Case Report

Vague Respiratory Symptoms as the Initial Presentation of Primary Cardiac Angiosarcoma: A Case Report

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Primary cardiac angiosarcoma is a rare and aggressive tumor. Its symptoms and signs are often diverse and nonspecific, often leading to delayed diagnosis. Here we report a case of primary cardiac angiosarcoma with vague respiratory symptoms as the first presentation, possibly due to pulmonary metastasis.

The patient is a 58-year-old woman with shortness of breath for several weeks. She further developed a dry nonproductive cough. Other symptoms include diarrhea, nausea and vomiting, fever, and fatigue. Her past medical history included ankylosing spondylitis, fibromyalgia, hypertension, and tobacco use. Chest CT without contrast showed numerous bilateral pulmonary nodules scattered throughout her lungs. The main clinical differential diagnosis includes infectious endocarditis with septic pulmonary emboli or other possible multifocal infections. However, a computed tomography angiography (CTA) showed no evidence of pulmonary embolic disease. After being admitted into the hospital, a 2-dimensiomal echocardiogram was performed, revealing a sessile ovoid mass in the right atrium measuring 3.5 x 4.3 cm. MRI confirmed the above findings.

A CT-guided left lower lobe lung biopsy was performed, revealed lung parenchyma with areas of vascular proliferation lined by atypical cells showing high nuclear/cytoplasmic ratio, hyperchromatic nuclei, and frequent mitosis. These atypical cells are positive for CD31 and CD34, consistent with endothelial origin. TTF-1, CK7, CAM5.2, and CAMTA1 were all negative. Subsequently, a right atrial biopsy was also performed, showing scant neoplastic cells with significant nuclear atypia, frequent mitotic figures, and frequent intracytoplasmic vacuoles. The neoplasm appeared to be forming vaguely vascular spaces in a few minute areas combined with a diffuse pattern of growth, consistent with a neoplasm of vascular origin. Similar to the lung biopsy, neoplastic cells from right atrium are strongly positive for CD31, focal positivity for CD34, and negative for TTF-1, BER-EP4, MOC-31, CK5/6, calretinin, and HHV8. In addition, MIB-1 expression showed a high proliferative index. CAMTA immunostaining for epithelioid hemangioendothelioma was also negative. Based on the overall clinical, radiological, histological and immunohistochemical features, a final diagnosis of cardiac angiosarcoma with multifoci of lung metastasis was made. Outside pathological consultations agreed with this diagnosis.

Because the clinical presentation of cardiac angiosarcoma can be variable and nonspecific, raising awareness that the vague respiratory symptoms as one of its first presentation can avoid delayed diagnosis.
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Key Words: *Cardiac angiosarcoma, vascular neoplasm, lung metastasis, malignant tumor*

INTRODUCTION

Primary cardiac neoplasms are very rare.[1,2] The incidence of primary cardiac tumors determined from autopsy cases is 0.001 to 0.3%.[1,2] While many of the tumors found in the heart consist of benign neoplasms, approximately 25% of all cardiac tumors demonstrate malignant features.[1] The most common cardiac malignant tumor is cardiac angiosarcoma.[1] Cardiac angiosarcoma is a rare cardiac malignant neoplasm characterized by endothelial differentiation.[3] The major clinical symptoms of cardiac angiosarcoma are congestive heart failure, arrhythmias, and hemopericardium with or without tamponade.[3] Dyspnea, chest pain, and syncope are other commonly found symptoms.[3] The vast majority of

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cardiac angiosarcomas are located in the right atrium while less than 5% occur in the left atrium.[1,3] Literature review performed on PubMed digital database reveals 578 cases diagnosed with primary cardiac angiosarcoma and 18 cases have pulmonary metastasis. Due to the aggressive nature of the neoplasm, the prognosis for patients with primary angiosarcoma of the heart is very poor.[3,4] In addition, the tumors often invade into the adjacent tissues eliminating surgical resection as a therapeutic option.[3,4] We report a case of a 58-year-old female with primary cardiac angiosarcoma presenting with multiple lung metastases and minimal non-specific symptoms.

CASE PRESENTATION

A 58-year-old female with past medical history of anxiety, ankylosing spondylitis, fibromyalgia, hypertension, obstructive sleep apnea, and tobacco use presented to her primary care physician for several weeks of shortness of breath for which she received steroids. She felt better for approximately 2 days before feeling unwell again. She further developed a dry nonproductive cough. Other symptoms include diarrhea, nausea and vomiting, fever, and fatigue. Outpatient computerized tomography (CT) chest without contrast was performed revealing numerous bilateral pulmonary nodules scattered throughout her lungs ranging in size from a few millimeters up to 1.5 cm on the right and up to 2.1 cm on the left. The pulmonary nodules were possibly related to infectious endocarditis with septic pulmonary emboli or other possible multifocal infections.

In the emergency room, the patient's physical exam and routine blood work were relatively unremarkable. Urinalysis, influenza A, respiratory syncytial virus, and covid-19 swabs were negative. A computed tomography angiography (CTA) of the chest was obtained revealing innumerable parenchymal lung nodules, a small pleural effusion, and a large pericardial effusion. No evidence of pulmonary embolic disease was identified. The patient was admitted to the hospital for further evaluation and management.

During her hospital course, a 2-dimensiomal echocardiogram was performed revealing a small pericardial effusion, as well as a sessile ovoid mass in the right atrium measuring 3.5 x 4.3 cm. Cardiac magnetic resonance imaging (MRI) confirmed a large abnormal multilobulated mass measuring 4 cm x 6 cm predominantly localized to the anterior wall with the inferior extent of the mass partially occluding the inferior venous cava ostium.

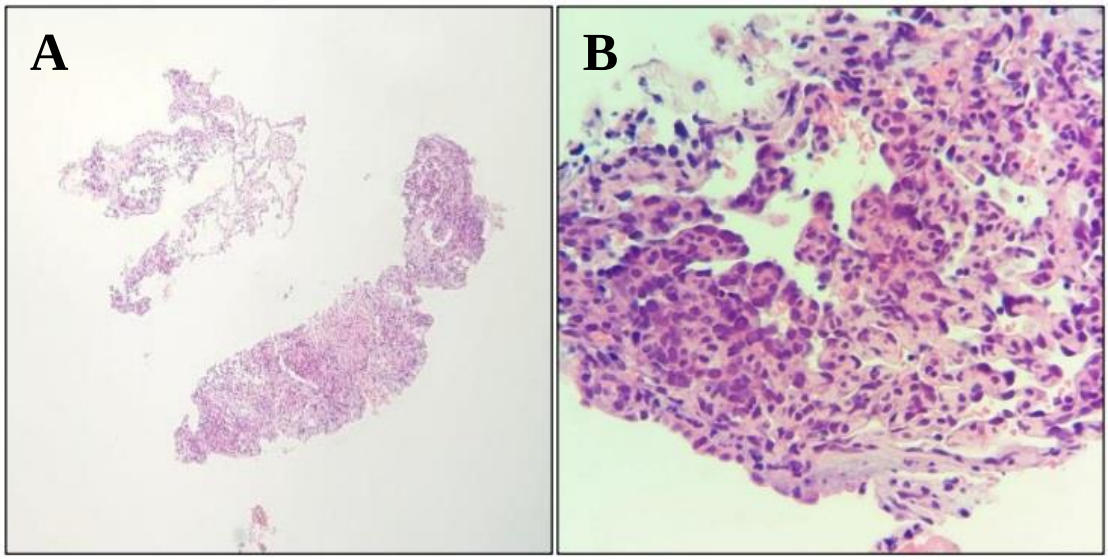

Figure 1. Lung Biopsy (Hematoxylin and Eosin Stain): **A)** Low magnification, 40x; **B)** High magnification, 400x.

A CT-guided left lower lobe biopsy revealed lung parenchyma with areas of vascular proliferation lined by atypical endothelial cells (**Figure 1**). The atypical endothelial cells showed high nuclear/cytoplasmic ratio, hyperchromatic nuclei, and frequent mitosis. Immunohistochemical staining showed positive CD31 (**Figure 2-A**), CD34 (**Figure 2-B**), vimentin (**Figure 2-C**), and focal CD10 staining. TTF-1 (**Figure 2-D**), CK7, CAM5.2, and CAMTA1 were negative.

Later, a right atrial biopsy consisted of scant groups of neoplastic cells ranging from 50 to 200 cells in multiple fragments of tissue (**Figure 3-A**). The cardiac biopsy consisted of very scant small groups of neoplastic cells ranging from 50 to 200 cells in multiple fragments of tissue. The neoplastic cells showed significant nuclear atypia, frequent mitotic figures, and frequent intracytoplasmic vacuoles. The neoplasm appeared to be forming vaguely vascular spaces in a few

minute areas combined with a diffuse pattern of growth (**Figure 3**). Immunohistochemically, the neoplastic cells were strongly positive for CD31 (**Figure 4-A**), focal positivity for CD34 (**Figure 4-B**), and negative for TTF-1 (**Figure 4-C**), BER-EP4, MOC-31, CK5/6, calretinin, and HHV8. In addition, MIB-1 expression showed a high proliferative index (**Figure 4-D**). Hematoxylin and eosin stains suggested a vascular origin neoplasm while immunohistochemistry stains supporting lung or mesothelial origin were negative. The CAMTA immunostain performed to rule out epithelioid hemangioendothelioma was also negative. Given the patient's history of the large right atrial mass and the presence of multiple pulmonary nodules, the final diagnosis was cardiac angiosarcoma and multiple lung metastasis. Outside pathological consultations were agreeable with the diagnosis. The patient followed-up with oncology for palliative systemic therapy.

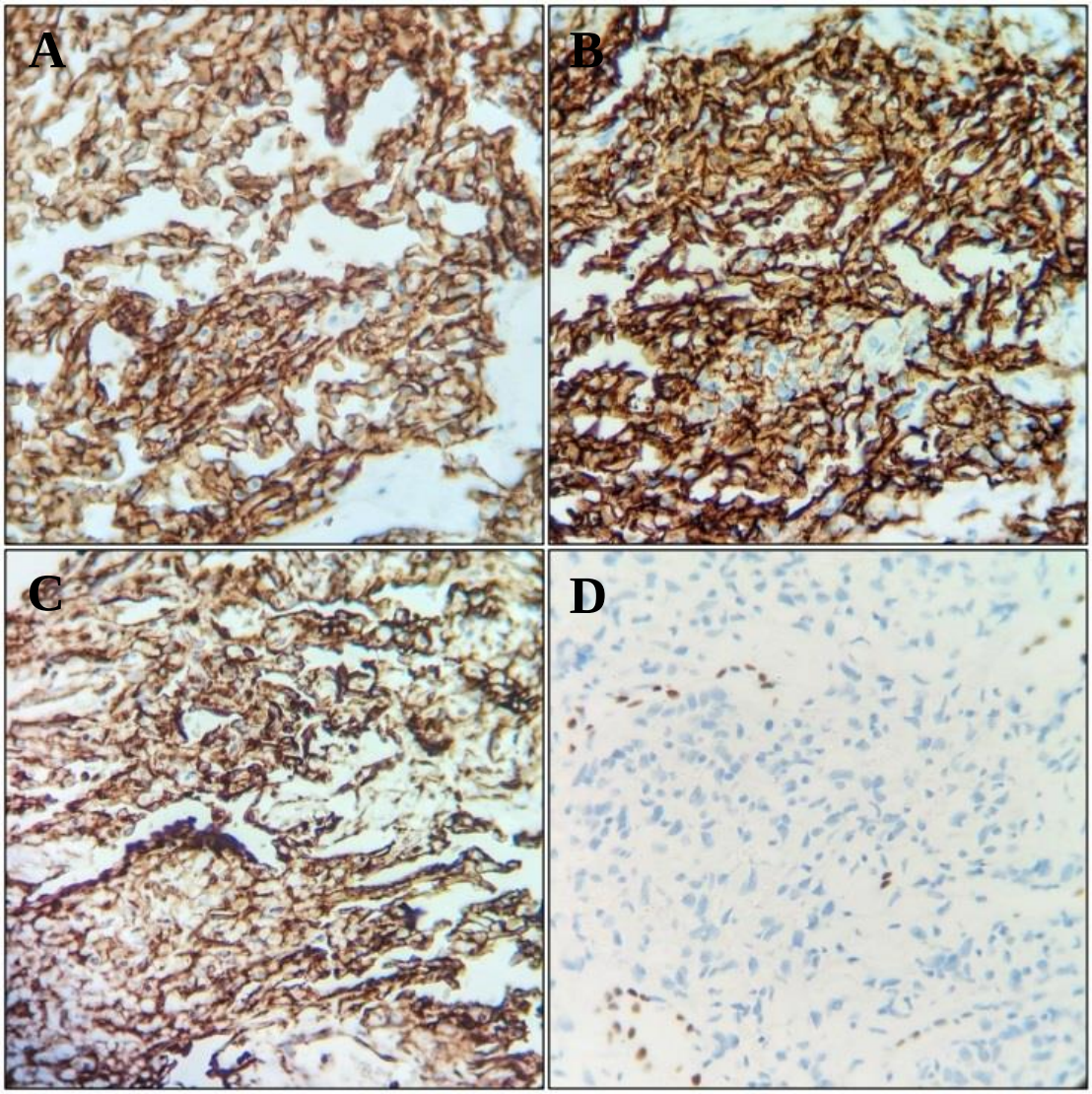

Figure 2. Lung Biopsy Immunohistochemistry Stain: **A)** CD31, **B)** CD34, **C)** Vimentin, **D)** TTF1.

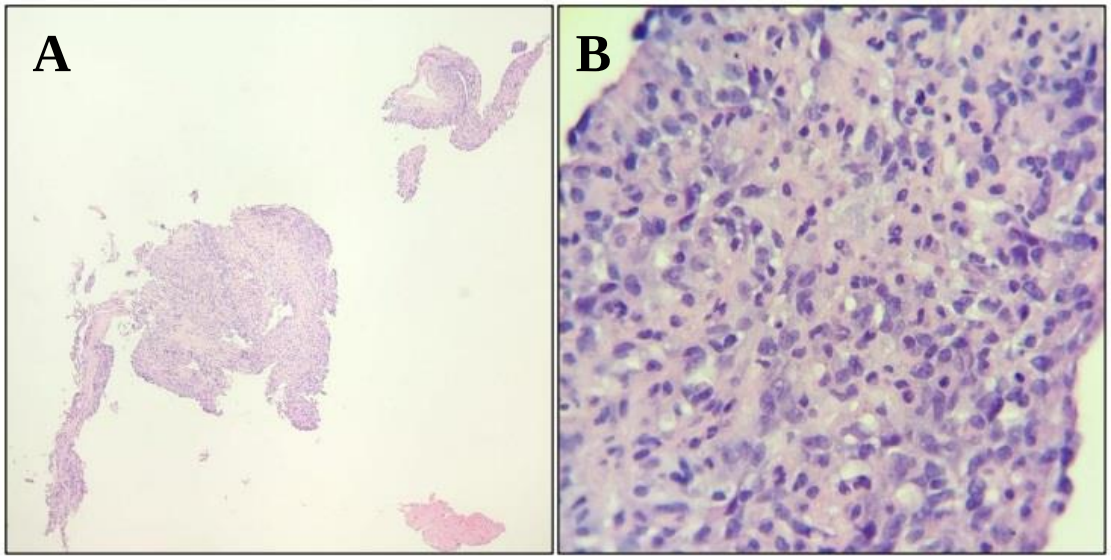

Figure 3. Cardiac Biopsy (Hematoxylin and Eosin Stain): **A)** Low magnification, 40x; **B)** High magnification, 400x.

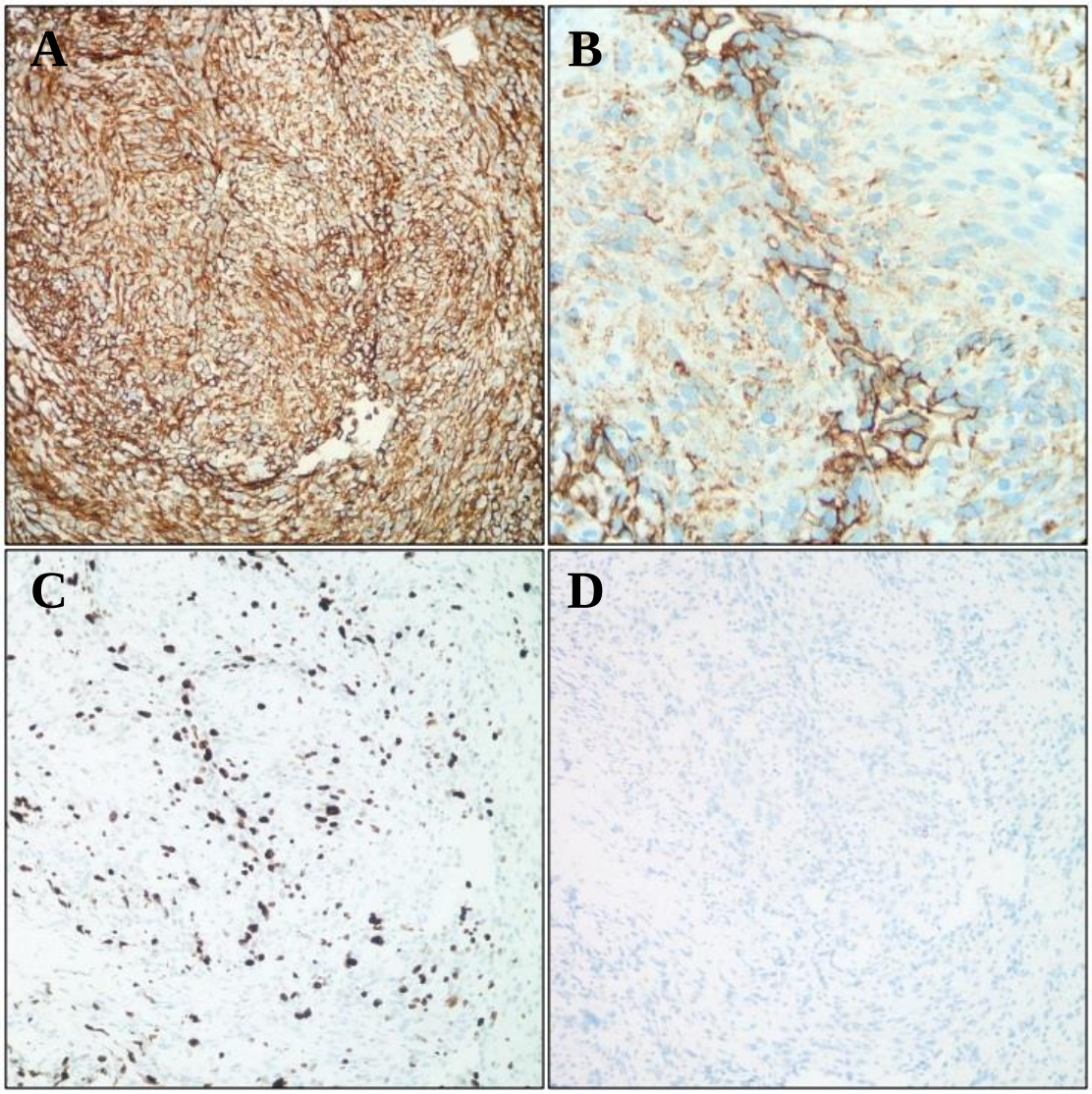

Figure 4. Cardiac Biopsy Immunohistochemistry Stain: **A)** CD31, **B)** CD34, **C)** MIB-1, **D)** TTF1.

DISCUSSION

Primary cardiac angiosarcoma is extremely rare and is often overlooked as an initial diagnosis because of its rarity. Most patients with primary cardiac angiosarcoma are asymptomatic until the size of the tumor reaches a certain size or after the patient has developed regional spread or metastases. Because the location of primary cardiac angiosarcoma is within the heart, its clinical presentation can be diverse and nonspecific, frequently causing delayed diagnosis.[17] The most common symptom is dyspnea, which is present in the majority of cases.[1] Other symptoms include (but not limited to) weight loss, anemia-related fatigue, malaise, chest pain, pericardial effusion, cardiac tamponade, and valvular dysfunction.[17] In some cases, patients with cardiac angiosarcoma may develop systemic symptoms due to metastasis.[17] In our case, shortness of breath and dry nonproductive cough may be caused by his pulmonary metastasis.

This case exhibited clinical and histological diagnostic difficulty. The diagnostic approach of cardiac angiosarcoma is based on TTE, CT, MRI, histopathology, and immunohistochemistry.[5] In most cases, transthoracic echocardiography (TTE) is the initial examination for evaluating primary cardiac angiosarcomas with a 75% sensitivity.[5,6] Transesophageal echocardiography (TEE) is also considered as it has a 97% sensitivity in detecting more information about tumor structure.[1,5] Cardiac CT and MRI characterizes tumor distinction, site of implantation, and myocardial invasion.[5,7,8]

Histologically, cardiac angiosarcoma is a very aggressive, rare malignant neoplasm characterized by atypical endothelial proliferation.[3] According to Patel et al, there are typically three varying patterns seen in cardiac angiosarcoma: a vascular area with anatomizing channels, a solid high-grade epithelioid area, or a spindle cell Kaposi-like area.[1] Many studies have investigated specific genes and pathways found in angiosarcoma. The most common are complex karyotype mutations such as trisomy 8, trisomy 17, and gain of 1q.[3,9,10] Other genes affected by point mutations include TP53, KRAS, PLCG1, KMT2 (MLL2), and KMT2D. [3,10] One case report described a cardiac mass containing a novel genetic marker, KDR (G681R), as well as a focal high-level amplification at chromosome 1q encompassing MDM4 gene through whole exome sequencing.[11] These mutations are potentially possible therapeutic targets for patients with advanced stage cardiac angiosarcoma.[11]

On the other hand, malignant epithelioid hemangioendothelioma (EHE) is a malignant vascular neoplasm composed of epithelioid endothelial cells characterized by cytoplasmic vacuoles, nuclear inclusions, and myxoid stroma. [3,12] EHE typically forms nodular nested architecture with hypercellularity at the periphery and hypocellular at the center.[3] EHE has two genetic mutations profile that can help distinguish EHE from other mimickers. [3] EHE with *WWTR1-CAMTA1* typically shows diffuse strong CAMTA1 expression[13] while EHE with *YAP1-TFE3* show TFE3 expression.[14] EHE is immunoreactive for CD31, ERG, CD34, CK7, CK8, CK18, and pancytokeratin expression.[3,12,15]

In this case, the patient presented with minimal pulmonary signs or symptoms. The multiple lung nodules found on CT scan prompted a concern for an infectious etiology, metastatic carcinoma or a primary lung neoplasm. However, the lung biopsy slides showed fragments of lung parenchyma with vascular proliferation lined by atypical endothelial cells (confirmed by positive CD31 and CD34 stains). TTF-1, CK7, and CAM5.2 immunostains highlighted the alveolar lining cells while the neoplastic cells stained negative, excluding the possibilities of metastatic carcinoma or a primary lung neoplasm.

The prognosis of patients with primary cardiac angiosarcoma is poor, with an overall 5-year survival rate of approximately 10.2%.[16] Poor prognostic factors include age greater than 45 years, tumor size greater than 50 mm, and tumor spread to adjacent or distant organs, and regional lymph nodes.[3] The existing treatment management for cardiac angiosarcoma includes a combination of surgical resection, chemotherapy, and radiation.[1,4,16] Regrettably, the current therapeutic regimens have not been entirely successful in completely suppressing the tumor.[4]

CONCLUSION

In conclusion, we described a difficult case of a malignant cardiac neoplasm in a patient who was medically stable with very few worrisome symptoms. Primary lung carcinoma and metastatic neoplasms are typically considered first on the differential diagnosis with other diagnosis such as epithelioid hemangioendothelioma following thorough workup evaluation. Although cardiac angiosarcoma is a well-recognized neoplasm, cardiac angiosarcoma is often missed due to its infrequent prevalence, wide range of clinical symptoms, and variable pathologic features. If there is any degree of suspicion, clinicians should not discount cardiac angiosarcoma. Early detection provides the opportunity to access various combined therapeutic modalities to delay progression of aggressive tumors, possibly reducing the patient's imminent death.

DISCLOSURE

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institution.

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