Primary Cardiac Angiosarcoma with Systemic Metastases; A Case Report and Review of the Literature

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Angiosarcoma is a relatively uncommon primary malignant tumor of the heart derived from the endothelial cells. The authors report a case of primary cardiac angiosarcoma of the right atrium with pulmonary, hepatic, cerebellar and bony metastases in a 46-year-old man who clinically presented as pulmonary hemorrhage. The patient's occupational history had occasional exposure to polyvinyl chloride. The autopsy examination of the cardiac angiosarcoma characterized macroscopically by a right atrial tumor and histologically by anastomosing vascular channels and minute atypical pleomorphic endothelial cells. Immunohistological stainings were positive CD31, CD34 and focal positive factor VIII-related antigen. Clinical and pathologic features with briefly reviewed relevant literatures are discussed. This is the first reported description in the literature of a primary cardiac angiosarcoma with systemic metastases to multiple organs in Thailand.

Keywords : *Angiosarcoma, Heart, Malignant, Metastases, Polyvinyl chloride*

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Angiosarcoma is a relatively uncommon primary malignant cardiac tumor demonstrating endothelial differentiation, which is characterized by vascular channels lined by atypical endothelial cells or cellular vacuoles containing red blood cells[1-4]. The incidence of primary tumors in the heart at autopsy ranges from 0.001 to 0.03[5]. In adults, approximately 25% of primary cardiac tumors are malignant and one third of these tumors are angiosarcomas[5]. The tumor has a high mortality rate due to a high incidence of systemic metastasis[5]. Most patients died within 9 months after symptom onset[5-8].

The purpose of this report is to illustrate an autopsy case with a right atrial angiosarcoma which first presented clinically as bilateral multiple pulmonary reticulonodular appearance with cardiomegaly on chest radiographs. The patient's occupational history had occasional exposure to polyvinyl chloride. This is the first reported description in the literature of primary cardiac angiosarcoma with systemic metastases to multiple organs in Thailand.

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Case Report

A 46-year-old Thai married male patient living in Bangkok Thailand was admitted to Ramathibodi Hospital in June 2003, because of productive cough, dyspnea on exertion together with weight loss of one month's duration. He had worked regularly as a litter truck driver. There was a 20 pack-year history of cigarette smoking. The patient had no history of significant illness in the past. His younger sister had a history of breast cancer. There was no history of tuberculosis among members of the family. A few days before hospitalization, he was seen by a general practitioner in a local hospital, who diagnosed multiple pulmonary nodules on chest radiography suggestive of miliary pulmonary tuberculosis. He was placed on antituberculous drugs (isoniazid 300 mg, rifampicin 600 mg, pyrazinamide 1,500 mg, ethambutol 800 mg) and transferred to Ramathibodi Hospital.

Physical examination revealed dyspnea with slightly peripheral cyanosis. There was no peripheral edema. The vital signs revealed a respiratory rate of 32/min, pulse rate 114/min, and blood pressure 145/75 mmHg. Jugular venous pressure was elevated to the level of the angle of the mandible. The cervical lymph

node could not be palpated. Cardiovascular examination revealed cardiomegaly. No murmurs or extra sounds were heard. Both lower lungs showed coarse crepitation. Liver and spleen were not palpable. There were clubbing of the toes. The neurological examination was normal.

Relevant laboratory investigations included: hemoglobin 11.8 g/dl, hematocrit 39.5%, white blood cell count 15,100 per mm^3 and consisted of 80% neutrophils, 12% lymphocytes, 7% monocytes and 1% basophil. Serum electrolytes revealed serum sodium 132 mmol/L, serum potassium 3.97 mmol/L, serum chloride 98 mmol/L, and serum bicarbonate 18.4 mmol/L. The serum blood urea nitrogen level was 11 mg/dl; the serum creatinine level was 1.1 mg/dl. The serum bilirubin level was 1.2 mg/dl. Three sputum smears revealed no acid-fast bacilli. Anti-human immunodeficiency virus was negative by ELISA technique.

A chest radiograph showed an enlarged cardiac silhouette with bilateral multiple pulmonary reticulonodular appearance. Electrocardiogram recorded sinus tachycardia, QRS axis +45 degree, right atrial hypertrophy low voltage in the chest wall leads and nonspecific ST-T wave changes.

The patient was treated with intubation, oxygen therapy and continuous antituberculous drugs. Two days later the patient noted increasing dyspnea with bleeding per the endotracheal tube. The chest radiograph showed diffuse alveolar hemorrhage. Bronchoscope examination revealed frank bronchial hemorrhage. Bronchial alveolar lavage showed clusters of malignant cells with enlarged eccentric nuclei and mucoid vacuolated cytoplasm suggestive of adenocarcinoma. The serum tumor markers revealed increasing CA 125 level more than 7 times of the upper normal limit and carcinoma embryonic antigen (CEA) level more than 2 times of the upper normal limit.

Over the next two days, the patient's status and chest roentgenogram were unchanged. The clinical diagnosis was acute diffuse pulmonary hemorrhage with bilateral multiple pulmonary reticulonodular appearance, cause unknown. The patient's condition deteriorated rapidly and he expired 5 days after admission. Autopsy was performed 4 hours later.

Autopsy finding

Macroscopic findings

The pericardial cavity contained a little hemorrhagic fluid with blood clots. Both visceral and parietal pericardiums were thickened and pearly-white in color. The heart was globoid enlarged and weighed 600 grams. The external pericardial surface was a variegated tan brown in appearance with dark areas of hemorrhage and pale areas of necrosis. On opening the heart, nearly the entire free right atrial wall was replaced by tumor tissue, variably dark and hemorrhagic to solid reddish to nodular pale beige (Fig. 1). A friable, lobulated, variegated mass measured 10 x 7.5 x 7 cm. In areas the tumor expanded into the atrial wall, thickness varied from 0.5 to 2 cm. The superior and inferior vena cava were surrounded but not compressed by the tumor. The internal surface of the superior vena cava showed one metastatic tumor measuring 1 x 0.5 x 0.5 cm, which was located at 6 cm above the orifice of the superior vena cava. The atrioventricular groove and left ventricular site showed metastatic tumor measuring 0.3 x 0.3 x 0.3 cm and 3 x 2 x 0.5 cm in diameter, respectively. There was no infiltration of the tumor to the atrioventricular nodal region. It was extending upwards almost up to the root of the aorta. The tumor bulged to the intima thereby reducing the capacity of the chamber, however, without protruding into the lumen. The underlying myocardium showed atrophy. The endocardium, myocardium and epicardium of the left atrium and left ventricle were free from the tumor. The pulmonic valve had a vegetation of tumor attached at

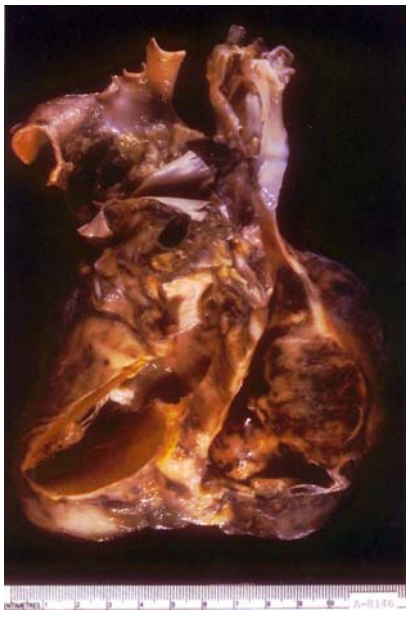

Fig. 1 Heart sagittal opening specimen shows solid reddish angiosarcoma involving nearly the entire free right atrial wall

the ventricular surface of the right and left pulmonic leaflets. For the mitral and aortic valves of the heart, the aorta and pulmonary trunk were normal. Similar friable raspberry-colored tumors were also found in the right and left lungs, liver, right cerebellum and iliac bones. Both lungs showed multiple hemorrhagic subpleural nodules ranging from 0.3 to 0.5 cm in diameter. The bilateral pulmonary parenchyma revealed irregular emphysematous changes. The liver weighed 1,600 grams and showed multiple hemorrhagic nodules ranging from 0.5 to 2.5 cm in diameter. The cerebellum showed red-brown nodules measuring 0.1 to 0.7 cm. in diameter, mainly located at the left cerebellar folia.

Microscopic findings

The sections of the right heart revealed immature anastomosing vascular channels and minute atypical pleomorphic endothelial cells. Haphazardly arranged, anastomosing vascular channels containing focal intraluminal papillary projection and compact nodular endothelial cell clusters were disclosed. The tumors were polygonal, epithelioid and spindle-shaped cells with scanty eosinophilic cytoplasm, high nuclear cytoplasmic ratios, having round to oval nuclei with relatively scant chromatin and indistinct nucleoli (Fig. 2). Numerous mitoses with pleomorphism and hyperchromatic bizarre nuclei were noted. There were multiple areas of necrosis and hemorrhage. Hemo-

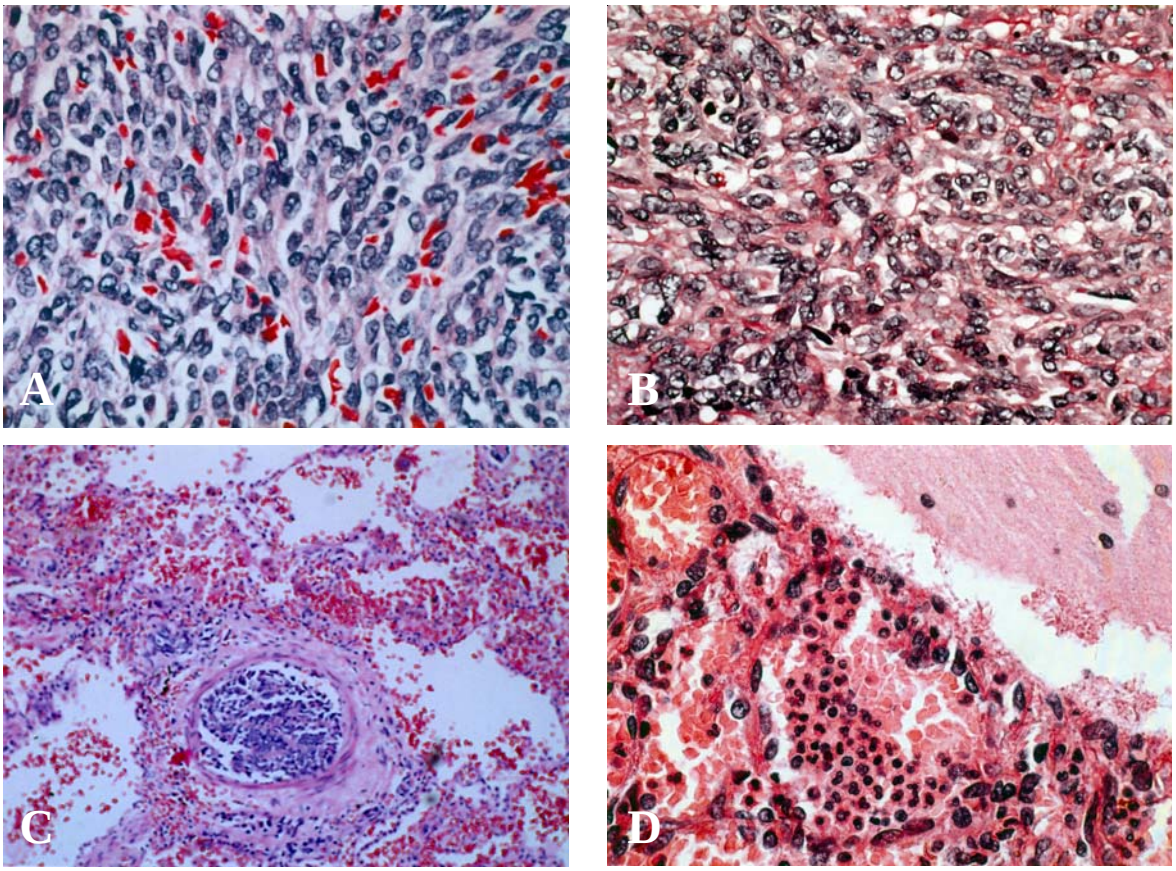

Fig. 2 A) Section of the right atrial tumor shows immature anastomosing vascular channels and minute atypical pleomorphic endothelial cell. H&E, X400
B) Section of the right atrial tumor shows polygonal, epithelioid and spindle-shaped cells with scanty eosinophilic cytoplasm, high nuclear cytoplasmic ratios, having round to oval nuclei with relatively scant chromatin and indistinct nucleoli. H&E, X400
C) Section of the lung shows metastatic angiosarcoma along the pulmonary artery with a background of pulmonary hemorrhage. H&E, X40
D) Section of the right cerebellum shows ill-defined metastatic angiosarcoma composing of malignant cell that forming vascular channels with focal inflammatory cells. H&E, X400

siderin depositions were noted together with evidence of fibrosis and hyalinization. Reticulin staining revealed the characteristic pattern of fibers lining vascular channels. No other mesenchymal elements or epithelial cells were noted. No intracytoplasmic and extracytoplasmic eosinophilic bodies were seen. Mucin stains were negative. The sections of both lungs showed multicentric ill-defined metastatic malignant tumors with a vascular channel formation centered along lymphatic pathways and pulmonary arteries with a background of pulmonary hemorrhage. Some of the tumor cells were poorly differentiated with sheets of cells. The sections of the liver, right cerebellum and iliac bones showed ill-defined metastatic tumors composed of malignant cells that formed vascular channels of different sizes and shapes.

Immunohistochemical findings

Immunohistochemical stains showed the tumor cells to be positive with endothelial cell markers, including CD31, CD34, CEA, vimentin and focal positive factor VIII-related antigen (Fig. 3) confirming the endothelial origin of the tumor. Tumor cells were negative for S-100, HMB-45, epithelial membrane antigen (EMA), pancytokeratin, sarcomeric actin and desmin excluding malignant melanoma, carcinoma and rhabdomyosarcoma. Neoplastic cells of both lungs, liver, right cerebellum and iliac bones were immunoreactive for CD34, CD31, CEA, vimentin and factor VIII-related antigen and immunonegative for pancytokeratin and cytokeratin 7.

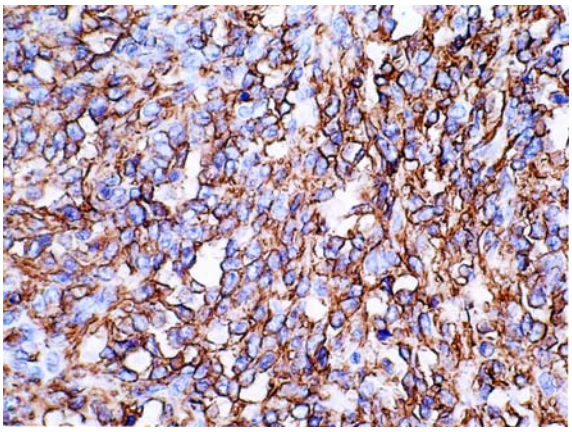

Fig. 3 Section of the right atrial tumor shows strongly positive reactivity to CD34 in the cytoplasmic membranes of the angiosarcoma cells. CD34, X400

Cause of death

The life threatening conditions included respiratory arrest caused by pulmonary metastases and acute diffuse pulmonary hemorrhage.

Discussion

Angiosarcoma is the most common malignant primary cardiac tumor, originating from the endothelial cells of arteries, veins or lymphatic channels[1,5,7,9-11]. This tumor shows a male predilection of approximately 2.5:1[1,2,5,7-9,11-15]. The average age at presentation occurs principally during the fourth to fifth decade [8,11,12,16]. The ages of patients range from 9 to 80 years old[8]. The tumor is found most exclusively involving the right atrium[1,2,5-18], although cases with involvement of the pericardium[5], right ventricle and left atrium[9] have been reported. Cardiac sarcomas usually remain asymptomatic until they produce a mass effect when the tumor obstructs cardiac output or venous return[2], local invasion[9], embolization or systemic manifes-tation[9]. The most frequently presenting symptoms of cardiac angiosarcoma are primarily dyspnea[6-8,16,19], pleuritic chest pain[5,6,9,14-16,20,21], congestive heart failure[9,14,16], palpitation[5,6], fever[6,9,14,16,18], myalgia[9], weight loss[6,8], arrhythmia [5,9], pericarditis[6], cough[6], hemoptysis[8,12,16] and occasionally pericardial effusion with temponade[2,5,9]. The physical signs include a pericardial friction rub, rales and raised jugular venous pressure[8]. The routine initial laboratory investigations are non-contributory[8]. The chest radiograph shows cardiomegaly or a globular heart[8]. The initial electrocardiograms frequently show right axis deviation, electrical alternans, atrial fibrillation, sinus tachycardia, nonspecific ST-T wave changes, T wave inversion or low voltage[8,22,23]. The imaging procedures such as echocardiography, computer tomography, magnetic resonance image, angiography and technetium scans may allow early recognition of malignant primary cardiac tumors[8]. However, conventional echocardiography may also miss the tumor due to technical difficulty in emphysematous patients[6]. Many authors reported causes of sudden death in patients with angiosarcoma such as pulmonary hemorrhage[12], hepatic metastatic tumor, metastatic intracerebral hemorrhage[5,17,24] or spontaneous rupture of omental metastatic tumor of angiosarcoma[25]. Diagnosis often is delayed because of protean non-specific and diverse clinical manifestations at presentation with resultant poor outcome resulting from metastatic disease[25].

The most common sites of metastases are the lung (51%)[2,7,8,14,15,17], liver (37%)[2,7,14,15,17], central nervous system (30%)[5,7,17], bone (21%) [2,5,7,17] and lymph node (16%)[7,14,15,17]. Diagnosis of cardiac angiosarcoma was made antemortem in only 50% of 46 cases reviewed in 1986[17]. Their review also emphasizes that antemortem detection and surgical treatment of cardiac angiosarcoma is increasing[8]. This tumor has a high mortality rate due to its rapid local relapse and a high incidence of systemic metastasis[25].

The macroscopic findings of angiosarcoma are red-pink to pink-gray, large and multilobular tumor arising in the right atrium and atrioventricular sulcus with extension into the caval veins, tricuspid valve and pericardium[1,2,7-19]. The tumor size ranges from 2 to 30 cm[8]. The microscopic findings demonstrate vascular channels with swollen atypical endothelial cells[1,2,7-17,19]. Large areas of spindling are present and most tumors have areas of necrosis[1,2]. Solid sheets of anaplastic pleomorphic cells with numerous mitotic figures are frequently observed[1,2]. Two thirds of cardiac angiosarcomas are composed of malignant endothelial cells that form papillary structures or vascular channels[1]. The remaining one third of cardiac angiosarcomas are focally or largely composed of anaplastic or spindle cells with poorly formed vascular channels and large numbers of extravascular erythrocytes[1]. Reticulin staining reveals the characteristic pattern of fibers lining vascular channels[8,11]. Immunohistological granular positive finding for factor VIII-related antigen is specific but not sensitive[1,2,6-8,11,15-17]. Positive staining for factor VIII-related antigen has been reported in only 45%, although a specific marker but is not particularly sensitive[1,8]. Immunohistochemical stains for CD 34 and CD 31 may be helpful in establishing the diagnosis of well-differentiated angiosarcomas[1,2,6-12,15].

The differential diagnosis of primary cardiac malignant neoplasms of the heart includes malignant fibrous histiocytoma (MFH), fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, and undifferentiated sarcoma[1-3,6,10,13,16]. MFH typically locates in the left atrium and histologically shows storiform areas with large, bizarre histiocytic cells[1-3,6,13,16]. Fibrosarcoma usually locates in the left atrium and is entirely composed of mild to moderate spindle cells intersecting at acute angles to form a herringbone pattern [1-3,10,13,16]. Leiomyosarcoma typically occur in the left atrium and characteristically show spindle cells foaming compact fascicles with intracytoplasmic glycogen and perinuclear vacuoles[1-3,6,13,16]. Rhabdomyosarcoma typically demonstrates rhabdomyoblasts which occasionally reveals cross-striations[1-3,6,13]. Undifferentiated sarcoma is most commonly located in the left atrium and histologically includes pleomorphic and small round cell varieties [1,2,6,10,13,16]. All histologic features of the differential diagnosis of an angiosarcoma were not found in the presented case. MFH is excluded as it does not recognize storiform areas and large, bizarre histiocytic cells. Negative results of immunohistochemical stains for desmin and sarcomeric actin may be helpful in excluding leiomyosarcoma and rhabdomyosarcoma. Fibrosarcoma is excluded, because it typically shows a herringbone pattern and is negative for specific immunohistochemical stains. Undifferentiated sarcoma typically lacks immunohistochemical stains for endothelial markers. The positive stains for factor VIII-related antigen, CD 31 and CD 34 with a histologic picture of anastomosing vascular channels and minute atypical pleomorphic endothelial cells are characteristic of an angiosarcoma.

Patients previously reported with angiosarcoma of the liver had been exposed to the vinyl chloride monomers in their working environment to doses as high as 1,000 parts per million in the 1950s, had a mean latent interval of about 20 years and a mean duration of exposure of 18 years[26]. Furthermore, there are two reports in the literature documenting vinyl chloride with angiosarcomas of the heart [14, 21]. Although, the patient's occupational history reported here work as a litter truck driver and had occasional exposure to factorial substances over a period of 25 years, the concentration of vinyl chloride monomer in the working environment was unknown. The authors do not consider that vinyl chloride monomer was definitely an etiology factor in this case, but the causal relationship cannot be established and the significance of this is not altogether clear. This is the third reported for documentation purposes.

Wide surgical excision remains the cornerstone of surgical management of cardiac tumors[7,9], since it improves survival, but there is almost always recurrence[5]. Complete surgical resection is rarely possible[5]. A few patients with cardiac sarcomas have received transplants, although the role of cardiac transplantation remains unclear[5,9,24]. The adjunctive therapy includes combination chemotherapy and radiation and possibly immunotherapy with interleukin-2[7]. If resection is incomplete, the tumor may recur even after chemotherapy and the patient may die of metastatic disease[9]. With unresectable

sarcomas, radiation and chemotherapy with adriamycin give a limited response[9]. The mean survival time is 4 months for the patients treated nonsurgically and 10 months for surgically treated patients[5]. This report describes a primary cardiac angiosarcoma in a 46 year-old man of a macroscopically, histologically and immunohistochemically identical tumor. The authors believe that, this is the first complete autopsy report in the literature of Thailand.

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รายงานผู้ป่วยมะเร็งปฐมภูมิของหัวใจพบร่วมกับการแพร่กระจายของมะเร็งทั่วร่างกาย

นพดล ลาภเจริญทรัพย์, อรุณี สิงห์เสน่ห์, ไพศาล ลีละชัยกุล

รายงานผู้ป่วยมะเร็งปฐมภูมิของหัวใจที่ห้องหัวใจขวาบน พบร่วมกับการแพร่กระจายของมะเร็งไปปอด, ตับ, สมองน้อย และกระดูก ในผู้ป่วยชายไทยอายุ 46 ปี มีอาการเลือดออกจากปอด อาชีพทำงานสัมผัสสารโพลีไวนิวคลอไรด์เป็นครั้งคราว ตรวจพบเป็นเนื้องอกมะเร็งปฐมภูมิที่หัวใจห้องบนขวา ตรวจทางกล้องจุลทรรศน์พบเป็นเซลล์ของเยื่อบุเส้นเลือดที่มีความผิดปรกติสร้างเป็นโครงสร้างของเส้นเลือด ตรวจทางอิมมูโนวิทยาเนื้อเยื่อพบว่าเซลล์ของเยื่อบุเส้นเลือดมีการแสดงออกของแอนติเจน CD 31, CD 34 และ มีการแสดงออกเป็นบางบริเวณต่อแอนติเจนของปัจจัยการแข็งตัวของเลือดที่ 8 (Factor VIII) ทางคณะผู้เรียบเรียงได้รายงานเรื่องมะเร็งปฐมภูมิของหัวใจ พบร่วมกับการแพร่กระจายของมะเร็งทั่วร่างกาย พบเป็นกรณีศึกษาแรกของประเทศไทย รวมกับทบทวนจดหมายเหตุการแพทย์โดยรวบรวมวิเคราะห์การแสดงออกทางคลินิกและพยาธิวิทยา