis of the left carotid artery. The tumour cells could be found in both the mural thrombotic material and the intima and media of the aortic wall [Figure 2(B)].



FIGURE 1 Imaging of the patient. (A) Full-body combined positron-emission tomography and computed tomography. (B) Brain computed tomography.

Numerous metastases were seen in the right cerebrum and cerebellum, likely arising from tumour emboli originating at the truncus brachiocephalicus. A large serrated adenomatous polyp, without evidence of carcinoma or metastasis, was found in the colon. No lesions in the lung, kidneys, adrenal glands, or soft tissue were found. The tumour within the aorta was thus the only plausible primary tumour found at autopsy, its location providing an explanation for the metastases in the supradiaphragmatic lymph nodes, brain, and bones.

Microscopically, the brain metastases [Figure 2(A)] and the primary tumour in the aorta [Figure 2(C)] both consisted of large pleomorphic cells, with large pleomorphic nuclei and prominent nucleoli. Immunohistochemical analysis of the aortic tumour and brain metastases demonstrated diffuse positivity for vimentin and p53, and focal S-100 staining. Tumour cells were negative for glial fibrillary acidic protein, Mdm2, CD31, CD34, desmin, pan-mela, thyroid transcription factor 1, and cytokeratins 7 and 20 [Figure 2(A–C)].

### 3. DISCUSSION

Aortic sarcomas are more common in men (2:1 male-to-female ratio), and mean age at diagnosis is



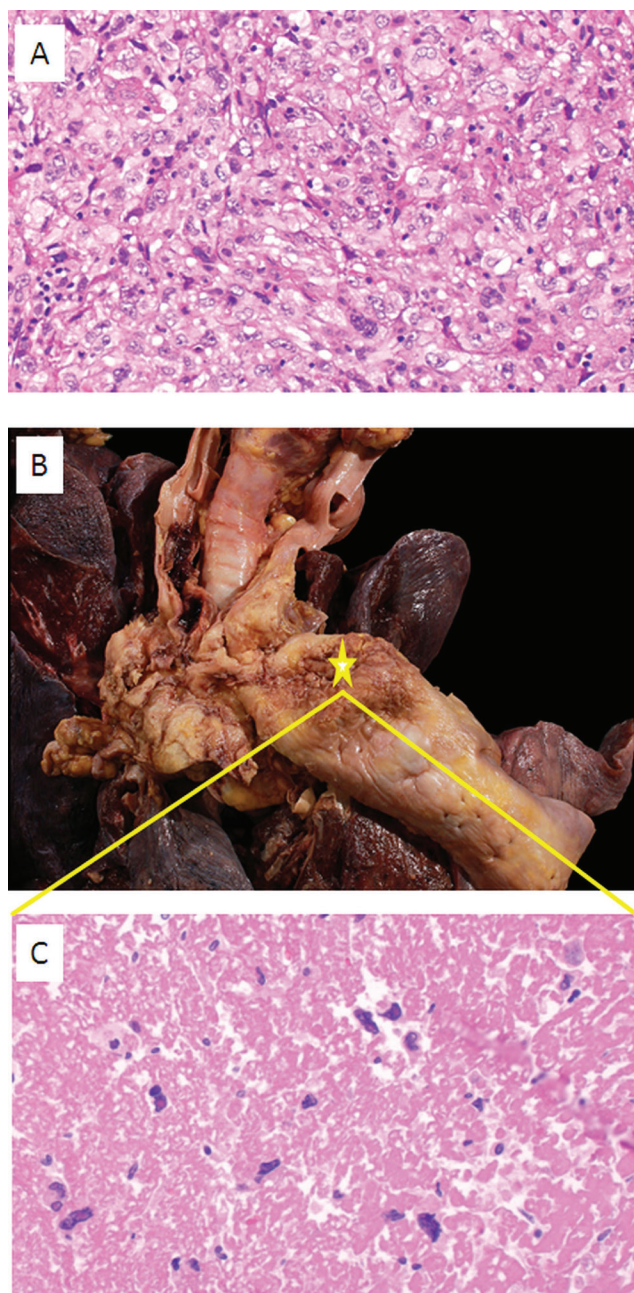


FIGURE 2 Histopathologic assessment of the patient's lesions. (A) Brain metastasis. (B) Autopsy specimen, showing location of the analyzed sample from the primary tumour. (C) Primary tumour.

60 years (range: 48–85 years)<sup>10,11</sup>. Here, we report a case of primary intimal sarcoma of the aortic arch in a 60-year-old woman. In the literature, fewer than 40 cases of this entity have been reported, and only about 10% have been located in the aortic arch<sup>1,2,6</sup>. The most common location is the abdominal aorta (about 40%), followed by the thoracic aorta (about 20%), the thoracoabdominal aorta (about 10%), and less commonly, the abdominal aorta and iliac or femoral artery (about 5%)<sup>1</sup>. Clinical presentation depends on the tumour

site. Most patients present with clinical symptoms attributable to embolic phenomena or vessel occlusion or obstruction<sup>2,3,7–9,12,13</sup>. Rarely, presentations such as cerebral infarction, deep-vein thrombosis, gastrointestinal hemorrhage, and ulcerated ischemic bowel have been reported<sup>10,14,15</sup>.

At time of diagnosis, metastatic disease is present in about 75% of patients<sup>3,11</sup>, and metastases preferentially occur in bone, lung, liver, spleen, kidney, and skin<sup>10,11</sup>. In our case, the patient initially presented with headache, ataxia, and hemiplegia because of numerous brain metastases. Although these clinical symptoms and metastases to brain are unusual, they can be explained by the localization of the primary tumour in the aortic arch.

The prognosis for patients with aortic sarcoma is poor because of the advanced stage at which the disease is diagnosed in most cases. Mean overall survival time is  $16 \pm 2.4$  months (range: 0–168 months), and the 3- and 5-year survival rates are about 11.2% and 8% respectively<sup>2,10</sup>. Our patient died about 2 months after presentation, an especially short survival time even for this type of disease.

The diagnosis of aortic sarcomas is challenging. Some studies suggest that magnetic resonance angiography with gadolinium is the most sensitive imaging method<sup>2,6,16,17</sup>. Magnetic resonance imaging might be of critical importance, because the tumour is often rather similar to an atherosclerotic plaque in CT imaging, and it is therefore often difficult to distinguish. Thus, to avoid a diagnostic delay when an aortic intimal sarcoma is suspected, magnetic resonance imaging might be the method of choice<sup>18</sup>.

Histologically, the diagnosis of intimal sarcoma is mostly a diagnosis of exclusion based on strict correlation with clinical presentation and imaging, because this tumour has no specific pattern of diagnostic markers. In a high percentage of intimal sarcomas (70%–80%), overexpression of the Mdm2 protein can be observed<sup>19,20</sup>; however, this finding is not specific, because many other tumours can also show this staining pattern.

Because of the low frequency of this disease, studies are currently unavailable, and therefore no standardized treatment protocols exist<sup>2</sup>. In the case of local disease without evidence of metastases, radical resection seems to represent the most effective therapeutic option. Chemotherapy or radiotherapy (or both) also appear promising for improving survival rates<sup>10,12</sup>. However, a large number of intimal sarcomas feature strong expression of platelet-derived growth factor receptor  $\alpha$  (PDGFRA) and of epidermal growth factor receptor, concurrent to PDGFRA activation. Further, activated PDGFRA and epidermal growth factor receptor frequently coexist with amplification and overexpression of the *MDM2* oncogene. Therapies that target PDGFRA, epidermal growth factor receptor, or Mdm2 in intimal sarcomas therefore seem to be a reasonable approach to this rare tumour entity<sup>19</sup>.

#### 4. SUMMARY

We report a challenging case of advanced intimal sarcoma of the aortic arch with numerous brain metastases and a single bone metastasis at initial presentation. Despite aggressive radiotherapy and chemotherapy, the patient died within a few weeks of presentation. This report clearly demonstrates the difficulties in diagnosing and treating this rare disease and the need for multicentre studies that will accrue more patients for investigations of optimal therapy.

#### 5. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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