

# Proliferative Lesions of the Heart and Vasculature in Rats

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## INTRODUCTION

Hyperplastic and neoplastic lesions are uncommon findings in the heart and vasculature of laboratory rats. The tumors that occur at these sites are usually considered incidental findings; however, instances of treatment-related cardiovascular tumors have been observed. A standardized nomenclature is proposed herein to classify and to facilitate communication among toxicologic pathologists.

## MORPHOLOGY

### HEART

#### *Endocardial Hyperplasia (Figures 1 & 2)*

Endocardial hyperplasia is characterized by non-invasive, subendocardial proliferation of fibroblast-like cells. This lesion occurs more often in older rats. The

ventricular endocardium is preferentially affected, and the change may be seen in atria or on valve leaflets. The overlying endocardium may be hypertrophied, and clear demarcation from the adjacent myocardium may or may not be present. This endocardial proliferation may be a precursor to schwannomas (4, 11, 21-23, 35).

#### *Schwannoma (Figures 3-6)*

Schwannoma occurs within the endocardium or myocardium (intramural). *Endocardial schwannoma* is the more common form and usually occurs as a single neoplasm in the left ventricle. The extent of myocardial invasion and the surface area of endocardial involvement is variable. Histologic appearance varies with the size of the neoplasm. Smaller neoplasms are composed of a mixed cell population. Spindle cells characterized by indistinct cytoplasm and fusiform hyperchromatic nuclei predominate. A lesser population, with indistinct cell boundaries and round to ovoid nuclei containing granular chromatin and prominent nucleoli, is also seen. Neoplastic cells are separated by a scant, pale eosinophilic matrix.

Larger, diffuse sub-endocardial schwannomas consist of two distinct layers, a superficial layer of round cells and a deeper layer of spindle cells. The spindle cells frequently form whorls around chordae tendineae or around

remnants of degenerated papillary myofibers. S-100 protein immunogold staining is usually positive within these larger neoplasms. With increasing extension into the myocardium, the spindle cells are admixed with pleomorphic, polygonal epithelioid cells. These epithelioid cells are characterized by eosinophilic cytoplasm, vesicular nuclei, single or multiple nucleoli, and indistinct cell boundaries. Mitotic figures are common. Metastases resembling the primary neoplasm may occur in the lung, liver, spleen, mediastinum, and bone marrow. Metastases are also S-100 protein-positive.

Occasionally, endocardial schwannomas may contain areas comprised of highly pleomorphic cells that may partially occlude the ventricular space and contain areas of ossification. The S-100 protein immunostaining properties of these less differentiated tumors have not been reported.

**Intramural schwannoma** occurs in the ventricular wall or interventricular septum and consists of spindle cells infiltrating between cardiac myofibers. The histologic appearance of these neoplasms, compared to endocardial schwannomas, is less variable. Small, solitary intracardial schwannomas are discrete foci of spindle cells with palisaded nuclei and occasional Verocay body formation. Larger intramural neoplasms consist of cells with loosely arranged eosinophilic fibrillar cytoplasm, oval nuclei with distinct nuclear membranes, and stippled chromatin. Cell boundaries are less distinct than seen in the smaller tumors. Neoplastic cells infiltrate between myocardial fibers and may extend to the epicardium. S-100 protein immunostaining is usually negative in intramural schwannomas (2, 4, 5, 7, 10, 14, 15, 19, 20, 26, 29, 30, 32, 36).

### **Mesothelioma (Figures 7-11)**

Mesothelioma may be classified as atriocaval or pericardial. **Atriacaval mesothelioma** is usually located on the epicardial surface of the right atrium and occasionally at the base of the inferior vena cava or in the atrial wall above the tricuspid valve. The predominant feature is the presence of numerous glandular/tubular structures. The structures are lined by a single layer of low, non-ciliated columnar to cuboidal cells with prominent round to irregular vesicular nuclei containing prominent nucleoli. The lumens contain cellular debris, erythrocytes, hematoidin crystals, pigment-laden macrophages, and/or occasional mineralized concretions. The stroma consists of fibroblasts, loose collagen, and a mixture of lymphocytes, macrophages, and occasional granulocytes. Hemorrhage and necrosis are prominent. The neoplasm may invade adjacent cardiac muscle and pericardial adipose tissue. Pulmonary metastases have been reported and the epithelial appearance is maintained by the metastases. Immunohistochemical staining for both vimentin and keratin are positive.

**Pericardial mesothelioma** consists of multiple, plaque-like tubular and papillary proliferations of mesothelial cells mixed with minimal to moderate fibrous stroma within the pericardial sac. Neoplastic cells are polygonal and have pleomorphic round to ovoid vesicular nuclei, eosinophilic cytoplasm, and indistinct cell borders. Metastases to other tissues have not been reported. Immunohistochemical stain for vimentin is positive. Very rarely, tumors with features of both atriocaval and pericardial mesotheliomas may occur (3, 6, 7, 12, 13, 19, 21, 27, 28, 31, 34, 38, 39).

### **Paraganglioma (Aortic Body Tumor)**

Paraganglioma is a rare lesion that may be found in the interatrial septum. The neoplasm consists of nests of round cells with granular, faintly basophilic cytoplasm, and vesicular stippled nuclei; the nests are surrounded by delicate reticulin fibers. Mitotic figures are rare. Metastasis has not been reported (2, 9, 11, 33, 38).

### **Hemangioma (Figure 12)**

Hemangiomas are discrete nodules composed of minute blood-filled cavities lined by a single layer of endothelial cells and separated by minimal stroma. Areas of hemorrhage, thrombosis, necrosis, and inflammation occur (1, 2, 25, 37).

### **Rhabdomyosarcoma**

The microscopic features of the few cardiac rhabdomyosarcomas observed in rats are similar to cardiac rhabdomyosarcoma in other species. The neoplasm is poorly demarcated. Neoplastic cells are pleomorphic and have abundant eosinophilic and slightly granular cytoplasm. Nuclei are large and vesicular with a prominent nuclear membrane. Multinucleated cells are common and are often large.

Some myocardial rhabdomyosarcomas do exhibit cross-striations; these myofibrils may be distinguished by polarized illumination or PTAH stain. Electron microscopy can also be used for recognition of myofibrils (10, 13, 20, 38).

### **Fibroma**

The histopathologic features of fibroma are similar to those in other tissues. The neoplasm is well demarcated and consists of well differentiated fibrocytes and fibroblasts surrounded by collagen. Positive staining for collagen by trichrome or other collagen stains could be used to differentiate fibroma from other benign mesenchymal neoplasms (1, 3, 17, 34).

### **Fibrosarcoma**

Fibrosarcomas of the heart are histopathologically similar to fibrosarcomas in other tissues. It is poorly demarcated and infiltrative and has an immature collag-

enous matrix. The fibroblast is the predominant cell. Pericardial fibrosarcoma may be distinguished due to the anatomical location of the neoplasm (1, 3, 8, 13, 20, 21, 26, 38).

### ***Myxoma***

Myxoma consists of poorly differentiated mesenchymal cells within a loose amorphous matrix substance. Positive staining of the matrix for glycosaminoglycans by PAS/alcian blue could be used to differentiate myxoma from other mesenchymal neoplasms (1, 3, 11, 25, 34).

### ***Lymphosarcoma***

Lymphosarcoma in the heart is similar to that in other tissues. Infiltrates vary from proliferating mature lymphocytes to undifferentiated lymphoid cells. Infiltration of the myocardium occurs in leukemic rats (3, 8, 11, 20, 25, 27, 39).

## **VASCULATURE**

Proliferative changes of the vasculature have been reported in blood vessels but not in lymphatic vessels.

### ***Hemangioma***

Hemangioma may occur in any organ in rats but is most commonly found in the liver or spleen. The histopathologic features have been described above.

### ***Hemangiosarcoma***

Hemangiosarcoma is composed of blood-filled spaces lined by pleomorphic polygonal to spindle shaped cells separated by connective tissue stroma. Mitotic figures and hemorrhage are common.

### ***Hemangiopericytoma***

Hemangiopericytomas occur in the spleen and subcutis. They consist of fusiform fibroblast-like cells arranged in whorls that surround small blood vessels. This can be confirmed by reticular stain. The presence of basement membrane around pericytes, ultrastructurally differentiates hemangiopericytoma from endothelial neoplasms (1, 8, 11, 21, 27, 34, 37).

## **DISCUSSION**

Spontaneously occurring proliferative lesions of the heart and vasculature are rare in most strains of laboratory rats (1, 27, 29). The type and incidence of spontaneous heart tumors varies with the strain of rat studied. Although the tumors that occur at these sites are usually considered to be incidental findings in most carcinogenicity studies, instances of treatment-related heart and vascular tumors

have been observed in rats. Several types of cardiac tumors including rhabdomyosarcoma, fibroma, fibrosarcoma, hemangioma, and myxoma are extremely rare and few examples of each have been reported. There are very few similarities in the morphologic features of the different types of cardiac tumors in the rat. Both immunohistochemistry and ultrastructural methods have been used to further characterize these tumors; however, each type can be readily identified and distinguished based upon their gross and microscopic morphologic features by routine H&E sections.

The most common spontaneous cardiac tumors in the rat are the endocardial and intramural schwannomas (1, 29). Endocardial tumors are more common than intramural tumors. The incidence of spontaneous endocardial schwannoma varies with the strain of rat. No endocardial tumors were identified in a group of 590 BDIX strain rats, while the incidence ranged from less than 0.1% in the F344 rat to 7.0% in the BN./Fih strain (29). Treatment-related endocardial schwannomas have been reported in several strains of rats administered derivatives of carbamates and acetylaminofluorene (18) and nitrosamines (4).

Reports in the literature list a number of different synonyms for cardiac schwannoma, including: benign and malignant endocardial mesenchymal tumor or endocardial tumor, neurinoma, neurofibromatosis, and endomyocardial disease. While the variance in terminology suggests an uncertainty in both the nature of the lesion and the cell of origin, there is a general consensus that this type of proliferative cardiac lesion represents a neoplasm. Many morphologic features previously described strongly support a Schwann cell origin. Based upon morphologic criteria, the small, non-invasive, focal proliferations in the subendocardium are diagnosed as hyperplasia. However, the morphologic distinction between the benign and malignant schwannoma is less clear. While some tumors have marked cellular pleomorphism, extensive myocardial invasion, and even metastatic foci, other examples of moderately invasive tumors have morphologic features similar to those seen in focal hyperplasia. For this reason an attempt to categorize these tumors as benign or malignant may have little biological significance.

Atriocaval mesothelioma is a rare tumor in many strains of rats. An incidence of less than 0.1% (8/79,971) was reported for the F344 rat (1) but an incidence of nearly 20% has been observed in the NZR/Gd strain (16). In both the F344 and NZR/Gd strains, atriocaval tumors are more common in males than in females. A treatment-related increase in atriocaval mesothelioma has been reported with nitrosododecamethyleneimine administration (16), and development of pericardial mesothelioma has been reported following intrathoracic administration of fibrous materials (18).

Paraganglioma (aortic body tumor) also is a rare cardiac tumor in rats. An incidence of less than 0.05% (3/

79,971) was reported in the F344 rat (1), but a 13% incidence of hyperplasia/neoplasia has been reported in the WAG/Fij strain (35). There have been no reports of a treatment-related increase in paraganglioma of the heart.

With the exception of a few hemangiomas that have occurred in the heart, spontaneous proliferative lesions of the vasculature are extremely rare in rats. Hemangiosarcoma has been induced in the spleen following oral administration of a number of aniline compounds (17), as well as in the liver with inhalation exposure to vinyl toluene (24).

Formalin-fixation, paraffin-embedding, and H&E-staining are reliable techniques for making morphologic diagnoses of most proliferative cardiovascular changes. In some cases, such as the schwannomas and mesotheliomas, electron-microscopic and immunohistochemical methods may be required for diagnosis. As specialized morphologic methods evolve, newer methods may be applied in the future in order to define more accurate criteria for equivocal diagnostic cases.

## RECOMMENDED NOMENCLATURE AND DIAGNOSTIC CRITERIA

### HEART

#### *Endocardial Hyperplasia*

1. Non-invasive, subendocardial proliferation of fibroblast-like cells
2. Ventricular endocardium is preferentially affected

#### *Schwannoma*

##### *Endocardial Schwannoma*

Small neoplasms

1. Composed of spindle cells with indistinct cytoplasm and fusiform hyperchromatic nuclei
2. Cells are separated by scant, pale eosinophilic matrix

Larger neoplasms

1. Have superficial layer of round cells and deeper layer of spindle cells
2. Cells form whorls around chordae tendineae or degenerated myofibers

Extensive neoplasms

1. Composed of pleomorphic spindle cells and polygonal epithelioid cells
2. Mitotic figures are common
3. Metastasis may occur in lung, liver, spleen, mediastinum, and bone marrow
4. Usually S-100 positive

##### *Intramural Schwannoma*

Small neoplasms

1. Spindle cells infiltrate between cardiac myofibers
2. Palisaded nuclei and Verocay bodies present
3. Usually S-100 negative

Larger neoplasms

1. Spindle cells infiltrate between myocardial fibers and may extend into epicardium
2. Loosely arranged eosinophilic fibrillar cytoplasm
3. Oval nuclei with distinct membrane and stippled chromatin
4. Indistinct cell boundaries
5. Usually S-100 negative

#### *Mesothelioma*

##### *Atriocaval Mesothelioma*

1. Numerous glandular/tubular structures lined with a single layer of low, non-ciliated columnar to cuboidal epithelial cells
2. Lumens contain cellular debris, erythrocytes, hematoidin crystals, pigment-laden macrophages, and/or occasional mineralized concretions
3. Hemorrhage and necrosis are prominent
4. Neoplasms may invade surrounding myocardium and pericardial fat

##### *Pericardial Mesothelioma*

1. Multiple, plaque-like tubular and papillary proliferations in the pericardial sac
2. Polygonal cells with pleomorphic round to ovoid vesicular nuclei, eosinophilic cytoplasm, and indistinct cell borders

#### *Paraganglioma*

1. Nests of round cells with granular, faintly basophilic cytoplasm
2. Surrounded by delicate reticulum fibers
3. Mitotic figures are rare

#### *Hemangioma*

1. Blood-filled cavities lined by a single layer of well-differentiated endothelial cells
2. Hemorrhage, thrombosis, necrosis, or inflammation may be present

#### *Rhabdomyosarcoma*

1. Poorly demarcated neoplasm composed of pleomorphic cells
2. Cells have eosinophilic, slightly granular cytoplasm; multinucleated cells are common
3. Myofibril demonstration by polarized illumination or PTAH stain, if present

#### *Fibroma*

1. Well-demarcated neoplasm consisting of fibrocytes and fibroblasts surrounded by collagen
2. Trichrome or other collagen stains can differentiate

fibroma from other benign mesenchymal cells

### **Fibrosarcoma**

1. Poorly demarcated
2. Composed predominantly of fibroblasts
3. Form fascicles/herring bone pattern

### **Myxoma**

1. Poorly differentiated mesenchymal cells surrounded by loose amorphous matrix substance
2. PAS/alcian blue stain glycosaminoglycans in the matrix

### **Lymphosarcoma**

1. Myocardium infiltrated by lymphocytes having varying degrees of differentiation

## **VASCULATURE**

### **Hemangioma**

1. Blood-filled cavities lined by a single layer of endothelial cells
2. Hemorrhage, thrombosis, necrosis, or inflammation may be present
3. Most commonly found in the liver

### **Hemangiosarcoma**

1. Blood-filled spaces lined by pleomorphic spindle-shaped to polygonal cells
2. Mitotic figures and hemorrhage are common

### **Hemangiopericytoma**

1. Fusiform fibroblast-like cells arranged in whorls surrounding small blood vessels
2. Basement membrane around pericytes
3. Found in the spleen and subcutis

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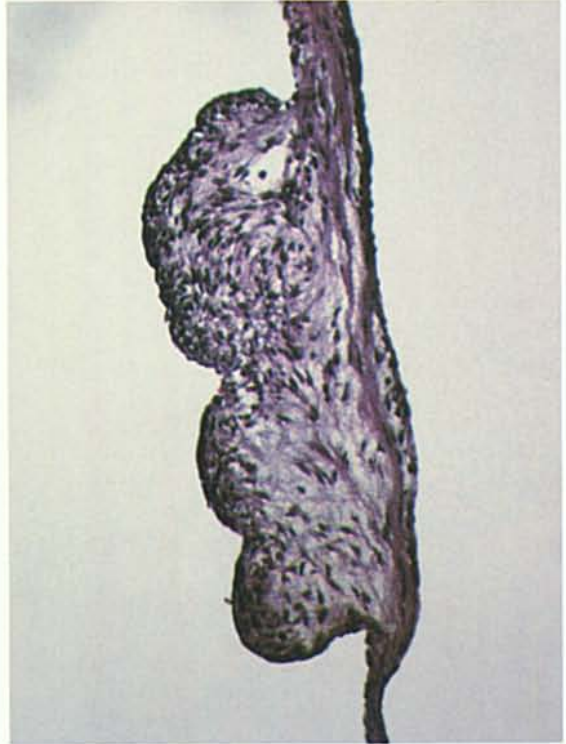
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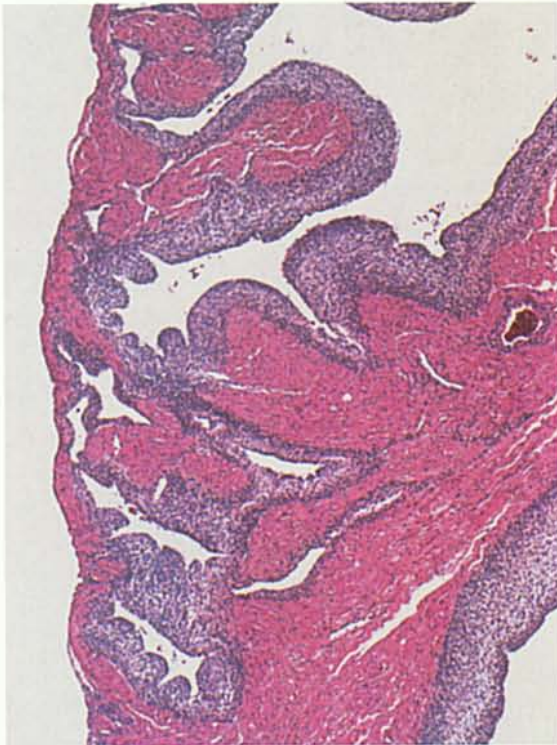




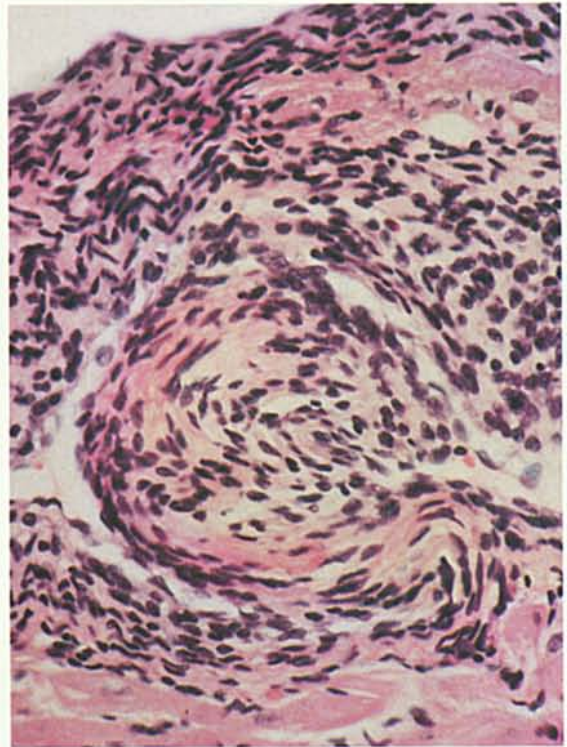
*Fig. 1 - Endocardial hyperplasia, ventricular (hematoxylin & eosin).*



*Fig. 2 - Endocardial hyperplasia, valvular (H&E).*

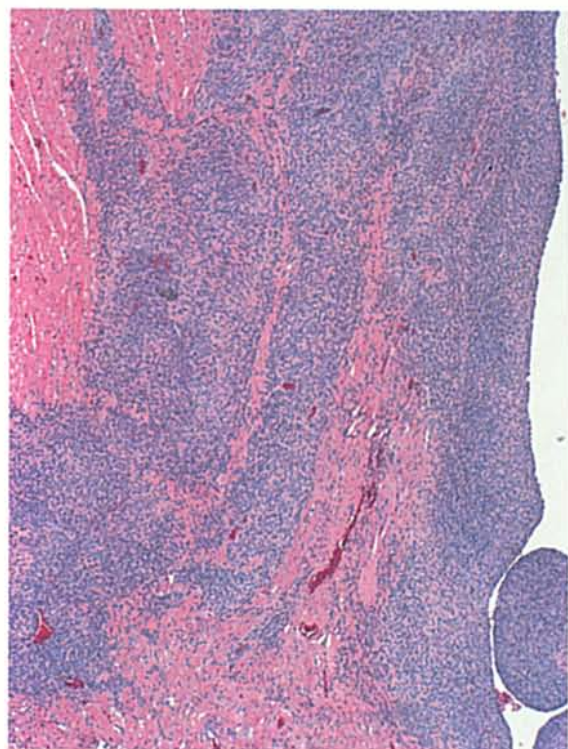


*Fig. 3 - Schwannoma, endocardial, low magnification (H&E).*

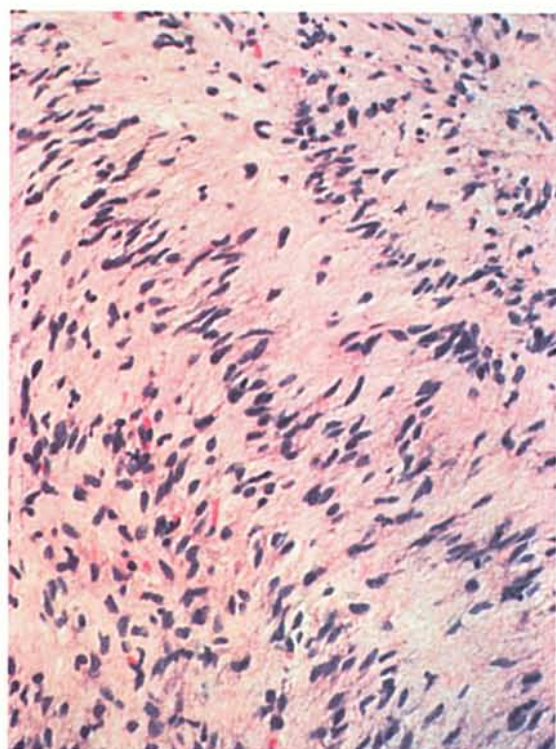


*Fig. 4 - Schwannoma, endocardial, high magnification (H&E).*

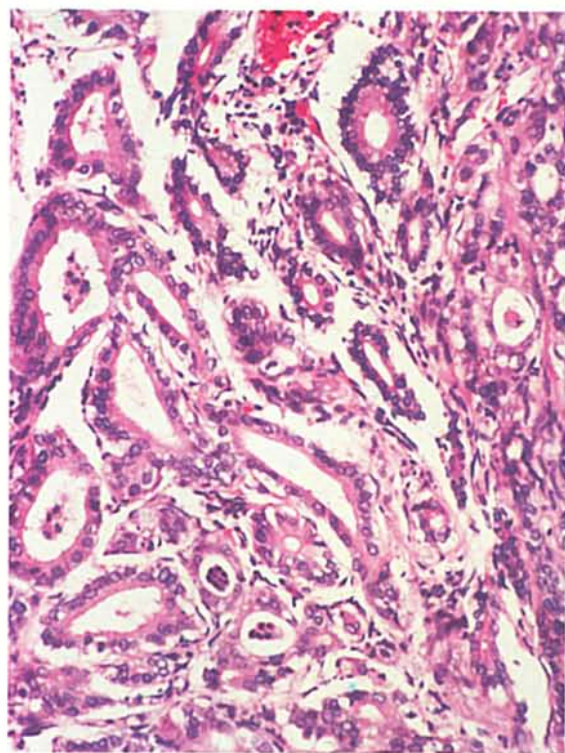




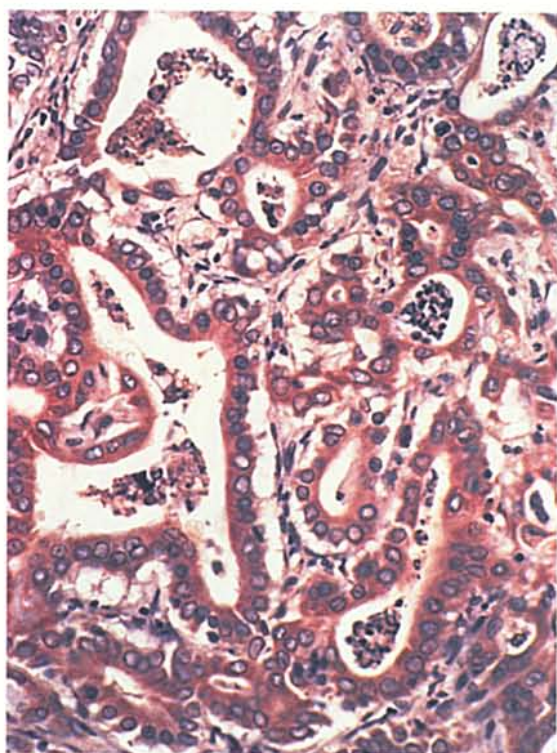
*Fig. 5 - Schwannoma, endocardial malignant (H&E).*



*Fig. 6 - Schwannoma, intramural, high magnification (H&E).*

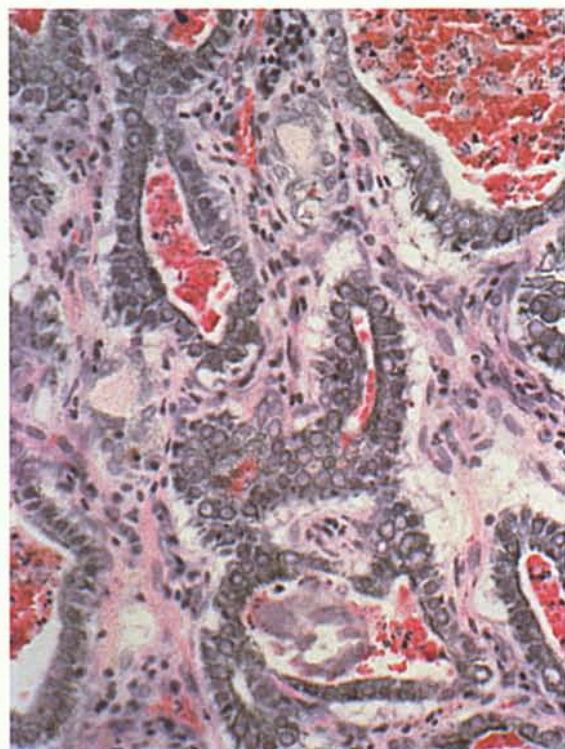


*Fig. 7 - Mesothelioma, atrio caval - glandular/tubular type, high magnification (H&E).*

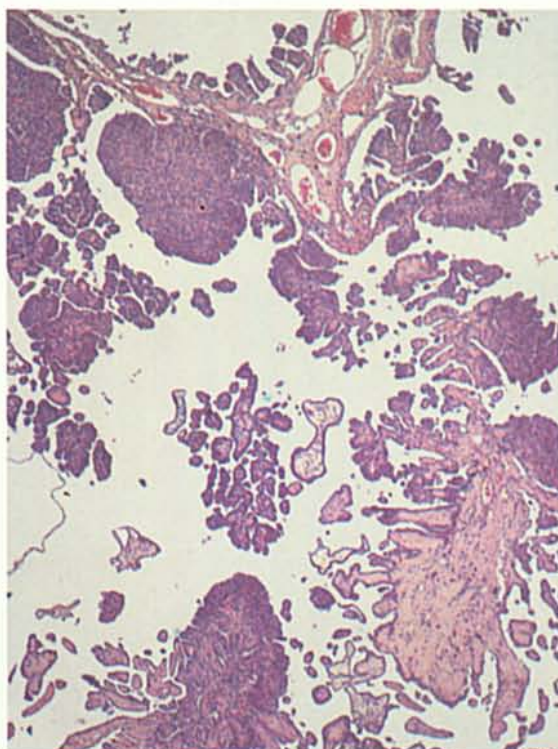


*Fig. 8 - Mesothelioma, atrio caval, positive immunohistochemical staining for vimentin.*

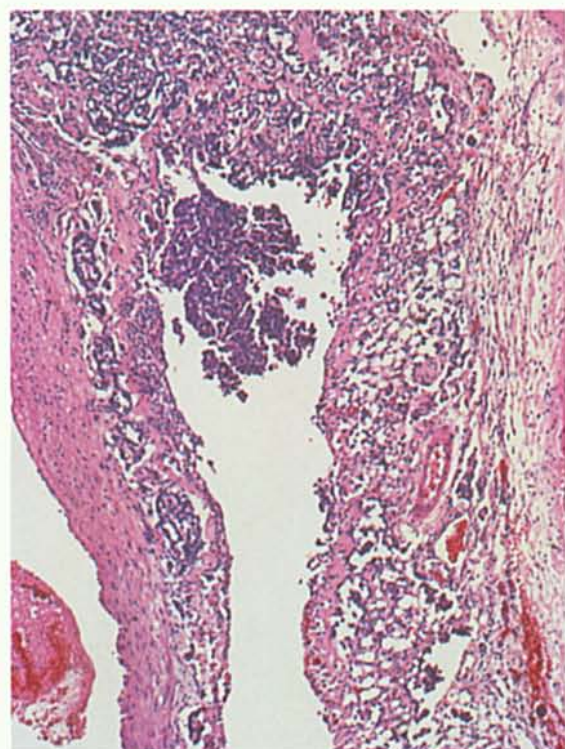




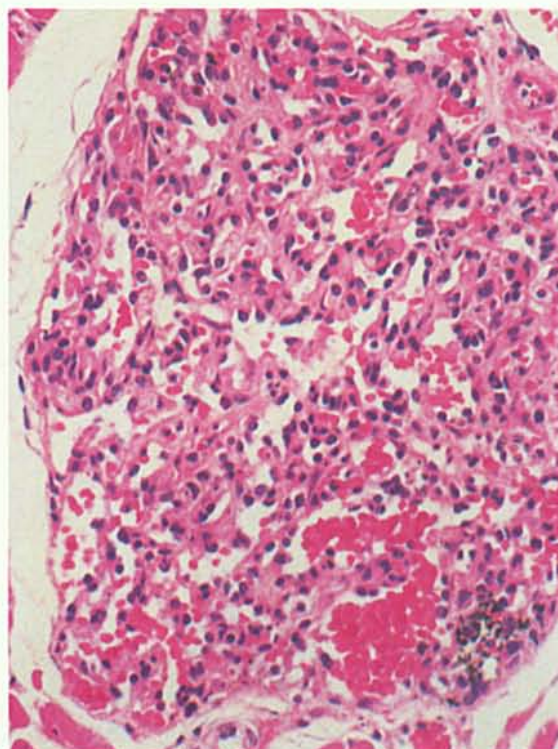
*Fig. 9 - Mesothelioma, atrio caval, positive immunohistochemical staining for keratin.*



*Fig. 10 - Mesothelioma, pericardial (H&E).*



*Fig. 11 - Mesothelioma, mixed, atrio caval and pericardial (H&E).*



*Fig. 12 - Hemangioma (H&E).*