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Generalised Angiosarcoma of the Heart

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Summary. A primary angiosarcoma, which formed multiple ventricular pericardial and myocardial nodules without atrial involvement, occurred in the heart of an 80-year old Caucasian female and caused death within three weeks of the onset of symptoms. There were neither cutaneous lesions to suggest Kaposi's sarcoma nor serological evidence of infection by Human T-cell Leukemia Virus and the rapidly fatal course of the patient's illness was similar to that of the typical atrial cardiac angiosarcoma. The distinction between primary cardiac angiosarcoma and Kaposi's sarcoma affecting the heart is discussed.

Key words: Heart-Angiosarcoma

Introduction

Primary angiosarcoma of the heart is an uncommon malignancy which usually presents as a mass in the right atrium (McAllister and Fenoglio 1978) but rarely forms multiple widespread ("generalised") deposits in the pericardium and myocardium resembling the multiple deposits of Kaposi's sarcoma in the heart (Poulias et al. 1981). Because cardiac angiosarcomas are also histologically similar to Kaposi's sarcoma (McAllister and Fenoglio 1978; Janigan et al. 1986), cases of the former have been described as "primary" Kaposi's sarcoma of the heart (Ayer et al. 1962; Levison and Semple 1976) and usage of these terms is recognised to have become confused (McAllister and Fenoglio 1978; Silver et al. 1984; Janigan et al. 1986). Nevertheless, Kaposi's sarcoma is now known to be a manifestation of Acquired Immunodeficiency Syndrome (AIDS) associated with infection with the Human T-cell Leukemia Virus-III (HTLV-III, Muggia and Lonberg, 1986), and its involvement of the heart has been distinguished from cardiac angiosarcoma by the presence of cutaneous lesions, an indolent clinical course and a lack of effect on cardiac function (Silver et al. 1984; Janigan et al. 1986). The present report describes a case of a generalised angiosarcoma of the heart which was rapidly fatal and occurred without any cutaneous lesion, or infection with HTLV-III. The case emphasises that cardiac angiosarcoma can be distinguished from Kaposi's sarcoma affecting the heart on clinico-pathological criteria.

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Report of a case

Clinical History. An 80-year old Caucasian widow complained of increasing shortness of breath on exertion, together with lethargy, anorexia and occasional vomiting for two weeks. In the past, she had been treated for arterial hypertension with methyl dopa, nifedapine and butemadine, but there was no history of major surgery, blood transfusion or unusual infective illness.

Physical examination revealed a blood pressure of 135/90 mm Hg, displacement of the apex beat of the heart to the anterior axillary line and bilateral crepitations of the upper and lower pulmonary lobes on each side. The hemoglobin was 11.3 g/dl, white cell count 13000/μl (85% neutrophils), serum urea 25 mMol/l and creatinine 0.17 mM/l. Chest X-ray revealed enlargement of the cardiac shadow and diffuse pulmonary opacities predominantly in the upper lobes. The electro-cardiogram demonstrated right bundle branch block. Treatment for congestive cardiac failure was begun together with erythromycin for suspected pulmonary infection but her condition deteriorated rapidly and she died on the sixth hospital day. Antemortem serum was negative when tested for anti-Human T-cell Leukemia Virus antibodies by an enzyme immunoassay technique (Abbott, Australasia, Sydney).

Autopsy findings. At autopsy, the pericardial sac contained 50 ml of blood stained fluid. The heart (500 g) was enlarged and exhibited approximately 100 tumour deposits, which mac-

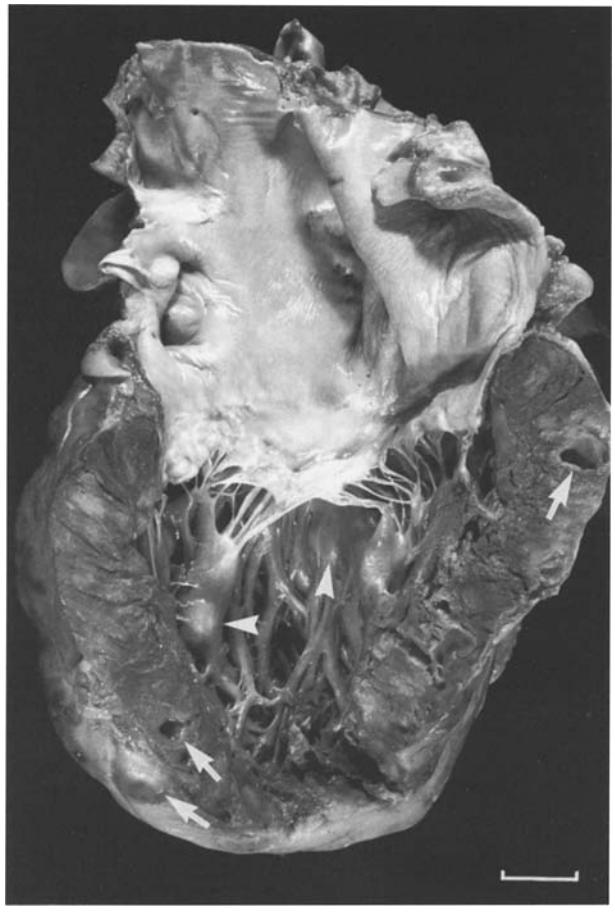

Fig. 1. Photograph of the heart displaying the left atrium and left ventricle. Soft blood-filled nodules are present in the ventricular epicardium and myocardium. *Arrows* indicate cavities of the nodules after evacuation of blood. Firmer white plaques (*arrowheads*) are situated in the endocardium and papillary muscle

roscopically were of two types. The first type consisted of soft, blood-filled nodules which were especially numerous in the epicardium and subjacent myocardium of the left ventricle (Fig. 1). On the right side of the heart, there was a single pedunculated blood-filled lesion of this type which measured 25×10 mm and was attached to the anterior wall of the right ventricle 20 mm below the pulmonary valve. The nodules were 0.2–2.0 cm in diameter, and when evacuated of blood, were found to have smooth, pale linings and walls of white tissue. The cavities often communicated with smaller, irregular, blood-filled channels which resembled vessels. The blood-filled nodules were scattered in the epicardium and myocardium from the atrioventricular sulcus to the apex of the heart, and were not related to any normal coronary blood vessel.

The second type of macroscopic lesion consisted of poorly-demarcated, firm white plaques measuring 3–20 mm in diameter and were most obvious in the subendocardial myocardium of both ventricles (Fig. 1). These lesions did not ulcerate the endocardium, and there was no mural thrombosis in any chamber of the heart. The interventricular septum and the papillary muscles on both sides of the heart were equally involved by these lesions, but the atrial musculature was spared. Additional white tumour deposits were also present in the ventricular epicardium and a single epicardial atrial lesion (8 mm in diameter) was located on the right side posteriorly. The valves were not affected.

The lungs, especially the upper lobes, contained multiple, small, poorly demarcated tumor deposits measuring 2–10 mm in diameter. The liver contained a 20 mm cystic tumor deposit and the thyroid a 12 mm deposit. Lytic bone metastases were present in the left clavicle, the left first rib and the occiput. No lesions in the skin, breasts, lymph nodes or other organs were found.

Light microscopic findings. Microscopic examination of the blood-filled tumor nodules revealed that they consisted of large cavities (Fig. 2a) which were lined by flattened cells resembling endothelium (Fig. 2b). The walls of the cavities were composed of concentric pleomorphic spindle cells wich faded off imperceptibly into sheets of randomly-arranged tumor cells with some resemblance to poorly differentiated fibrosarcoma (Fig. 2b). The white plaques were made up of sheets of randomly arranged tumor cells having essentially the same appearances as the tumor cells around the blood-filled cavities. However, in many of these areas, there were in addition, numerous anastomosing capillary and venular-sized vascular spaces with flattened cells resembling endothelium lining their lumina (Fig. 2c). The tumor cells in all areas had scant, pale, vacuolated, eosinophilic cytoplasm and moderately pleomorphic, elongated to polygonal nuclei having evenly distributed granular chromatin and indistinct nucleoli. Mitoses were sparse. Some areas of the tumor had a myxoid appearance with Alcian blue-staining material present between the cells. Masson's trichrome and Elastic van Gieson stains revealed no smooth muscle or elastin respectively associated with the tumor vessels. There was no significant inflammatory infiltrate.

The metastases in the lungs exhibited similar vascular neoplastic tissue, and in addition, intimal colonisation of small pulmonary arteries and veins by tumor cells was observed. Microscopic examination of the metastases in the liver, thyroid and bones revealed no additional features.

Immunohistochemical findings. Immunoperoxidase studies of both the heart and lung tumor sections showed that the cytoplasm of the cells was strongly positive for vimentin (Dakopatts, Denmark) but stains for cytokeratin (CAM 5.2, Becton Dickinson, California), S100 (Dakopatts), epithelial membrane antigen (Sera Labs, Australia), carcino-embryonic antigen (Hybritech, San Diego, USA) and lymphocyte common antigen (Dakopatts) were negative. Scattered single tumor cells in the solid parts of the tumor reacted weakly with anti-Factor VIII (Dakopatts) and with Ulex europeus (Vector, CA, USA) antibodies, but there was no reaction of the spindle cells in the walls of the large vessels, or of the flattened cells lining the vessels with these antibodies. Staining of frozen sections of the available formalin-fixed tumor tissue with these antibodies as described by Janigan et al. (1986), did not produce a reaction in any cell. Electron microscopy of the tumor tissue revealed pleomorphic cells with irregularly folded nuclei, but autolytic changes prevented study of their cytoplasmic features.

Discussion

Angiosarcomas of the heart are uncommon, rapidly fatal tumors which comprise one-third of all primary malignant cardiac neoplasms (McAllister and Fenoglio 1978). The most common site of origin of these tumors is the right atrium, where they

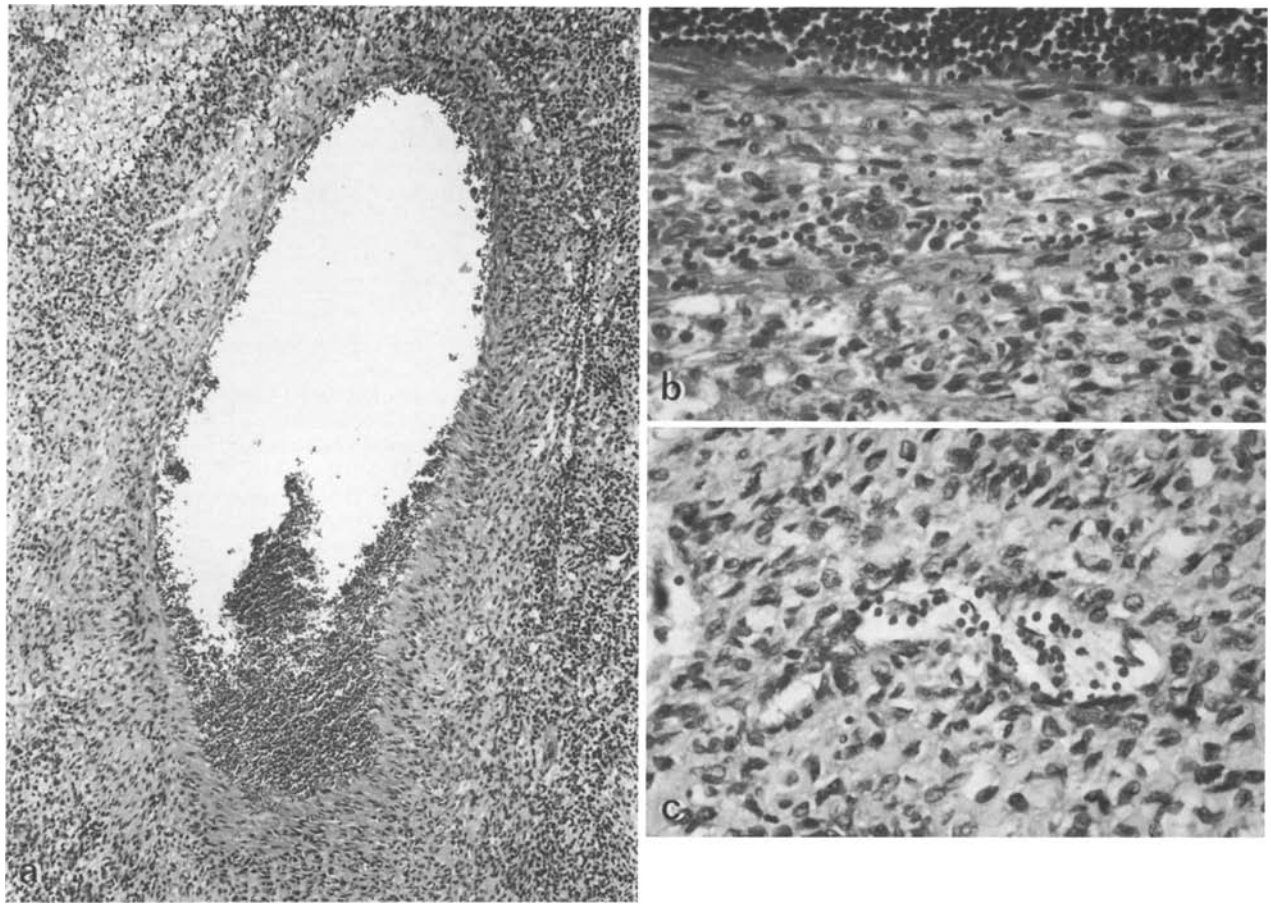

Fig. 2a. Photomicrograph of a soft, blood-filled nodule (lower space adjacent to middle arrow of Fig. 1) showing a large cavity having a wall of spindle-shaped cells. (H & E ×100). **b** Part of the wall of the cavity of a blood-filled nodule showing a lining of flattened cells resembling endothelium, and subjacent concentric bizarre spindle cells which fade away into randomly arranged tumor cells. (H & E ×350). **c** Photomicrograph of an area of a white plaque of tumor showing sheets of moderately pleomorphic tumor cells forming venule-sized vessels lined by flattened cells. (H & E ×350)

usually form a single mass and less commonly, involve the pericardium, right ventricle and the left side of the heart (McAllister and Fenoglio 1978). Cardiac angiosarcomas usually occur during the third to fifth decades with the ages of the previously reported cases ranging from 10 to 76 years (Janigan et al. 1986). Our patient is the oldest thus far reported. Histologically, angiosarcomas are usually composed of irregular spindle cells which form vascular spaces of various sizes. The large vascular spaces of the present tumor are unusual, but similar structures were illustrated in two previous reports (Greenberg and Angrist 1948; Aikat and Nirodi 1971). Poor staining of angiosarcomas with anti-endothelial antibodies in association with immunoperoxidase methods has been described by Janigan et al. (1986).

The most common sites of metastatic spread of cardiac angiosarcomas are to the lungs, followed by the liver and other organs. Colonisation of pulmonary vasculature by these tumours has been previously described (Hansson et al. 1970).

Angiosarcomas exhibiting multiple cardiac tumor deposits without a main mass are uncommon. McAllister and Fenoglio (1978) reported that in 5 of their 39 cases, the primary site of origin of the tumor within the heart could not be determined, but further details of these cases were not provided. Lothe and Murray (1962) reviewed 19 autopsied cases of Kaposi's sarcoma in Africans, and found cardiac involvement in 5. These authors included one previously described by Gelfand (1957) in which a malignant vascular tumor formed multiple raspberry-like lesions in the epicardium and myocardium, apparently without a single large mass. The patient's illness lasted four months, and death resulted from refractory heart failure. There were no cutaneous lesions and no

history of unusual infections, so that, by the clinico-pathological criteria of Janigan et al. (1986), (see below), this case could be considered a primary cardiac angiosarcoma. Poulias et al. (1981) described as "generalised" angiosarcoma, a tumor in a 58-year old man who died after an 11 month illness. The tumor, although exhibiting a right atrial mass, also showed considerable involvement of both ventricular walls and infiltration of the right papillary muscle. No history suggestive of cutaneous Kaposi's sarcoma or AIDS was given.

The distinction between primary angiosarcomas of the heart and Kaposi's sarcoma affecting the heart have been discussed by several authors. McAllister and Fenoglio (1978) defined Kaposi's sarcoma on histological grounds as "a vascular tumour composed of vascular spaces between which are spindle-shaped cells and reticulum fibres resembling a well differentiated fibrosarcoma", and, although finding foci compatible with this description in many of the cardiac tumours in their series, categorised only 1 of the 39 cases as Kaposi's sarcoma affecting the heart. Silver et al. (1984) distinguished cardiac angiosarcomas from Kaposi's sarcoma affecting the heart by the presence of cutaneous involvement with the latter tumor. Janigan et al. (1986), like McAllister and Fenoglio (1978), considered that the histological features of Kaposi's sarcoma overlapped with those of primary cardiac angiosarcoma and stressed the clinico-pathological distinction between the two conditions viz:-in Kaposi's sarcoma, there are epicardial or pericardial lesions which are usually small and asymptomatic, as well as skin lesions of Kaposi's sarcoma or risk factors for the disease, while in cardiac angiosarcoma, the cardiac lesions are usually large and symptomatic, and there are no skin lesions of Kaposi's or relevant risk factors. Using these criteria, the present case can be recognised as an example of an unusual "generalised" macroscopic form of primary cardiac angiosarcoma.

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