Angiosarcoma Identified by Diffuse Alveolar Hemorrhaging Associated with Disseminated Intravascular Coagulation

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ABSTRACT — Background. Primary angiosarcoma of the bone is an extremely rare form of vascular bone tumor, accounting for <1% of primary malignant bone tumors. Its histological findings are characterized by formation of anastomosing blood vessels lined by endothelial cells. It tends to involve the long, tubular bones of the extremities, and more than half of cases are found with metastasis, especially to the lung. Once metastasis to the lung has occurred, patients usually present with symptoms such as dyspnea, chest pain, and hemoptysis. Case. An 80-year-old woman was referred to our hospital for the further evaluation of abnormal X-ray findings of her right humerus, with only slight range of motion restriction. Upon arrival, she was also diagnosed with anemia, thrombocytopenia, and elevated D-dimer levels, which satisfied the criteria for disseminated intravascular coagulation. In addition, chest X-ray showed diffuse infiltrative shadows in both lungs, and chest computed tomography (CT) showed bilateral consolidation with ground-glass opacity. The further investigation of the lungs was prioritized over her shoulder pain, and bronchoalveolar lavage was performed. The fluid collected was fresh and blood-like and contained hemosiderin-laden macrophages, confirming the diagnosis of diffuse alveolar hemorrhaging. In addition, a biopsy of the right humerus was performed at the site where magnetic resonance imaging showed a destructive lytic lesion with irregular borders of fractured bone. Immunohistochemical staining revealed the tumor cells to be positive for cluster of differentiation 31 and 34 and negative for cytokeratin and thyroid transcription factor-1, and she was diagnosed with angiosarcoma. Conclusion. We herein report a rare case in which angiosarcoma was coincidently diagnosed in connection with diffuse alveolar hemorrhaging without CT findings suggesting lung metastasis. Neoplastic diseases should not be forgotten as differential diagnoses of diffuse alveolar hemorrhaging.

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KEY WORDS — Diffuse alveolar hemorrhaging, Angiosarcoma, Disseminated intravascular coagulation

INTRODUCTION

Angiosarcoma, a malignant tumor originating in vascular endothelial cells, is an uncommon subtype that accounts for <2% of all sarcomas.1,2 Although these tumors can develop in any organ of the body, only approximately 44% of all angiosarcomas have their primary site in the bone.1,3 Angiosarcoma arising in the bone commonly tend to involve the long, tubular bones of the extremities, particularly the femur and tibia, followed by the pelvis, vertebral column, and bones of the upper limbs.3 More than half of cases of angiosarcomas are found with metastasis, and the lung is the most common site involved in metastasis.2

Diffuse alveolar hemorrhaging (DAH) is a life-threatening condition that frequently presents with hemoptysis, shortness of breath, and a fever.1 It is associated with various conditions, such as immune disorders, connective tissue disorders, infectious diseases, and idiopathic diseases. However, it has rarely been associated

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with malignant neoplasm, such as angiosarcoma.\textsuperscript{5}

We herein report a case that was diagnosed as angiosarcoma, originating from the right humerus, with DAH as the pivotal presentation.

**CASE REPORT**

An 80-year-old woman with right shoulder pain was referred to our hospital for the further evaluation of abnormal X-ray findings of the right humerus. She had no additional medical history, except for a fracture in the right humerus that had been treated with open reduction and internal fixation 5 years ago. She was a non-smoker, consumed alcohol occasionally, and did not use illicit drugs.

At the time of admittance to the hospital, her blood pressure was 157/84 mmHg, pulse rate was 89 beats/min, transcutaneous oxygen saturation was 97% (room air), and body temperature was 36.8°C. A physical examination only revealed conjunctival pallor. A whole-body diagnostic work-up, including blood test, X-ray and magnetic resonance imaging (MRI) of the right shoulder, and chest-abdominal-pelvic computed tomography (CT), was performed. A hematological examination detected severe anemia, thrombocytopenia, and elevation of fibrinogen degradation product and D-dimer. Other laboratory findings, including the liver and kidney function; bleeding and clotting time; and antinuclear antibody, immunoglobulin and complement, antineutrophil cytoplasmic antibody, and β-D glucan levels, showed no significant abnormalities, except for increased serum lactate dehydrogenase and C-reactive protein levels. The levels of tumor markers, such as carcinoembryonic antigen, pro-gastrin-releasing peptide, and cytokeratin 19 fragment, were within normal ranges, except for soluble interleukin-2 receptor (Table 1). Based on the laboratory findings, she was diagnosed with disseminated intravascular coagulation (DIC).

No tubercle bacilli or fungi were found in the sputum. Chest X-ray performed at the time of admission showed diffuse infiltrative shadows in both lungs, and chest CT showed bilateral consolidation with ground-glass opacity (GOO), particularly localized around bronchovascular bundles (Figure 1a). Since there was only a small amount of pleural effusion, and given her DIC condition, we did not perform thoracentesis. However, since the estimated pulmonary artery pressure was 63 mmHg on echocardiography and there were no findings or data suggesting a hepatic, renal, or cardiac disorder, we assumed that the pleural effusion was due to pulmonary hypertension caused by a pulmonary lesion. In addition, MRI of the humerus showed areas of low T1-weighted and high T2-weighted signal intensity (Figure 2a, 2b). The pulmonary findings were considered in urgent need of management, and further investigations of the lungs were initiated.

Based on these clinical findings and laboratory data, DAH was deemed the most likely diagnosis. However, other possible diagnoses, such as infectious disease (viral, tuberculous, or *Pneumocystis jirovecii* pneumonia) and pulmonary proteinosis were also considered. Despite two weeks of antibiotic treatment, the patient’s symptoms persisted. Chest CT performed 15 days after admission revealed worsening of GOO and pleural effusion (Figure 1b). To determine the cause of the lung infiltrates, bronchoalveolar lavage (BAL) was performed, and the obtained fluid was fresh and blood-like, containing hemosiderin-laden macrophages and a total cell count of \(4.48 \times 10^6/\text{ml}\) with 58.5% macrophages; however, no acid-fast bacilli, fungus antigens, or *Pneumocystis jirovecii* microorganisms were detected. A cytological examination demonstrated no malignant findings (Table 1). A transbronchial lung biopsy was not performed because of the patient’s thrombocytopenia. Based on these findings, the diagnosis of DAH was confirmed.

Considering the clinical symptoms, laboratory data, and CT findings, several potential causes of DAH, such as collagen disorder and infectious disease, were immediately ruled out. The only remaining possible diagnosis was a malignant neoplasm. As there was no evidence of a malignant neoplasm, \(^{67}\)gallium scintigraphy and \(^{18}\)F-fluorodeoxyglucose-positron emission tomography (FDG-PET) were scheduled for the whole-body evaluation and diagnosis confirmation. However, these tests were canceled because of the patient’s progressive anemia and hypoxemia. Alternatively, to obtain a definitive diagnosis, a bone biopsy was performed with the consent of the patient’s family. A needle biopsy was conducted at the site at which MRI of the humerus had shown a destructive lytic lesion with irregular borders of the fractured bone. The histological examination of the biopsy samples revealed variable spindle-shaped cells of irregular shape and size forming dense vascular channels (Figure 2c). Immunohistochemical staining was positive for vascular antigens, including cluster of
Table 1. Laboratory Data on Admission

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Serology</th>
<th>Urinary antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 9460/μl</td>
<td>CRP 12.1 mg/dl</td>
<td>St. pneumoniae (−)</td>
</tr>
<tr>
<td>Neu 88.2%</td>
<td>IgG 780 mg/dl</td>
<td>L. pneumophila (−)</td>
</tr>
<tr>
<td>Lym 5.3%</td>
<td>IgA 127 mg/dl</td>
<td></td>
</tr>
<tr>
<td>Mono 5.0%</td>
<td>IgM 43 mg/dl</td>
<td></td>
</tr>
<tr>
<td>Eosino 1.3%</td>
<td>C3 105 mg/dl</td>
<td>Urine-specific gravity 1.019</td>
</tr>
<tr>
<td>Baso 0.2%</td>
<td>C4 28 mg/dl</td>
<td>pH 6.5</td>
</tr>
<tr>
<td>RBC 1.97 × 10⁶/μl</td>
<td>RF &lt;10</td>
<td>Glucose (1 +)</td>
</tr>
<tr>
<td>Hb 5.2 g/dl</td>
<td>ANA &lt;40</td>
<td>Protein (−)</td>
</tr>
<tr>
<td>Ht 18.5%</td>
<td>Anti-CCP Ab &lt;0.6 U/ml</td>
<td>Occult blood (1 +)</td>
</tr>
<tr>
<td>Plt 4.4 × 10⁹/μl</td>
<td>Anti-DNA &lt;2.0 IU/ml</td>
<td></td>
</tr>
</tbody>
</table>

Coagulation
| PT 13.3 sec | PR3-ANCA <1.0 U/ml | Urinary sediment RBC 5-9/HPF |
| APTT 38.6 sec | MPO-ANCA <1.0 U/ml | WBC 1-4/HPF                  |
| Fibrinogen 205 mg/dl | Anti Jo-1 Ab (−) | Hyaline cast (−)             |
| D-dimer 47.4 μg/ml | Anti SS-A Ab <1.0 | Granular cast (−)           |

Biochemistry
| TP 6.5 g/dl | Anti Sm Ab <1.0 | Bronchoalveolar lavage        |
| Alb 3.6 g/dl | Anti Scl-70 Ab (−) | Recovery rate 63/150 ml      |
| T.Bil 2.1 mg/dl | Anti ARS Ab <5.0 | Total cell count 4.48 × 10⁹/ml |
| ALP 287 IU/l | ACE 3.6 U/l | Macrophage 58.5%             |
| γGTP 20 IU/l | Lysozyme 6.5 μg/ml | Lymphocyte 13.5%            |
| AST 13 IU/l | KL-6 186 U/ml | Neutrophil 18.5%            |
| ALT 13 IU/l | SP-D 210 ng/ml | Eosinophil 20.0%            |
| LDH 422 IU/l | β-D glucan <5.0 μg/ml | Basophil 1.5%               |
| BUN 22.6 mg/dl | Aspergillus-antigen (−) | CD4/CD8 1.21                |
| CRE 0.47 mg/dl | Cryptococcus-antigen (−) | Bacteria (−)                |
| Na 143 mmol/l | CEA 3.4 ng/ml | M. tuberculosis (−)          |
| K 133 mmol/l | CA19-9 29.1 U/ml | TB-PCR (−)                   |
| Cl 33 mmol/l | CYFRA 2.9 ng/ml | MAC-PCR (−)                  |
| Glu 105.0 mg/dl | ProGRP 38.3 pg/ml | Carini-PCR (−)              |
| BNP 71.4 pg/ml | sIL-2R 1350 U/ml | Cytology Class II          |

Mycoplasma-antigen (−)

Figure 1. Radiological findings of DAH. a: Chest CT on admission showing bilaterally spread multiple GGO associated with pleural effusion. b: CT performed 15 days later showing worsening of GGO and pleural effusion.
differentiation (CD) 31 and 34, while being negative for cytokeratin and thyroid transcription factor-1 (Figure 2d). The definitive diagnosis was confirmed as a primary angiosarcoma of the humerus. Therefore, we diagnosed the patient with DAH and concomitant DIC induced by angiosarcoma.

By the time angiosarcoma was diagnosed, the patient’s hypoxemia and anemia had progressed despite oxygen inhalation and repetitive blood transfusions. Because of the patient’s poor general health status, she was not considered a candidate for chemotherapy and was unresponsive to glucocorticoid administration. She was therefore given palliative care as per her family’s wishes. The patient ultimately succumbed to respiratory failure. Her family declined permission to perform an autopsy.

**DISCUSSION**

Angiosarcoma is a high-grade aggressive neoplasm that can occur in numerous sites but is most commonly found in the skin and soft tissues. Approximately 46% of all angiosarcomas are found in the bone, and it tends to develop in the long bones of the extremities, most often affecting the femur, tibia, and humerus. Primary angiosarcoma of the bone is very rare, accounting for <1% of primary malignant bone tumors, which can occur anytime during adulthood and affects men nearly twice as often as women. The typical initial clinical features of angiosarcoma of the bone include local pain and swelling along with other symptoms, such as neuro-
logical deficit, depending on the size and location of the
tumor. There are no specific radiographical findings
typically associated with angiosarcoma of the bone, but
CT images can give information about the lesion and its
multiplicity, and on MRI, lesions of angiosarcoma show
a decreased or variable signal intensity on T1-weighted
images and intermediate-to-high signal intensity on T2-
weighted images, similar to that observed in our pa-
tient.

When assessing angiosarcomas, 66% of cases have
been found to have metastasis to parenchymal organs. The
lungs are the most common sites of metastatic in-
volvement, followed by the liver, cervical lymph nodes,
and spleen, whereas the brain and heart are rarely sites
for primary or metastatic lesions. Once it spreads to
the lungs, angiosarcoma may clinically manifest as
dyspnea, hemoptysis, chest pain, pneumothorax, or dif-
fuse pulmonary hemorrhaging. Kakegawa et al. sum-
marized 14 cases of pulmonary angiosarcoma in which
single, double, or multiple solid masses were detected,
and other reports have pointed out that solid masses
are typically surrounded by GGO and consolidation dis-
tributed mainly at the peripheral portions. In addi-
tion, it may be accompanied by interlobular septal
thickening, representing lymphangitic spread. Sup-
ported by Adem et al.’s report that 5 out of 7 cases re-
quired a biopsy or autopsy to confirm pulmonary me-
tastatic angiosarcoma in cases with DAH as the initial
presentation, with a tranbronchial biopsy proving non-
diagnostic, diagnosing metastatic angiosarcoma in
lungs is abstruse. In addition, although we lack support
for our hypothesis since we were unable to perform a
lung biopsy or FDG-PET, the CT findings showed no
key radiographic indications of metastasis of angiosar-
coma in our case.

Chest CT in the present case showed diffusely spread
consolidation, GGO without a solitary mass, and a small
amount of pleural effusion. Since pulmonary hyperten-
sion was proven by echocardiography, we concluded
that it was the result of elevated venous pressure due to
right heart failure secondary to pulmonary hyperten-
sion. Elevated venous pressure can obstruct pleural
lymphatic drainage and increase hydrostatic pressure
in the bronchial and chest wall veins, leading to pleu-
ral effusion. However, pleural effusion is an uncommon
symptom of pulmonary hypertension, and without per-
forming thoracentesis, etiologies such as inflammation
and metastasis remain potential causes of pleural effu-
sion.

DAH is commonly recognized by the clinical presen-
tation of dyspnea, hemoptysis, anemia, and diffuse ra-
diographic pulmonary infiltrates. A number of diseases
can cause DAH, including antineutrophil cytoplasmic
antibody-related vasculitis, Goodpasture syndrome, an-
tiphospholipid antibody syndrome, connective tissue
disorders, infectious or toxic diseases, and coagulation
disorder. Generally, neoplastic diseases are not consid-
ered in the differential diagnosis of DAH, and DAH is
rare as a manifestation of angiosarcoma.

DAH is characterized by the disruption of alveolar
and capillary basement membranes, leading to the ac-
cumulation of widespread extravasation of intra-
 alveolar red blood cells originating from alveolar capil-
laries. It is a clinical syndrome attributed to dissemi-
nated injury of large, medium, and small pulmonary
vessel, and the most common underlying histology is
vasculitides involving the microvasculature, known as
pulmonary capillaritis. The etiology of pulmonary
capillaritis is cytoclasia of infiltrating neutrophils and
the accumulation of nuclear debris within the intersti-
tium, causing subsequent loss of integrity and disrup-
tion of alveolar-capillary basement membrane that re-
sults in bleeding into the alveolar space. It is the most
common histology associated with DAH, and since pul-
monary capillaries are small vessels only found in the
lung, and this may be the reason why the lung was the
single organ in which a DIC state was observed.

Chest CT in our case showed bilateral consolidation
with GGO located around the bronchovascular bundles
instead of a nodule or mass, which is typical of DAH
and not a metastatic lesion. Since the chest CT findings
were not typical for a metastatic lesion, we hypothe-
sized that the DAH indicated DIC related to angiosar-
coma. DIC can be induced by angiosarcoma through
any or all of several mechanisms, including (1) the acti-
vation of the host’s hemostatic system by expressing a
variety of procoagulant molecules, such as tissue fac-
tors and cancer procoagulants; (2) creating a hypofibri-
nolytic state by expressing fibrinolytic inhibitors, such
as plasminogen activator type 1; and (3) inducing the
formation of microthrombi by releasing thromboplastin
and exposing the basal membrane. Another possible
way in which angiosarcoma causes DAH may involve
pseudovasculitis. Büyüksinir et al. reported a case of
primary cardiac angiosarcoma with DAH that lacked a metastatic lesion in the lung when PET was performed. In that case, pseudovasculitis secondary to myxoma was concluded as the cause of DAH.\textsuperscript{18} While we cannot prove this, as an autopsy was not performed, angiosarcoma may have been complicated with pseudovasculitis in the present case.

Angiosarcoma of the humerus is rare, with only 6 cases reported worldwide in English thus far. Furthermore, only 16 cases of angiosarcoma complicated with alveolar hemorrhaging have ever been reported,\textsuperscript{12} and most of them required a pathological autopsy to make a diagnosis. Because angiosarcoma is a fatal condition, we want to emphasize the importance of considering malignancy as a differential diagnosis of DAH, regardless of the presence of metastasis lesions, and the need for a systematic approach to recognize malignancy as early as possible.

No potential conflicts of interest are disclosed.

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REFERENCES