Clinical Case Report

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Angiosarcoma in the chest: radiologic–pathologic correlation

Case report

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Abstract

Rationale: Angiosarcomas are rare, malignant vascular tumors.

Patient concerns: They represents about 2% of all soft tissue sarcoma, which can often metastasize through the hematogenous route. The radiological features have been analyzed in 4 patients with metastatic angiosarcoma in the chest.

Diagnoses: The main radiologic findings included nodules, cysts, nodules with halo sign, and vascular tree-in-bud. Morphologic features, as observed in the histologic specimen, have been correlated with radiologic appearance.

Lessons: Metastatic angiosarcomas to the lung are characterized by a wide variety of radiologic appearances that can be very characteristic. Computed tomographic findings observed include bilateral solid nodules, cystic, and bullous lesions sometimes associated with spontaneous hemopneumothoraces.

Abbreviations: AE1/AE3, CD31, CD34, CT = computed tomography, CVD = collagen vascular disease, H&E = hematoxylin and eosin, PE = pulmonary embolism, PET-CT = positron emission tomography – computed tomography.

Keywords: angiosarcoma of the atrium, case report, CD 31, halo sign, metastatic angiosarcoma, neoplastic thrombotic microangiopathy

1. Introduction

Angiosarcomas are rare, malignant vascular tumors, representing about 2% of all soft tissue sarcomas. The most frequently primarily affected sites include the heart, liver, breast, skin, and scalp, and they have a high rate of metastases to the lungs and, less commonly, liver, regional lymph nodes, and bone.[1]

Primary extrapulmonary angiosarcomas originating in the chest include those in the heart, aorta, or great vessels and, because of their rarity, are poorly characterized.[2–4]

They have a clinical presentation that can include dyspnea, chest pain, or syncope. Their radiological findings are characterized by filling defects occupying the lumen of great vessels, or thickening of one of the heart chambers.[4]

Pulmonary artery sarcomas may include an angiosarcomatous component, but often they show patterns of other soft tissue sarcomas and must also be distinguished from chronic pulmonary embolism (PE). The extravascular spread/invasion of the lesion and the heterogeneous enhancement of contrast medium in the mass occupying the lumen typically characterize this lesion. Pulmonary artery sarcoma can also be suspected in patients undergoing a computed tomography (CT) angiography with a low to intermediate probability of PE.[5]

On the contrary, metastatic angiosarcoma to the lung is much better characterized and may exhibit a wide variety of radiologic appearances.[6–9]

CT findings can include bilateral solid nodules[2] or cystic and bullous lesions sometimes associated with spontaneous hemopneumothoraces.[10–12] Tateishi et al[10] also described cystic lesions with air fluid level related to recent hemorrhage. In addition, they reported areas of ground glass attenuation related to areas of focal hemorrhage and nodules with miliary distribution.[10]

A distinctive feature in some metastatic angiosarcomas is a halo of ground glass change around nodules representing perinodular hemorrhage into alveoli, the so-called "halo sign."[13,14]

Most published series of metastatic angiosarcoma to the lung have detailed either the radiologic or pathologic changes. The aim of this report is to review the radiological-pathological correlation based on review of the literature and on 4 additional cases of angiosarcoma in the chest that we describe.

The clinical findings of the 4 cases are summarized in Table 1 and the radiologic features are summarized in Table 2.

An 84-year-old male (Patient 1), former smoker, with a prior history of gastric and prostatic cancer, both surgically resected,

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Table 1

Summary of the clinical data.

Pt	Age	Gender	Symptoms	Primary tumor site	Chest involvement	Metastasis/Outcome
1	84	M	Hemoptysis	Right atrium	Alveolar hemorrhage Nodules with halo (5–8 mm) Neoplastic thrombotic microangiopathy	Bone (7th right rib and sacrum) at diagnosis
2	55	M	Chest pain	Right foot	Alveolar hemorrhage Nodules with halo (8–15 mm) Right pleural involvement (15–75 mm)	Bone (cervical spine) after 2 years DOD 3 years later
3	47	M	Hemoptysis	Lung	Hemorrhage Consolidations (2–6 cm)	DOD 3 months later
4	50	M	Chest pain	Right upper limb	Nodules with halo (8–20 mm) Cystic lesions (9–24 mm) Bilateral hydropneumothorax Pneumomediastinum	DOD after 3 years from diagnosis

DOD = dead of disease, LTFU = lost to follow-up.

Table 2

Radiological features of pulmonary lesions.

Pt	GGO	Nodules with halo*	Consolidations†	Vascular tree-in-bud	Cysts§	Pleural lesions‡
1	Yes	No	No	Yes	No	No
2	Yes	Yes	No	No	No	Yes
3	No		Yes	No	No	No
4	No	Yes	No	No	Yes	No

* 8–20 mm measuring in size.
† 2–6 cm measuring in size.
§ 9–24 mm measuring in size.
‡ 15–75 mm measuring in size.

presented with a recent episode of hemoptysis. No other respiratory symptoms were present.

CT scan of the chest without contrast showed numerous tiny solid pulmonary nodules, measuring 2 to 5 mm in size, most of them in the periphery of the lung, forming a vascular tree-in-bud pattern. Furthermore, some slightly bigger lesions (measuring 5–8 mm) surrounded by ground glass ("halo sign") were also visible, mainly in the left upper lobe.

A mild smooth thickening of interlobular septa was also present in both lower lobes (Fig. 1).

No pleural effusion or adenopathy was present. Bone window settings showed an osteolytic lesion of the seventh left rib, with a complete erosion of cortical profile.

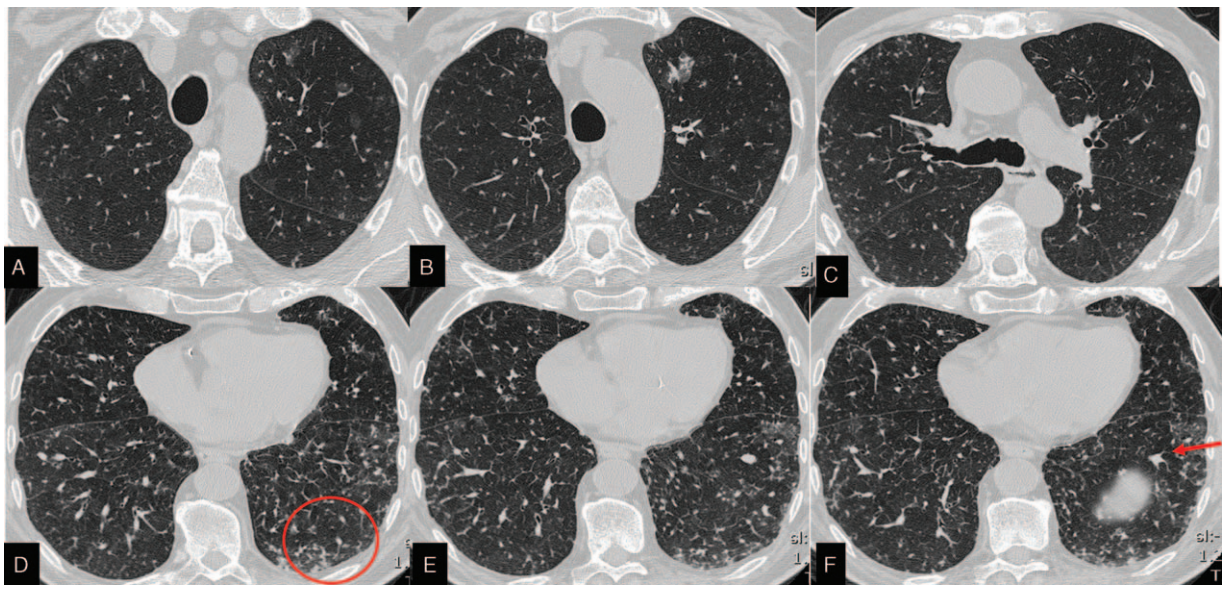

Figure 1. Patient 1. CT scan shows numerous bilateral tiny nodules mainly in the middle and lower zones of hemithoraces. Many of these nodules show a vascular tree-in-bud pattern related to neoplastic thrombotic microangiopathy (red circle). Moreover vascular branches are focally enlarged. This finding is particularly evident in the left lower lobe (red arrow). A mild smooth thickening of interlobular septa is also present in both lower lobes.

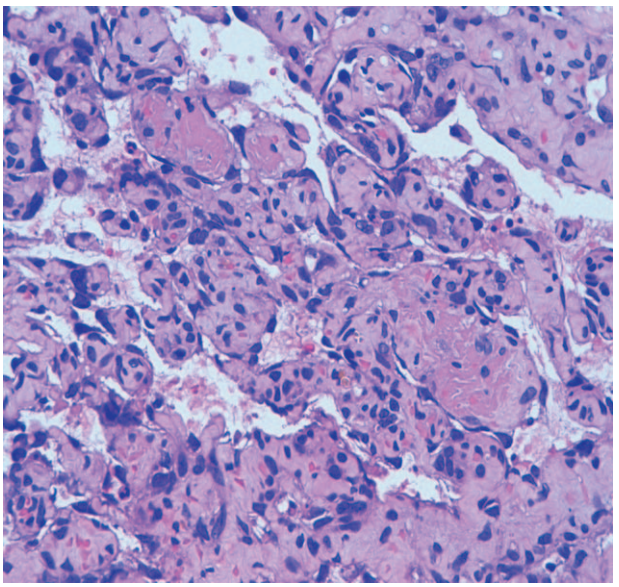

Figure 2. Patient 1. CT-guided biopsy of sacrum. H&E, midpower. Dissecting vascular channels lined by endothelial cells showing various degrees of cytologic pleomorphism and nuclear atypia.

Figure 3. Patient 2. PA Chest X ray. Presence of 2 contiguous opacities in the middle zone of right hemithorax, both subpleural and with an obtuse angle with the pleural margin, suggesting the feature of pleural lesions.

Differential diagnosis of these findings included a neoplastic thrombotic microangiopathy associated with one of his prior carcinomas, particularly gastric cancer.[15] The halo sign was considered unusual for metastatic gastric cancer. The bone lesion was not sclerotic (as would be typical for metastatic prostate carcinoma). The patient underwent PET-CT scan that showed 3 sites of uptake highly suggestive of neoplastic lesions located in the bone (seventh left rib and sacrum) and in the wall of right atrium. However, the numerous pulmonary lesions did not show any uptake, possibly because of their small size. The trans-oesophageal ultrasound confirmed the presence of a posterolateral thickening of the right atrial wall, with a homogeneous density and irregular margins, consistent with a neoplastic process. The patient underwent broncho-alveolar lavage (BAL) that showed evidence of chronic hemorrhage. Subsequently, a transbronchial cryobiopsy was performed in the lateral segment of left lower lobe, confirming the presence of multiple alveolar hemosiderin laden macrophages in airspaces and a mild lymphocytic infiltrate. No neoplastic cells were identified. The patient underwent CT-guided biopsy of sacrum that confirmed presence of angiosarcoma showing vasoformative regions and confirmed as endothelial in origin by immunohistochemistry (CD31) (Fig. 2).

A 55-year-old male (Patient 2) underwent resection of an enlarging mass of the right foot. The specimen showed an epithelioid neoplasm with positivity for CD31 and a focal positivity for cytokeratin AE1/AE3. CD34 was negative. The proliferative activity evaluated by Ki-67 antibody was about 60%. The histological findings were highly suggestive of epithelioid angiosarcoma. After a minor trauma, 1 month later, the patient presented to the Emergency Department because of an intense chest pain on the right side. Chest X-rays documented a large right pleural effusion, and no rib fractures were present (Fig. 3). Thoracentesis showed a hemorrhagic pleural effusion with reactive mesothelial cells seen cytologically. CT scan with contrast showed 2 adjacent parietal pleural lesions measuring 75 and 15 mm in greatest dimension, respectively (Fig. 4). These lesions had smooth margins and did not cause erosion on the ribs, whereas they completely obliterated the extrapleural space. In addition, moderate diffuse thickening of the pleura was visible in the whole right hemithorax. CT-guided biopsy of 1 of the lesions confirmed metastatic angiosarcoma (Fig. 5). Multiple sites of pathological uptake were then confirmed with PET-CT in the

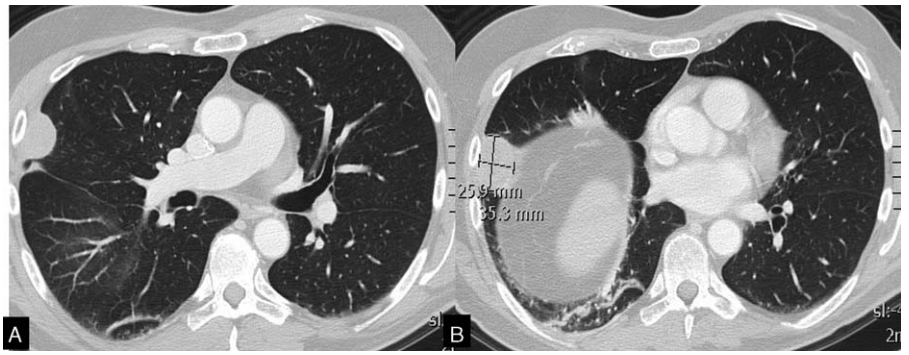

Figure 4. Patient 2. CT scan confirms the presence of 2 pleural lesions, the biggest one measures 2.6 × 3.5 cm and it is in the right middle lobe.

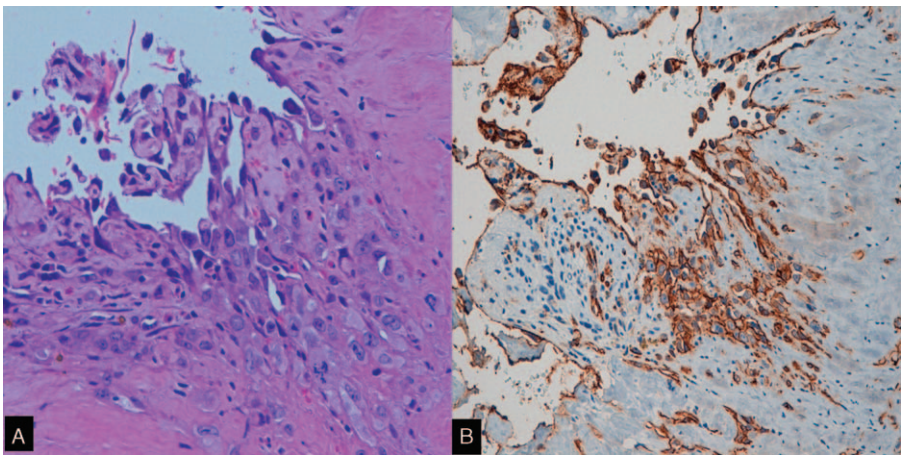

Figure 5. Patient 2. CT-guided biopsy of the pleural lesions. (A) Atypical, multilyering pleomorphic cells often forming tuft small papillae (H&E, midpower). (B) These cells are positive with the vascular marker CD31.

right hemithorax suggesting multiple secondary pleural metastases. Uptake was also visible in the right foot, suggesting a local recurrence.

The patient underwent radiotherapy to the right foot recurrence and the right pleural lesions. He also underwent several cycles of chemotherapy first with taxol and, afterwards, ifosfamide and epirubicin. The pleural lesions remained relatively stable.

Two years later, he developed osteolytic secondary lesions in the cervical spine at the level of C3 and C4 with invasion of the spinal canal for which he underwent radiotherapy and surgical stabilization.

One year later, 3 years after initial diagnosis, the patient showed multiple new bilateral pulmonary nodules with halo sign, measuring 8 to 15 mm in size consistent with metastases (Fig. 6). Two months later, he developed a severe worsening of respiratory symptoms and repeated CT angiography of the chest to exclude PE. Multiple areas of diffuse interlobular septal thickening were in association of crazy paving pattern related to diffuse alveolar hemorrhage (Fig. 7).

The patient died 10 days with progressive worsening of symptoms.

A 47-year-old male (Patient 3), truck driver, former smoker, presented with recent episodes of hemoptysis, in absence of dyspnea or chest pain. His medical history was noncontributory except for an allergic history and recurrent upper airway symptoms.

Chest CT scan of the chest showed several bilateral consolidations, ranging from 20 to 60 mm in size, most of them with a halo sign (Fig. 8). Laboratory data showed only a mild increase of C reactive protein (6.8 mg/L; normal value <5 mg/L) and erythrocyte sedimentation rate was normal.[12] PR3-anticytoplasmic autoantibodies, myeloperoxidase antibodies ANCA, anticardiolipin antibody IgG and IgM, and antibeta 2 glycoprotein 1 antibody IgM and IgG were negative. The patient underwent bronchoscopy with BAL.

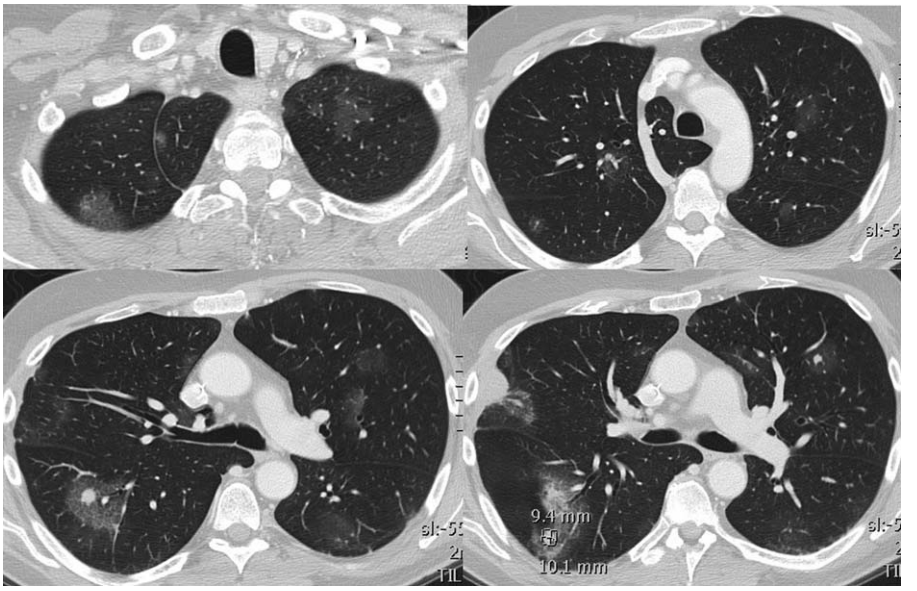

Figure 6. Patient 2. CT shows bilateral pulmonary metastatic lesions characterized by nodules with halo sign (the biggest measuring about 1 cm) and ground glass lesions.

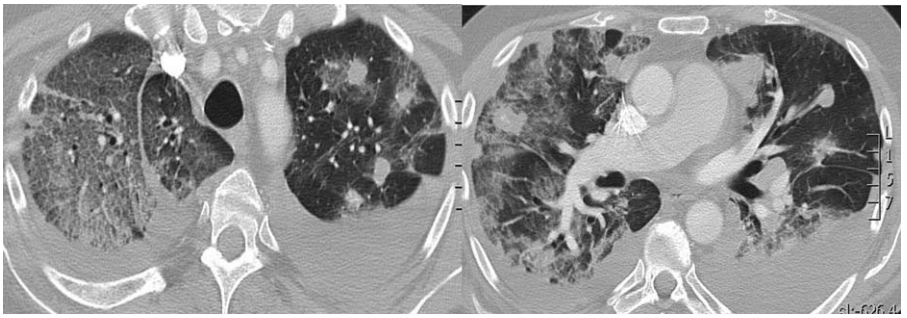

Figure 7. Patient 2. CT scan 2 months after the evidence of pulmonary progression shows the increase of pulmonary nodules, bilateral pleural effusion and wide ground glass attenuation, mainly in the right upper lobe.

BAL showed red blood cells and numerous hemosiderin laden macrophages; however, no neoplastic cells were identified.

CT-guided needle biopsy showed organizing pneumonia. In absence of serological or clinical data supporting the hypothesis of a CVD or vasculitis, a surgical lung biopsy was performed for diagnosis (Fig. 9).

This showed small pulmonary arteries with the lumen completely obliterated by CD31+ neoplastic cells that showed cytoplasmic vacuoles. The surrounding alveolar spaces were full of red cells and contained hemosiderin-laden macrophages. The findings were highly suggestive of metastatic angiosarcoma. Patient underwent PET-CT scan that confirmed the uptake of the multiple lesions in the chest. Moreover, the PET-CT identified a moderate uptake in the thyroid gland. However, ultrasound did not identify any focal lesion.

So, the final diagnosis was metastatic angiosarcoma. The biggest one, in the middle lobe, was considered the primary tumor. The patient died 3 months after the diagnosis in spite of the chemotherapy.

A 50-year-old male (Patient 4) presented to the Emergency Department with shortness of breath and chest pain. His clinical history record showed an amputation of the right upper limb and ipsilateral scapula for soft tissue angiosarcoma of the right arm, two years earlier.

CT scan of the chest showed bilateral hydropneumothorax with a large pleural effusion on the left side and smaller one on the right side. Furthermore, several cystic lesions (measuring from 9 to 24 mm in size) and solid nodules (from 8 to 20 mm) were present in the lungs bilaterally, suspicious of metastatic lesions (Fig. 10). The patient had a bilateral pleural drainage showing hemorrhagic fluid. His respiratory deterioration continued and

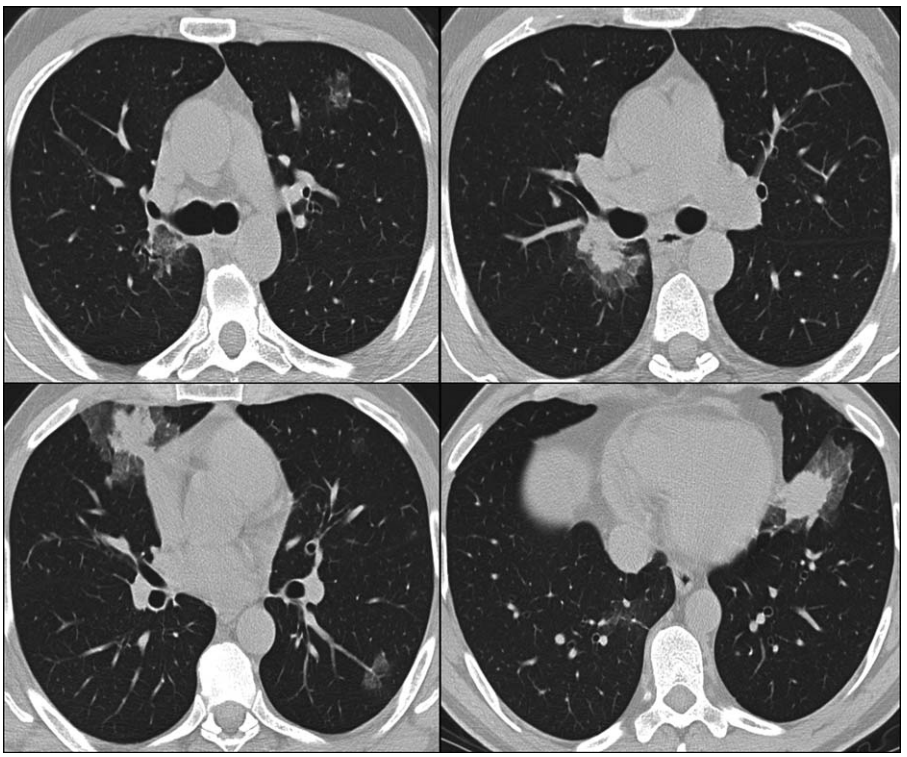

Figure 8. Patient 3. CT scan shows several consolidations with halo sign, the biggest in the right middle lobe. Some ground glass lesions are also present; the biggest in size is in the posterior segment of right upper lobe.

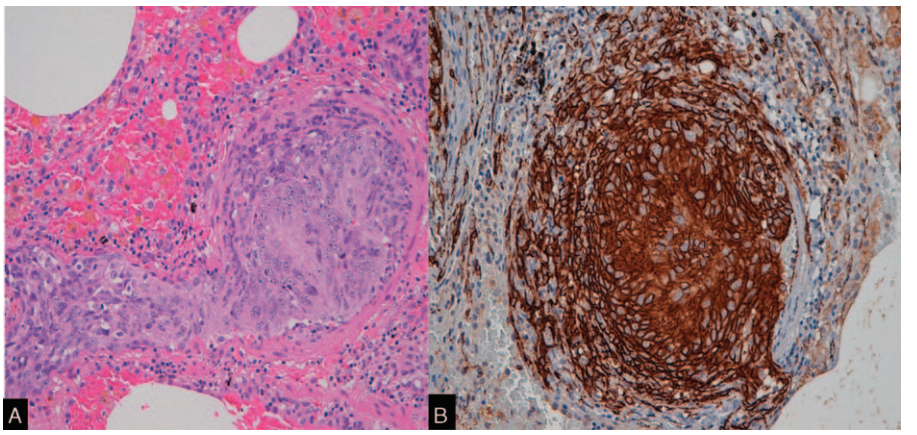

Figure 9. Patient 3. Surgical lung biopsy. (A) A small pulmonary artery has the lumen completely obliterated by neoplastic cells. The surrounding airspaces are filled by red cells and hemosiderin laden macrophages (H&E, midpower). (B) These cells show strong CD 31 positivity.

he developed worsening subcutaneous emphysema. CT scan confirmed widespread subcutaneous emphysema and associated pneumomediastinum (Fig. 11). Three weeks later, the patient had partial resolution of the hydropneumothorax and pneumomediastum, and some of the pulmonary pre-existent nodules had become cystic and the pre-existing cysts were bigger (Fig. 12). The patient died 2 months later of progressive disease.

2. Proposal for radiologic and pathologic correlation

The key features of metastatic angiosarcoma in the lung can be summarized as high variability of radiologic manifestations dependent on the extent of growth in the vessel lumen, the extent of (typically perivascular) nodule production, and the presence and extent of associated (usually perinodular) alveolar hemorrhage.

Considering the findings described in the literature (Table 3)[16–18] and those that we have observed on CT scans in the 4 patients described, we can delineate a correlation with pathologic changes summarized in Table 4 and as follows:

1. Ground Glass Opacity (GGO). The radiologic findings of a diffuse or patchy ground glass attenuation were histologically characterized by areas of extended or focal alveolar hemorrhage, as was present in Patient 3, and, in the advanced

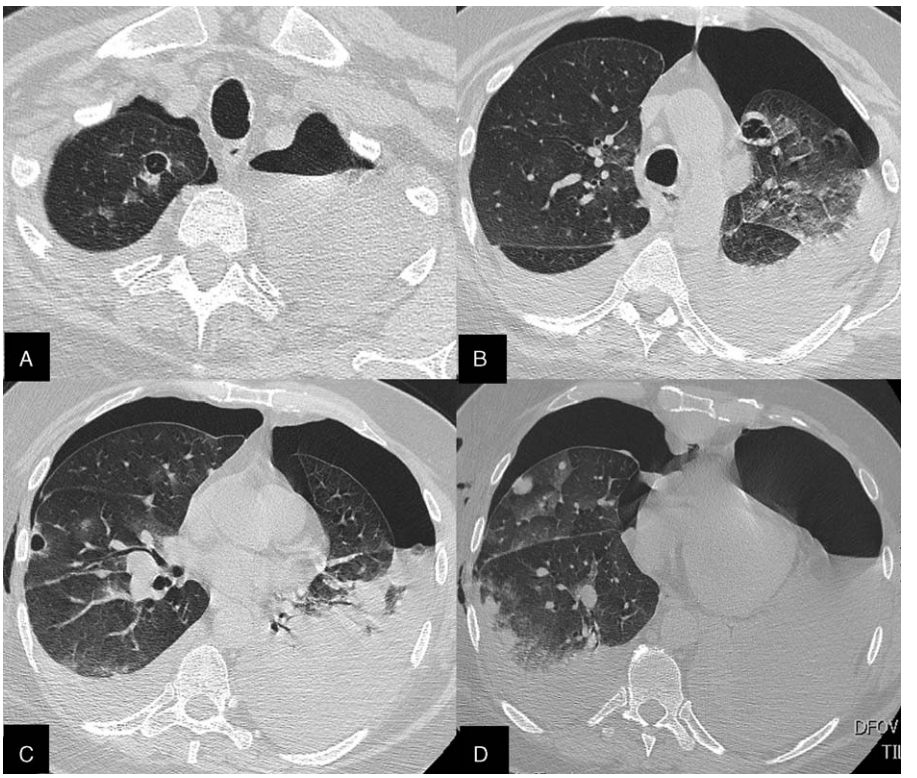

Figure 10. Patient 4. CT scan shows bilateral cysts, some of these with thick wall as in the anterior segment of left upper lobe. Some solid nodules are also present, particularly in right middle and lower lobe. Both the cystic lesions and nodules are suspicious of metastatic lesions. Bilateral hydropneumothorax is present.

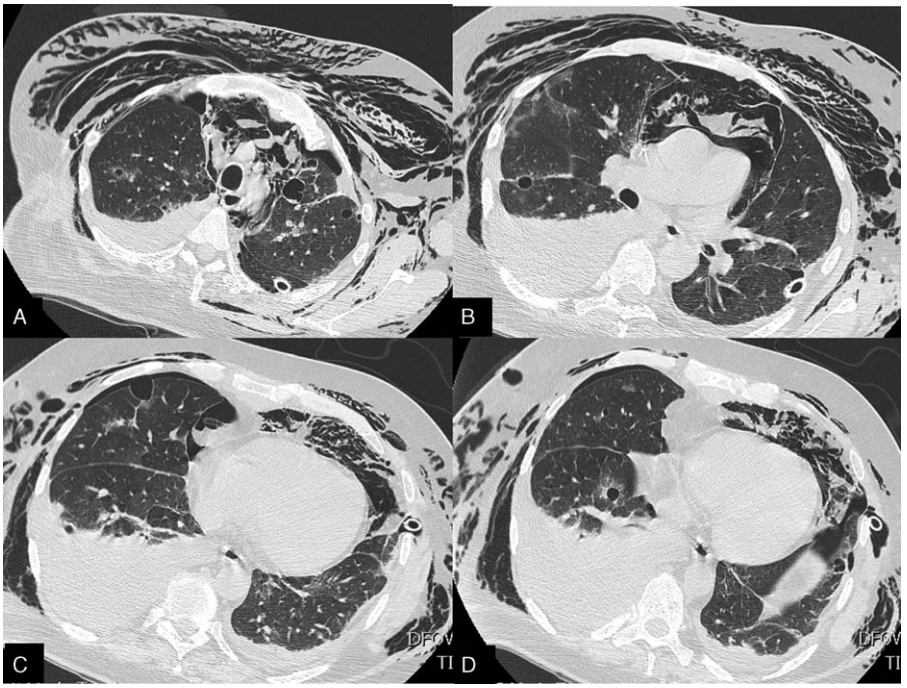

Figure 11. Patient 4. CT scan shows left plural drainage and the onset of bilateral severe subcutaneous emphysema. Pneumothorax is significantly reduced, remaining bilaterally in a small size. A small bilateral pneumothorax and pneumomediastinum are also present.

phase of Patient 2. This pattern may present clinically as a diffuse alveolar hemorrhage syndrome.[6]

2. Nodules (often) with halo. Metastatic pulmonary nodules with a halo sign corresponded to lesions with alveolar hemorrhage in the surrounding parenchyma. This finding also justified the presence of wide areas of ground glass attenuation surrounding also tiny (less than 6 mm) nodules. This appears to be the most common pattern in the literature; some cases may mimic pulmonary emboli.[6,10,14,19]
3. Consolidation. When solid metastatic lesions enlarge, like in Patient 3, they can become consolidative usually without air bronchograms. The halo sign may be present. The presence of associated organizing pneumonia may also partially explain the consolidated appearance. Furthermore, the focal dilatations of bronchi peripherally to the lesions could be related to a postobstructive bronchial dilatation. This finding is relatively uncommon, with a single report describing consolidation as a secondary lesion.[19]
4. Cysts. In the relatively advanced lesions, the alveolar walls are disrupted and cystic lesions can develop, sometimes very quickly. This is particularly remarkable, if we consider Patient 4, in which solid lesions evolved into cystic lesions in only 3 weeks. The immediate consequence of this evolution is represented by complications such as pneumothorax and pneumomediastinum, particularly when cysts are beneath the pleura. Even though only few reports describe cysts as secondary lesions,[12,14,16,17] they may explain pneumothorax as a manifestation of metastatic angiosarcoma.[1]
5. Tree-in-bud. The diffuse tree-in-bud pattern was observed in our first case; the airways were not involved as shown by transbronchial cryobiopsy. This is not surprising, if we consider that all the lesions were located inside the arteriolar

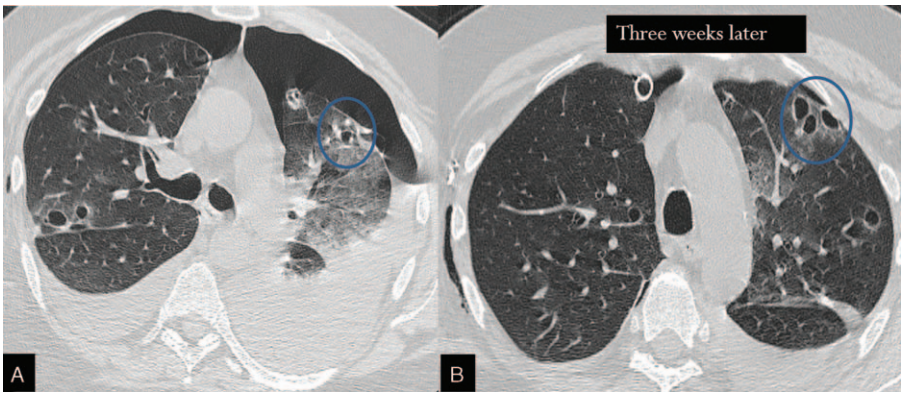

Figure 12. Patient 4. Comparison between baseline CT scan and control 3 weeks later shows that the cystic lesions are bigger and more numerous than the prior, suggesting a rapid disease progression. Moreover, nodules that were visible in the prior examination now have a cystic shape (blue circle). Informed consent from patients was obtained.

Table 3

Summary of literature on radiologic findings of secondary lesions from angiosarcoma.

Articles	Authors	Radiologic findings	Cases no.	Ref. no.
1	Patel and Ryu[2]	Nodules (0.5–3 cm) Linear infiltrates Diffuse "alveolar" Pneumothorax	15	2
2	Adem et al[7]	Bilateral infiltrates	7	7
3	Bocklage et al[1]	Nodules* Bilateral infiltrates Bilateral ground glass pattern Pneumothorax Percardium effusion	21	1
4	Tateishi et al[10]	Nodules (6–30 mm) Nodules with halo* Solitary nodules (mean size: 26 mm) Ground glass attenuation Miliary spread Linear opacities	24	10
5	Chen et al[16]	Cysts Nodules* Bilateral pneumothorax	1	16
6	Rai et al[6]	Nodules with halo* Ground glass opacities	1	6
7	Chen et al[9]	Nodules* Right pleural involvement	2	9
8	Somasekharan Nair et al[17]	Cysts Pneumothorax	1	17
9	Fiorelli et al[8]	Bilateral nodules (5 mm to 4 cm)	1	8
10	May et al[12]	Cysts Pneumothorax	1	12
11	Demirag et al[18]	Bilateral nodules* Mass (6.5 cm)	1	19
12	Aversa et al[19]	Nodules with halo* Consolidations	1	21
13	Yogi et al[14]	Nodules (3–16 mm) Cysts (4–27 mm) Nodules with halo Pleural effusion Pneumothorax	33	14

* Size not reported.

lumen, suggesting a neoplastic trombotic microangiopathy. The anatomic localization of the primary tumor in the right atrium probably facilitated the endovascular spread of the neoplastic emboli. The literature includes only 1 report of metastatic angiosarcoma-induced thrombotic microangiopathy; tree-in-bud change is not mentioned.[20] It could be argued that this finding is just tumor emboli filling the arteries and not truly thrombotic in pathogenesis.

3. Discussion

Angiosarcomas, although rare entities, represent the most common histologic subtypes of primary tumors in the heart, and tumors of the great vessels of the chest.

Because of the propensity of angiosarcoma to involve the right atrium, patients may present with right-sided heart failure and lung metastases. In addition, regardless of the primary site, the most frequent sites of metastatic spread from an angiosarcoma are in the chest. In this report, we have reviewed our experience of 4 cases of angiosarcoma in the chest, matching clinical, radiological, and pathological data and comparing them with the literature.

From a review of literature (Table 3) and of our group of patients, we have identified 4 main radiological patterns of lung metastasis: alveolar hemorrhage, nodules with halo sign, masses, and cysts. From these 4 findings, other possible complications can arise, including pneumothorax, hydropneumothorax, and pneumomediastinum. Our observations show a concordance with larger series already published[14]: significant representation of nodules with halo sign; the halo sign representing surrounding alveolar hemorrhage from these highly vascular neoplasms involving pre-existing vessels in the lung.

The halo sign is one of the most important findings for suspecting metastasis from angiosarcoma; it may occur even around very small nodules as illustrated in Patients 1, 2, and 3. Moreover, bilateral patchy ground glass attenuation alone can be present, likely due to alveolar hemorrhage, as we observed in the advanced stage of the Patient 2 or as focal lesion in Patient 3.

A relatively rare finding in metastatic angiosarcoma to the lung is represented by large consolidations; in the literature, only 2 cases have been reported.[19] In our case, we observed the coexistence of organizing pneumonia, as demonstrated in the first nondiagnostic biopsy in Patient 3. Case 3 showed an interesting ancillary finding: focal bronchial dilatation in the periphery of the lesions, likely related to postobstructive bronchiectasis.

Another uncommon finding in metastatic angiosarcomas to the chest is pleural involvement as was present in Patient 2. Only 1 case in literature[9] reported pleural involvement.

Of anecdotal interest is the fact that pleural lesions showed a relative stability after radiotherapy and chemotherapy, for about 3 years, at which time the patient dramatically progressed in the bone and lung.

With regard to the other radiologic findings, on the basis of Patient 4 history, we may also infer the natural history of cystic metastases of angiosarcoma in the lung. Secondary nodules with halo sign rapidly evolved to cysts, and cysts may rupture and lead

Table 4

Radiologic–pathologic correlation.

List	Radiologic finding	Pathologic correlation
1	GGO	Hemorrhage
2	Nodules	Secondary lesion
3	Nodules with halo sign	Secondary lesion with hemorrhage in the surrounding parenchyma
4	Consolidation with halo	Lesions with foci of organizing pneumonia and hemorrhage in the surrounding parenchyma
5	Cysts	Cavitation of the initial secondary nodule
6	Tree-in-bud	Tumor thrombotic microangiopathy

GGO = ground glass opacity.

to pneumothorax and pneumomediastiun,[16,17] and if blood also leaks out, a hemorrhagic pleural effusion and hydropneumothorax may be encountered. Pleural effusion without pneumothorax may also be seen as, in Patient 2, and in the case described by Chen et al.[9] In the literature, 4 mechanisms have been proposed for the genesis of cystic metastases, including excavation of a solid nodules, infiltration of tumor of preexisting bullous lesions, distension through the ball-valve effect of the tumor, and tumor cell proliferation to form blood-filled cystic spaces.[10,18]

In our case 1, we identified small centrilobular nodules with tree-in bud pattern, which did not involve airways, and was consistent with of endovascular and perivascular spread/growth of small tumor emboli.

With regard to metastatic angiosarcoma, this finding has been described in literature only by Demirag et al[18] who identified pulmonary thrombotic tumor microangiopathy (PTTM) from metastatic epithelioid angiosarcoma solely as a histologic finding, in absence of tree-in-bud pattern on CT scan.

The tumor thrombi within small arteries and arterioles and associated fibrocellular and fibromuscular intimal proliferation are histological features of PTTM. Their most common CT finding is represented by tree-in-bud pattern, as firstly described by Franquet et al.[21]

The most common tumors associated with PTTM are metastatic gastric adenocarcinomas and ovarian carcinoma.

In summary, clinical and radiologic presentation of angiosarcoma in the chest can be pleomorphic[10,19] and its rarity makes diagnosis challenging. Bocklage et al[1] enumerated several differential diagnoses in their series, including infection, metastatic tumor of unknown primary site, multiple pulmonary emboli, granulomatosis with angitis, Goodpasture syndrome, and idiopathic pulmonary hemorrhage.

In our series, differential diagnosis included several conditions. In the first case, the vascular tree-in-bud pattern was consistent with the hypothesis of neoplastic thrombotic microangiopaty; gastrointestinal tract tumor, pancreatic cancer, and metastatic angiosarcoma were the most probable diagnosis.

The second case had a radiologic presentation of localized pleural lesions. Knowing the primary tumor of the foot, pleural findings were highly suggestive of metastatic lesions of the pleura. Differential diagnosis also included loculated hemothorax following the prior trauma.

The third case showed bilateral ground glass and consolidations with halo sign. Differential diagnosis included poliangiitis with granulomatosis, angioinvasive aspergillosis, adenocarcinoma, Kaposi sarcoma, and angiosarcoma. Absence of specific clinical settings except for hemoptysis should be helpful in the suspicion of angiosarcoma.

The fourth case presented with bilateral hydropneumothorax associated with solid and cystic lesions in the lungs. These aspects are quite unusual and suggestive of a variety of neoplastic cystic lesions such as metastatic sarcomas, mesenchymal cystic hamartoma, and infections (cystic evolution of *Pneumocystis jirovecii* pneumonia). This case had similarities with the cases described by Yogi et al.[14]

In conclusion, our series shows that metastatic angiosarcoma in the chest may present with a variety of CT scan features and that these aspects are the result of specific morphologic lesions.

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