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Cardiac myxomas: immunohistochemical study of benign and malignant variants

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Summary. Immunohistochemical investigation of 11 cardiac myxomas (CMs) including one malignant metastasizing CM showed a co-expression of epithelial (lu-5 and CAM 5.2), mesenchymal (vimentin) and neuroendocrine antigens (neuron-specific enolase) in all tumour cells. Factor VIII was found in the endothelial cells of capillaries only. In the subendocardium of fetal heart tissue close to the foramen ovale myofibroblasts reacting with the panepithelial antibody lu-5 were detected. We conclude that CMs are neoplasms that may develop from embryonic cell remnants.

Key words: Cardiac myxoma – Immunohistochemistry – Histogenesis

Introduction

The origin of cardiac myxomas (CMs) has been much debated but today most authors agree with the view that they are neoplasms rather than thrombotic masses (Ferrans and Roberts 1973; Sayler et al. 1975; Wold and Lie 1980). The histogenesis of CMs is still unclear in spite of histochemical, ultrastructural, immunohistochemical and tissue culture studies (Johansson 1989). Since CMs most often arise on the lower circumference of the foramen ovale, it has been suggested that they develop from the undifferentiated embryonic remnants which are found in that region (Boxer 1984; Johansson 1989). From immunohistochemical studies, it has been concluded that CMs are derived from endothelial cells because of positive staining of stromal myxoma cells with factor VIII (Morales et al. 1981).

The aim of our study was to obtain more insight into the histogenesis of benign and malignant variants of CMs using immunohistochemistry.

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Patients and methods

Eleven patients (6 females, 5 males) with a mean age of 47 years (19–60) were treated surgically for CMs between 1969 and 1987 in the Kantonsspital Basel (Table 1). Five patients suffered from mechanical obstruction and three from non-specific symptoms typical of myxoma. Three patients presented with symptoms of multiple systemic emboli, but without evidence of development of metastases. Only case 11 had malignant CM with metastases in the right gastrocnemius muscle, over the right scapula, in the left thigh, in the lung and the brain. The first two lesions had been resected and histological and immunohistochemical findings were identical to the primary tumour, resected from the heart 2 months before. Total brain irradiation was carried out during 2 months because of rapid tumour growth. In the meantime the pulmonary metastases and the metastases in the left thigh had been detected and required systemic chemotherapy. Twenty-two months after the cessation of chemotherapy the patient is well and tumour free as documented by several CT scans.

The resected tumour specimens were fixed in 4% buffered formaldehyde (pH 7.2) and embedded in paraffin. Sections 5 µm thick were used for conventional light microscopy and immunohistochemistry. For light microscopy, the slides were stained with haematoxylin and eosin, elastic van Gieson, Prussian blue for iron and alcian blue-periodic acid-Schiff reagent (AB-PAS). For the immunohistochemical investigation the ABC method was used (Hsu et al. 1981). Immunoreactivity, source and dilutions of the 13 antibodies used are listed in Table 2. Formalin-fixed and paraffin-embedded fetal tissue from the circumference of the foramen ovale, from three stillborn infants with a gestational age of 27, 28 and 34 weaks, was treated as described above. The staining reaction of the antibodies was scored as negative or from + to +++ for low, medium and high intensity, respectively. If only groups of cells were stained, "f" for focal was recorded.

Results

Ten CMs (Table 1) were located in the left atrium, 4 of them at the lower border of the foramen ovale. Seven were pedunculated, whereas 3 attached directly to the atrial wall, without pedicle. Case 9 was multicentric in left and right atrium. The mean tumour diameter was 6 cm. Most tumours showed the typical myxoid, vitreous glossy aspect with lobulated surface.

Table 1. Overview of the cases

Case	Age	Sex	Localization	Main symptoms	Macroscopy	Special histological features
1	32	F	Left atrium near superior pulmonary veins orifices	Systemic embolism	Pedunculated myxoma 5 × 4,5 × 2 cm	Multinucleated giant cells
2	62	M	Left atrium lower border of foramen ovale	Mechanical obstruction	Pedunculated, polypoid myxoma 7 × 6,5 × 2 cm	Myxoid matrix, haemorrhagic areas
3	57	F	Left atrium lower border of foramen ovale	Mechanical obstruction	Non-pedunculated papillary and glossy myxoma 7 × 6,5 × 2 cm	Place of attachment rich in blood vessels, tumour cells single or in files
4	60	M	Left atrium near the anterior mitral valve	Mechanical obstruction	Pedunculated, polypoid myxoma with villous and papillary surface 7 × 4 × 3 cm	Large necrotic areas
5	51	M	Left atrium lower border of foramen ovale	Systemic embolism	Non-pedunculated, polypoid and glossy myxoma 7 × 6,5 × 5 cm	Low cellularity
6	52	F	Left atrium at the septum, near anulus fibrosus	Myxoma disease	Pedunculated, polypoid myxoma with glossy gelatinous and brown areas 6 × 4 × 3,5 cm	Large blood vessels at the place of attachment
7	39	M	Left atrium lower border of foramen ovale	Myxoma disease	Pedunculated, polypoid myxoma with haemorrhagic areas and calcifications 7 × 6 × 4,5 cm	Many giant cells, areas of necrosis, degenerative polymorphism of cells and nuclei
8	44	F	Left atrium at the septum, near mitral valve	Myxoma disease	Pedunculated, polypoid myxoma with glossy gelatinous and haemorrhagic areas 5 × 4 × 3 cm	Myxoid matrix rich in blood vessels, glandular structures
9	19	F	Left and right atria multicentric	Systemic embolism	Pedunculated and non-pedunculated polypoid gelatinous myxomas 5 × 5 × 1,6 cm	Many giant cells
10	66	F	Left atrium at the septum, near superior pulmonary veins orifices	Mechanical obstruction	Non-pedunculated, glossy gelatinous myxoma 5 × 5 × 3 cm	Low cellularity
11	31	M	Left atrium at the septum	Mechanical obstruction	Non-pedunculated polypoid and papillary myxoma with cystic and gelatinous areas 6 × 6 × 3 cm	Spindle and polygonal cells with polymorphic, hyperchromatic nuclei with high mitotic rate Same histology in two different metastases

Light microscopic examination displayed the typical features of CMs in all cases. There was a myxomatous stroma with vascular channels of different size and scattered inflammatory cells such as macrophages, neutrophils and lymphocytes. The stroma was rich in neutral and acidic mucopolysaccharides, as demonstrated with AB-PAS stain. Several CMs revealed foci of haemorrhage. Calcification was present in 1 case. The tumour cells embedded in the stroma were mostly stellate or polygonal but round or spindle-shaped forms were also seen. In 4 specimens multinucleated giant cells were recognized. The cellularity varied from tumour to tumour. Blood vessels were often surrounded by tumour cells but in other sites they were distributed as single cells, small solid groups or pseudotubules. One tumour showed a widespread glandular pattern. Cellular atypia was not prominent. Nearly all tumours were covered by a single layer of cells, but in some the surface was even multilayered.

The malignant variant (case 11) was exceptional in that it displayed prominent cellular and nuclear atypia with numerous mitotic figures. This diagnosis was confirmed by the clinical course, with metastases to several sites.

All tumours (Table 3) reacted with the panepithelial antibody lu-5 (Fig. 1). The intensity was mostly scored as medium and in 3 cases the reaction was focal. A similar but weaker staining pattern was obtained with the anti-cytokeratin antibody Cam 5.2. With both epithelial markers vascular structures remained unstained.

Table 2. List of antibodies used in the study

Antibody antigen		Source	Working dilution
lu-5	Cytokeratins (Ck 1, 5, 6, 8, 14, 18, 19) (m/m)	Roche	1/4
Cam 5.2	Cytokeratins (Ck 8, 18, 19) (m/m)	Becton Dickinson	Prediluted
CEA	Carcinoembryonic Ag (m/m)	Amersham	Prediluted
b 12	Secretory glycoprotein (m/m)	Roche	1/500
Vim	Vimentin (m/m)	Boehringer	1/40
Desmin	Desmin (m/m)	Dako	1/100
SMA	Alpha-smooth muscle actin (m/m)	Sigma	1/4000
F.VIII	Factor-VIII-related Ag (m/m)	Amersham	Prediluted
UEA	*Ulex europaeus* agglutinin I (lectin)	E+Y Laboratories	1/100
NSE	Neuron specific enolase (m/m)	San Bio	1/50
S-100	S-100 Protein (r/p)	Dako	1/4000
CGA	Chromogranin-A (m/m)	Hybri Tech	1/1500
GFA	Glial fibrillary acidic protein (r/p)	*[a]	1/2000

For visualization of the reaction ABC kits from Vector were used. For abbreviations of antigens, please see text. m/m, mouse/monoclonal; r/p, rabbit/polyclonal

[a] Gift from L.F. Eng, Palo Alto

Table 3. Results of immunohistological staining in myxomas and fetal heart

Case	Cell type	Epithelial marker				Mesenchymal marker				Neuroendocrine marker				
		lu-5	Cam 5.2	CEA	b 12	Vim	Desmin	SMA	F.VIII	UEA	NSE	S-100	CGA	GFA
1	Tumour cells	++	+	neg	++/f	++	neg	+++	neg	neg	+/f	neg	neg	neg
	Endothelium	neg	neg	neg	neg	+++/f	neg	neg	+	+	neg	neg	neg	neg
2	Tumour cells	++/f	++	neg	neg	++	neg	+++	neg	neg	+/f	neg	neg	neg
	Endothelium	neg	neg	neg	neg	+++	neg	neg	+	+++	neg	neg	neg	neg
3	Tumour cells	++	+	neg	+/f	+++	neg	++	neg	neg	++/f	++/f	neg	neg
	Endothelium	neg	neg	neg	neg	+++	neg	neg	+/f	+/f	neg	neg	neg	neg
4	Tumour cells	+/f	+	neg	neg	++	neg	++	neg	neg	+/f	+/f	neg	neg
	Endothelium	neg	neg	neg	neg	++	neg	neg	++	++	neg	neg	neg	neg
5	Tumour cells	+	+	neg	neg	++	neg	++	neg	neg	+/f	neg	neg	neg
	Endothelium	neg	neg	neg	neg	++	neg	neg	++	+/f	neg	neg	neg	neg
6	Tumour cells	++	+	neg	+/f	+++	neg	++	neg	neg	+/f	neg	neg	neg
	Endothelium	neg	neg	neg	neg	+++	neg	neg	++	+	neg	neg	neg	neg
7	Tumour cells	++	+	neg	+/f	+++	neg	+++	neg	neg	+++/f	++/f	neg	neg
	Endothelium	neg	neg	neg	neg	+++	neg	neg	+++	++/f	neg	neg	neg	neg
8	Tumour cells	++	+	neg	++/f	+++	neg	+++	neg	neg	+/f	+++/f	neg	neg
	Endothelium	neg	neg	neg	neg	+++	neg	neg	++	++	neg	neg	neg	neg
9	Tumour cells	++	++/f	neg	neg	++	neg	++	neg	neg	+/f	++/f	neg	neg
	Endothelium	neg	neg	neg	neg	++	neg	neg	++	++	neg	neg	neg	neg
10	Tumour cells	+	+	neg	neg	++	neg	+++	neg	neg	+/f	+/f	neg	neg
	Endothelium	neg	neg	neg	neg	++	neg	neg	++	++	neg	neg	neg	neg
11	Tumour cells	++/f	+/f	neg	neg	+++	neg	neg	neg	neg	+	neg	neg	neg
	Endothelium	neg	neg	neg	neg	++	neg	neg	+	+	neg	neg	neg	neg
Forman ovale in fetal heart														
	Myofibroblasts	+++	++	neg	neg	+	++	+++	neg	neg	neg	neg	neg	neg
	Endothelium	neg	neg	neg	neg	+	neg	neg	++	+	neg	neg	neg	neg

Intensity Scores: +, Low; ++, medium; +++, high; neg, negative; f, focal

Monoclonal antibody b12, recognizing secretory epithelial cells, gave a low and focal reaction in 5 tumours. Vimentin was found in all tumour cells and all blood vessels (Fig. 2).

Factor VIII and *Ulex europaus* agglutinin (UEA), both markers of endothelium, stained all vascular elements in the 11 tumours but not the tumour cells. In most specimens, neuron-specific enolase (NSE) antibody reacted with CM cells focally and weakly. The antibody directed against S-100 protein stained tumour cells in 5 cases.

Alpha-smooth muscle actin (SMA) stained the tumour cells of all CMs (Fig. 3) except the malignant case. Endothelial cells were always negative. Carcinoem-

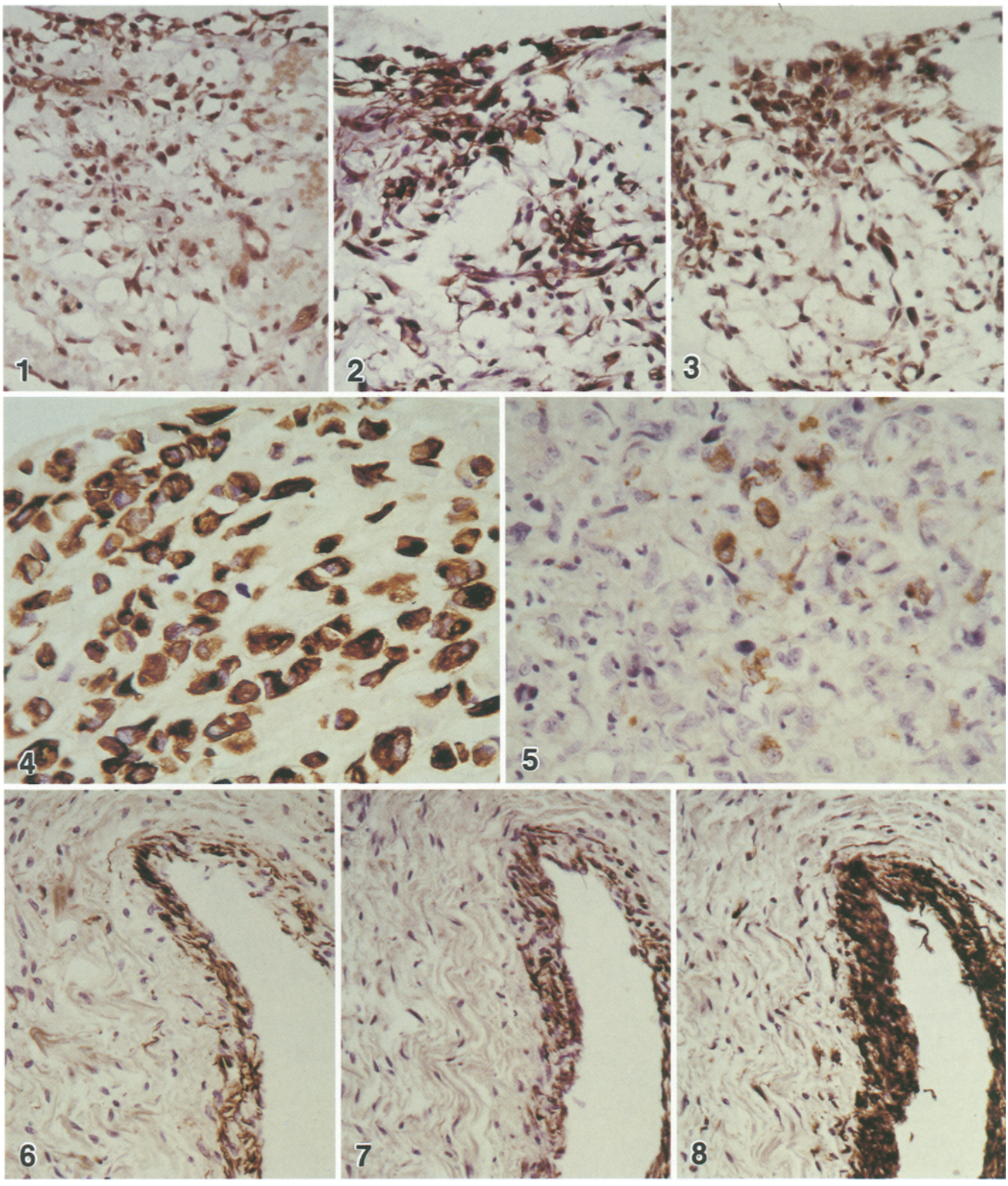

Fig. 1. Positive reaction of cardiac myxoma (CM) cells with lu-5 antibody; vascular structures are not decorated. ×210

Fig. 2. Positive reaction of CM cells and vascular structures with anti-vimentin, same sector as in Fig. 1. ×210

Fig. 3. Positive staining of CM cells but no reaction of endothelium with anti-alpha-smooth muscle actin. ×210

Fig. 4. Malignant CM, primary tumour in the heart stained with lu-5 antibody. ×335

Fig. 5. Metastasis of the malignant CM from the lefthigh showing a positive reaction with lu-5 antibody but of lower intensity. ×335

Fig. 6. Fetal heart near foramen ovale, positive reaction of subendocardial cells with lu-5 antibody. ×210

Fig. 7. Fetal heart near foramen ovale, positive reaction of subendocardial cells with desmin antibody. ×210

Fig. 8. Fetal heart near foramen ovale, positive reaction of subendocardial cells with anti-alpha-smooth muscle actin. ×210

Table 4. Summary of immunohistochemical results with overview of the literature

Reference	Cytokeratins		F.VIII		UEA		Actin		Vimentin		Desmin		S-100		CEA	
	Tumour cells	Endothelium	Tumour cells	Endothelium	Tumour cells	Endothelium	Tumour cells	Endothelium	Tumour cells	Endothelium	Tumour cells	Endothelium	Tumour cells	Endothelium	Tumour cells	Endothelium
Morales et al. 1981			18/18	18/18												
Boxer 1984			0/11	11/11			0/11	11/11								
McComb 1984			0/7	7/7												
Abenzoa and Sibley 1986	1/1[a]	0/1	0/1	0/1	1/1	1/1	1/1	0/1	1/1	1/1	0/1	0/1			1/1[a]	0/1
Landon et al. 1986			5/5f	5/5	5/5f	5/5										
Goldman et al. 1987	2/2[a]	0/2	0/2	2/2											2/2[a]	0/2
Schuger et al. 1987	0/7	0/7	0/7	7/7					0/7	7/7						
Tanimura et al. 1988			0/21	21/21	21/21	21/21										
Govoni et al. 1988	0/8	0/8	8/8	8/8			8/8	0/8	8/8	8/8	8/8	0/8				
Johansson 1989	4/19f[a]	0/19	0/19	19/19					0/19	19/19	0/19	0/19	10/19	0/19		
Own study 1991	11/11	0/11	0/11	11/11	0/11	11/11	10/11	0/11	11/11	11/11	0/11	0/11	6/11	0/11	0/11	0/11

Blank, note done; f, focal
[a] Glandular epithelium only

bryonic antigen (CEA), desmin, chromogranin-A (CGA) and glial fibrillary acidic proteni (GFA) were negative in all cases. The staining pattern found in the metastases of the malignant CM was identical to that of the heart tumour (Figs. 4, 5).

In the fetal heart immunohistochemistry revealed subendocardial myofibroblasts in the vicinity of the foramen ovale which gave a positive reaction for the epithelial markers lu-5 (Fig. 6) and Cam 5.2 as well as for desmin (Fig. 7), vimentin and smooth muscle actin (Fig. 8). No reaction with CEA, b12, factor VIII, UEA, NSE, S-100, CGA and GFA was seen in these cells, although some decoration was seen in other structures such as endothelial cells (Table 3).

Discussion

Cardiac myxoma is the most common primary tumour of the heart. About 75% of CMs are located in the left and 15% in the right atrium. The remaining 10% are located in the ventricles or are multicentric (Gould 1968; Pomerance and Davies 1975; Moser et al. 1978; McAllister 1979). The distribution of the localization in our cases agrees with these data.

A radical surgical excision is required for CM, but relapses are reported in 5–14% of cases (Richardson et al. 1979) where solitary or multifocal relapses occur months or even years after resection of the primary tumour (Read et al. 1974). Incomplete resection of the tumour with re-growth, intracardiac implantation of locally spread tumour cells or multiple tumour foci are all discussed as reasons for recurrences. There are no histological findings with predictive value for clinical behaviour.

Malignant CM is a rare entity and its existence is not universally accepted (Read et al. 1974; Seo et al. 1980; Rupp et al. 1989). The well known tendency to generalized embolism of CM fragments is an argument against malignancy and metastases. In fact, in 3 of our patients with systemic embolic disease, local growth was not found. Metastasis was therefore excluded and malignancy was not diagnosed. In contrast, infiltrative and progressive disease at distinct sites in 1 patient (case 11) together with severe atypia of the tumour cells was considered to be clear evidence of malignancy. Differential diagnosis includes tumours of different histogenesis, either primary or metastatic to the heart. Recently a case of angiosarcoma of the left atrium mimicking cardiac myxoma was described (Keohane et al. 1989). In contrast to our malignant CM these authors found atypical cells lining and protruding into vascular lumens. These cells and individual tumour cells in solid areas were stained by UEA. Factor-VIII-related antigen was found in cells lining vascular channels of the angiosarcoma; this was also found in CMs, but a wide spectrum cytokeratin antibody failed to react with angiosarcoma cells. This profile excludes an angiosarcoma in our case 11 and confirms the diagnosis of malignant CM. Our malignant variant of CM did not react with SMA in contrast with the benign variants; this is in favour of a lower degree of differentiation of the malignant tumour cells.

The co-expression of cytokeratin, demonstrated for two different epithelial markers (lu-5 and Cam 5.2) and of SMA, is identical to that found for subendocardial myofibroblasts near the foramen ovale of fetal heart. These subendocardial cells in fetal heart resemble the tumour cells morphologically. These findings militate against the derivation of CM from organized thrombi and strongly suggest that these tumour cells correspond to undifferentiated mesenchymal embryonic cell rests, with the ability to co-express epithelial and mesenchymal cytoskeleton structures. Johansson (1989) reported a positive reaction of Cam 5.2 anti-cytokeratin antibody in only 3 of 19 CMs, especially in one case with glandular structures. Two other studies described a positive reaction for cytokeratin antibodies in a single case of CM and two cases of CM with glandular structures, respectively (Abenzoa and Sibley 1986; Goldman et al. 1987). However, Govoni et al. (1988) failed to find tumour cells stained with cytokeratin antibodies in eight CMs although they also described glandular structures. These partly contradictory findings could probably be explained by the different types of cytokeratin antibodies used. The positivity found with the mucin-associated antibody b12 favours a further differentiation of glandular and of individual tumour cells. Intestingly staining was not confined to the glandular structures.

Vimentin positivity in all CM cells has also been found in previous studies (Abenzoa and Sibley 1986; Schuger et al. 1987; Johansson 1989). Since co-expression of vimentin with other intermediate filaments is quite common, the presence of this mesenchymal marker is not diagnostic, in terms of histogenesis. The overall intense reaction of SMA argues for a myogenic or myofibroblastic origin. Only once was a positive reaction with an actin antibody reported (Abenzoa and Sibley 1986). Desmin-positive cells, which would have favoured myogenic derivation, were not found. This corresponds with earlier reports (Abenzoa and Sibley 1986; Schuger et al. 1987) but is in contrast to recent findings in which 5 of 19 CMs were positive (Johansson 1989)

We could not conform the findings of different reports (Morales et al. 1977; Landon et al. 1986; Govoni et al. 1988) which have shown positivity of the tumour cells for factor-VIII-related antigen. However, our results are in agreement with several further studies (Boxer 1984; McComb 1984; Abenzoa and Sibley 1986; Goldman et al. 1987; Schuger et al. 1987; Tanimura et al. 1988; Johansson 1989). The positive reaction of tumour cells with neuroendocrine markers (NSE and S-100) may indicate a close relationship to the myoendocrine cells situated in the left and right atrium and producing atrial natriuretic peptide, or cardiodilatin, and other polypeptides (Forssmann 1986). The third neuroendocrine marker CGA failed to stain the tumour cells. Subendocardial fetal cells were, however, always negative for these markers. Only one recent study reported a variable positivity for S-100 protein in 10 of 19 CMs (Johansson 1989).

We conclude that the mixture of epithelial, mesenchymal and neuroendocrine markers found in CMs and in embryonic, pluripotent subendocardial myofibroblasts

or myogenic cells near the foramen ovale suggests that CMs originate from the latter.

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