Primary sarcoma of the heart: a light and electron microscopic study of two cases

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SUMMARY Two cases of primary malignant cardiac neoplasms are presented. The first, an angiosarcoma of the right atrium, developed in a 44-year-old housewife, who survived 23 days from the time of presentation; diagnosis was made at necropsy. The second, an embryonal rhabdomyosarcoma of the right ventricle, developed in a 17-year-old student; diagnosis was made by angiocardigraphy. He underwent surgery and cytotoxic and irradiation therapy and died 14 months later.

Primary malignant cardiac neoplasms are very rare; sarcomata form the vast majority. In classifying these tumours, the first step is to consider whether the tumour is of vascular or myogenic origin; in this paper we describe one example of each. The first, an angiosarcoma of the right atrium, presented little difficulty in histological classification at necropsy. Although the case had not been diagnosed during life, the symptoms were strikingly similar to those of previously recorded cases. In the second case, a cardiac tumour was diagnosed during life by angiocardigraphy. Histological diagnosis here was more difficult. The finding of beaded intracytoplasmic filaments greatly supports the view that the tumour is of myogenic origin, although they are not pathognomonic ultrastructural features of this tumour (Toker, 1968). The filaments are in fact identical with those seen in the chick myoblast (Bauer and McGavran, 1974).

Material and methods

Material from case 1 was obtained at necropsy. Tissue for light microscopy was embedded in paraffin. Sections were stained with haematoxylin and eosin and with Gordon and Sweet's reticulin stain using a neutral red counterstain. Material for electron microscopy was fixed for 8 hours in 5% glutaraldehyde followed by overnight washing in cacodylate buffer. It was then osmicated, rinsed in distilled water, stained with 3% uranyl acetate, dehydrated with acetone, and embedded in Spurr resin. Sections

were cut and stained by 0.3% lead citrate (Reynold's method). Sections were examined in a Jeol 100 S transmission electron microscope.

Material from case 2 was obtained at necropsy, embedded in paraffin, and stained with haematoxylin and eosin, Mallory's phosphotungstic acid-haematoxylin, and Heidenhain's iron haematoxylin. Tissue for electron microscopy was obtained by dewaxing paraffin-embedded material with xylene. It was then hydrated in descending grades of alcohol, rinsed in distilled water, washed in cacodylate buffer overnight, and osmicated. The remainder of the procedure was as described for case 1.

CASE 1

A 44-year-old housewife was admitted with nausea, anorexia, epigastric fullness, and flatulence. She claimed that these symptoms had been present for six months and had worsened in the few days before admission.

A chest x-ray on admission showed cardiomegaly and a left pleural effusion. An electrocardiogram showed a low-voltage and non-specific flattening of the ST segment. A pericardial effusion was diagnosed by echocardiography. The patient deteriorated clinically, developing retrosternal pain, cough, severe weakness, and a persistent pyrexia of 100°F.

Extensive investigations were directed towards possible pericarditis, bacterial endocarditis, or systemic lupus erythematosus. Examination of a pleural aspirate showed blood and reactive mesothelial cells only. A pericardial tap failed. A repeat echocardiogram showed that the pericardial effusion was smaller. The patient's blood pressure dropped steadily and the jugular venous pulse rose. These

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signs were interpreted as malignant pericarditis. Terminal jaundice developed and death occurred 23 days after admission following cardiac arrest.

Necropsy (8 hours after death, PM No. 33/78)

The body was that of a moderately obese woman. The pleural cavities contained haemorrhagic effusions (300 ml in each).

The heart weighed 950 g. Several brown-coloured tumour nodules projected through the pericardium. The latter was adherent to the epicardium all over the heart by a layer of brown-haemorrhagic tumour. The tumour ulcerated into the wall of the right atrium, and narrowing of the superior vena cava was evident.

A careful search for possible primary sites for an extracardiac tumour was undertaken without success.

Light microscopy

The tumour consisted of extensively anastomosing vascular channels. The latter were lined by pleomorphic cells having ill-defined pink cytoplasm and large oval or round vesicular nuclei (Fig. 1). Reticulin-stained sections showed the complex vascular spaces lined by plump neoplastic endo-

thelial cells and surrounded by reticulin fibres which took on a ring-like pattern in places. Tumour necrosis was extensive. Micrometastases were noted in the adrenal glands and lungs where the tumour formed delicate angiomatous patterns. The liver showed intense centrilobular venous congestion with necrosis.

Electron microscopy

Figure 2 shows three neoplastic endothelial cells. Despite postmortem autolysis the following features are discernible. The cells contain voluminous cytoplasm with irregular borders. The cells are arranged in a haphazard fashion and have clearly abandoned any attempt to line vascular channels. Numerous cytoplasmic vesicles are evident.

Figure 3 shows a fibrillar component in the cell cytoplasm and a large amount of rough endoplasmic reticulum and membrane-bound vesicles. The nucleus has an irregular outline, clumped chromatin forming a dense layer around the nuclear membrane. The extensive extracellular matrix, in which the tumour is set, is evident. This is composed of fibrillar and flocculent material and corresponds to the basal lamina in which the neoplastic endothelial cells are set.

Fig. 1 Typical appearance of angiosarcoma. Anastomosing vascular channels lined by malignant endothelial cells having abundant cytoplasm and large vesicular nuclei. Haematoxylin and eosin $\times 400$.

Fig. 2 Electron micrograph of three neoplastic tumour cells from the angiosarcoma. They contain abundant cytoplasm filled with membrane-bound vesicles and rough endoplasmic reticulum. Basement membrane like material presumably secreted by the tumour cells is seen in the centre (arrow). $\times 5750$.

CASE 2

A 17-year-old male student was referred to a cardiology outpatient clinic at this hospital because of palpitations on exertion. An electrocardiogram showed right bundle-branch block, and a chest x-ray showed a normal cardiac profile with a suggestion of oligoemic lung fields. Atrial septal defect was suspected. He deteriorated rapidly over a period of three months and was admitted as an emergency with severe dyspnoea and central cyanosis (Pao_2 35 mmHg; 4.7 kPa). An apical systolic murmur had now developed and the second heart sound was widely split. He was transferred to another hospital where right heart catheterisation showed globular filling defects in the right atrium, right ventricle, and pulmonary artery. At operation a large tumour was found arising just inside the tricuspid valve, filling most of the right ventricle and spreading out in two large globular masses into both branches of the pulmonary artery. It had also spread

back into the right atrium. The tumour and tricuspid valve were removed and a prosthetic valve was inserted. Grossly the tumour measured 10 cm long by 4 cm wide arising from a 2.5 cm wide base. It had a smooth, shiny surface with some splitting into villiform processes at its distal end. In places the mass was soft and jelly-like.

The patient was discharged, remained well for about one month, and was re-admitted with severe exertional dyspnoea. Cytotoxic agents and irradiation were administered with benefit, but 14 months after surgery the patient was re-admitted to this hospital moribund and died within hours.

Necropsy (14 hours after death, PM No. 36/77)

The body was that of a thin man.

The heart weighed 900 g. On opening the pericardium multiple soft white tumour nodules were present, studding the anterior and diaphragmatic visceral pericardium and covering the epicardium.

Fig. 3 Double arrow points to fibrillar material noted in tumour cell cytoplasm. Note (single arrow) extracellular fibrillar and flocculent material, presumably basement membrane, typical of this neoplasm. $\times 9600$.

The right atrium contained an intact valve prosthesis. The right ventricle contained a large gelatinous tumour mass filling the ventricle and extending into the main pulmonary trunk. When the left atrium was opened a 5 mm atrial septal defect (secundum type) was revealed. The left ventricle was normal.

Light microscopy

Sections through the tumour (Fig. 4) showed it to be composed of small spindle cells arranged in a parallel fashion and some cells had a moderate amount of pink cytoplasm. Mitoses were numerous, and some areas had a loose myxoid stroma. Cytoplasmic cross striations were not seen on haematoxylin and eosin sections, nor did the use of phosphotungstic acid haematoxylin and Heidenhain's iron haematoxylin stained material help to reveal them.

Micrometastases were present in the lungs. The

impression was that of an embryonal rhabdomyosarcoma, the large cells having pink cytoplasm representing rhabdomyoblasts.

Electron microscopy

Figures 5 and 6 show poor preservation of cytoplasmic detail. However, definite accumulations of cytoplasmic fibrillar material are evident. We believe these to be myofilaments, identical with those seen in the chick myoblast.

Discussion

Though primary cardiac neoplasms are rare (Leach, 1947), their clinical significance has assumed increasing importance. The diagnosis of benign neoplasms by angiography and echocardiography has resulted in surgical cure. Malignant neoplasms present greater diagnostic difficulties, and the results of surgery, chemotherapy, and irradiation

Fig. 4 *Appearance of embryonal rhabdomyosarcoma. Tumour composed of sheets of small spindle cells with dark condensed nuclei and pink (on H and E) cytoplasm streaming from one end. H and E $\times 250$.*

Fig. 5 *Despite postmortem autolysis a band of filaments is seen in a tumour cell cytoplasm. $\times 9600$.*

Fig. 6 EM appearance of filaments in embryonal rhabdomyosarcoma measuring $140 \text{ \AA}$ in diameter. Note dark bodies and parallel arrangement of filaments. Highly suggestive of myogenic origin. No cross striations seen. $\times 28\,750$.

have been disappointing. Case 1, an angiosarcoma, is among the least common of primary malignant tumours of the heart (McNally *et al.*, 1963). The majority of cases, including our own, occur in middle-aged adults, the usual primary site being the right atrium. In a recent case report (Rossi *et al.*, 1976), the striking similarity of the clinical presentations of the tumour has been pointed out; precordial pain, pyrexia, cough, and weakness are especially common symptoms. Cardiomegaly and non-specific ST changes on the ECG are frequently reported. Diagnosis is rarely made ante-mortem. In only one reported case were tumour cells found in a pericardial aspirate (Tacket *et al.*, 1950). Though metastases to bone are relatively infrequent, tumour cells have been found by bone marrow biopsy (Blanchard and Hethrington, 1952; Adgey *et al.*, 1977). A few cases were diagnosed by angiocardigraphy and pneumocardiography. The first case treated by excision using extracorporeal bypass has

recently been reported (Rossi *et al.*, 1976). The patient died four-and-a-half months later. The longest survivor on record was treated by surgical excision of the tumour from the left atrium (without extracorporeal bypass) and remained free of disease for three years (Hager *et al.*, 1970). The dominant malignant cell in angiosarcoma is endothelial. The light microscopic features of the tumour described here fulfil the criteria set forth for its classification as an angiosarcoma. The ultrastructural studies show some but not all of the features demonstrated in angiosarcomata of the spinal cord (Ramsey, 1966) and liver (Pollard and Millward-Sadler, 1974). The voluminous cell cytoplasm with irregular borders, the cytoplasmic vesicles and fibrillar bodies, and extensive extra cellular material are evident. Condensation of this extracellular material appears to give the characteristic reticulin pattern to angiosarcomata seen with silver stains (Ramsey, 1966). The high content of rough endoplasmic reticulum

may be a reflection of active production of basement membrane by the tumour cells.

The extensive cytoplasmic processes projecting into vascular lumina, which have been described in an angiosarcoma of the spinal cord (Ramsey, 1966), are not seen in our case.

In contrast, case 2, primary cardiac embryonal rhabdomyosarcoma, is commoner and occurs in all age groups. In a review of 30 cases (Porter *et al.*, 1961), the ages ranged from 3 months to 80 years. The right atrium was the commonest site of origin, but all four heart chambers were represented. Presenting symptoms included chest pain, pericardial effusion, and symptoms referable to valve obstruction. Atrioventricular conduction defects (Porter *et al.*, 1961) and pulmonic stenosis (Pund *et al.*, 1963) have also been presenting features. Angiography plays an important role in diagnosis (van der Hauwaert, 1971). The histological typing of the tumour in this case presented difficulties. The tumour was clearly a malignant sarcoma, and the presence of large cells, among the more immature spindle cells, with eosinophilic cytoplasm suggested nonstriated rhabdomyoblasts. The electron microscopic finding of cytoplasmic accumulations of filaments is identical with those found in a previous study of the fine structure of an embryonal rhabdomyosarcoma (Toker, 1968). The author observed that, taken on their own, these findings do not characterise the tumour as of myogenic origin. Nevertheless, taken with the rest of the evidence, the collections of fibres are almost certainly myofilaments, thus classifying the tumour as an embryonal rhabdomyosarcoma. It has been stated (Toker, 1968) that when cross striations cannot be found by convenient methods they will not be found by electron microscopy either, as in our case. However, a hint of Z band formation may be seen (Caulfield, 1972). It has been suggested that the tumour is recapitulating embryonic myogenesis, and similarities between the tumour cell and the chick myoblast have been pointed out.

In classifying rare sarcomata of the heart, Pomerance and Davies (1975) emphasise that a consideration of its possible vascular or myogenic origin is mandatory. It is suggested that many tumours classified as fibrosarcomata are in fact rhabdomyosarcomata (Pomerance and Davies, 1975). This paper has shown that electron microscopy used as an adjunct to conventional methods can aid greatly in such problematic cases.

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