Invited Review

The family of epithelioid vascular tumors

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Summary. Vascular tumors characterized by proliferation of epithelioid (histiocytoid) endothelial cells with abundant eosinophilic hyaline cytoplasm span a broad spectrum of histologic appearances and behaviour. They can occur in a wide variety of sites, such as soft tissues, skin, bone and visceral organs. On the benign end are the epithelioid hemangiomas (angiolymphoid hyperplasia with eosinophilia), which are composed predominantly of well formed vascular channels, and are frequently accompanied by an infiltrate of lymphocytes and eosinophils. In the literature, they have often been confused with Kimura's disease, an idiopathic allergic-inflammatory condition. There have also been controversies as to whether these lesions are neoplastic or reactive. In the middle of the spectrum are the borderline or low grade malignant epithelioid hemangioendotheliomas, characterized by isolated, cords and nests of epithelioid endothelial cells disposed in a hyaline or myxoid matrix; cytoplasmic vacuoles are common. However, the morphologic variations on this theme are very wide rendering recognition of these tumors difficult sometimes. On the malignant end are highly aggressive epithelioid angiosarcomas showing predominantly solid growth and significant nuclear pleomorphism. In addition, there are also cases showing histologic features straddling the borderline areas between the above three defined categories. In this review, the broad morphologic appearances of these epithelioid vascular tumors are discussed and illustrated.

Key words: Epithelioid vascular tumor, Epithelioid hemangioma, Angiolymphoid hyperplasia with Eosinophilia, Epithelioid hemangioendothelioma, Epithelioid angiosarcoma

Introduction

Vascular neoplasms characterized by proliferation of epithelioid endothelial cells span a broad clinicopathologic spectrum from benign epithelioid hemangioma on one end to frankly malignant epithelioid angiosarcoma on the other, with epithelioid hemangio-endothelioma occupying an intermediate position in both morphology and behaviour (Weiss et al., 1986; Enzinger and Weiss, 1988, Chan et al., 1992). There are, however, also cases falling into the «grey» areas between these three «discrete» points on the spectrum (Chan et al., 1992). There is no doubt that epithelioid hemangio-endothelioma and epithelioid angiosarcoma are genuine vascular neoplasms. However, the nature of epithelioid hemangioma is more controversial (Rosai, 1982; Chan et al., 1989; Fetsch and Weiss, 1991).

Epithelioid endothelial cells can also be present in other vascular lesions such as lobular capillary hemangioma, Masson's tumor and cellular hemangioma of infancy (Weiss et al., 1986). However, these lesions are characterized primarily by features other than epithelioid endothelial cells, and the epithelioid endothelial cells are focal if they occur at all. Epithelioid changes are also prominent in the endothelium of the endometrial blood vessels of the placental bed.

The concept of «histiocytoid hemangioma»

The designation «histiocytoid hemangioma» was proposed by Rosai et al. in 1979 for a group of vascular neoplasms occurring in diverse sites but unified by the characteristic «histiocytoid» appearance of the proliferated endothelial cells (Rosai et al., 1979). The histiocyte-like endothelial cells have even been demonstrated to possess some enzymes typically associated with histiocytes (Rosai et al., 1979; Rosai, 1982). On review of this classic paper, it is apparent that the authors have included what are now popularly known as epithelioid hemangioma and epithelioid
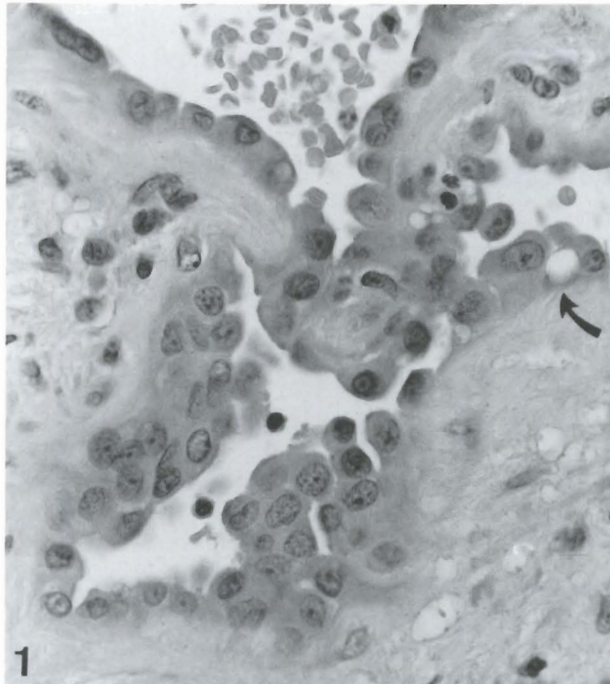
Fig. 1. Epithelioid endothelial cells in an epithelioid hemangioma showing the characteristic polygonal or hobnail outline and dense hyaline cytoplasm. The nuclei are oval or folded, with fine chromatin and occasional grooving. A cytoplasmic vacuole is indicated by an arrow. H&E. x 300
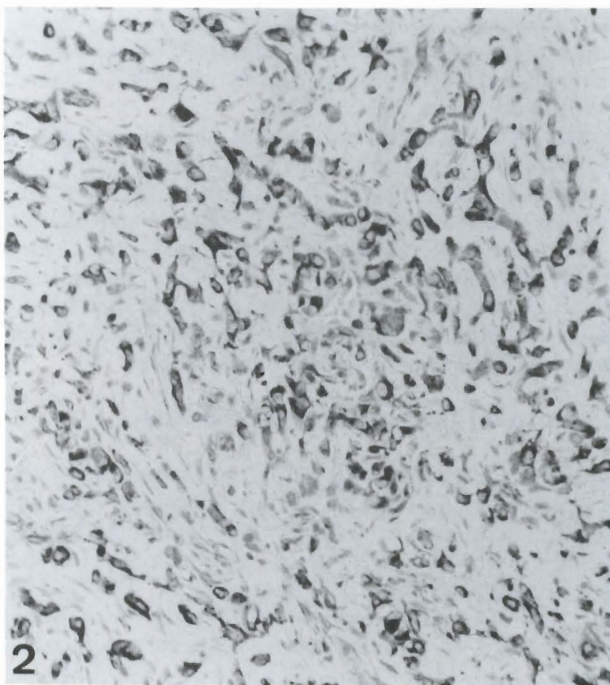
hemangioendothelioma (and even possibly epithelioid angiosarcoma) under this embracing label. In view of the different clinicopathologic features of these conditions, it is advisable to drop the term «histiocytoid hemangioma» from routine usage, while recognizing the contribution of these authors in the introduction of this important unifying concept (Rosai et al., 1987; Cooper, 1988).

It should be noted that the lesion considered by Rosai et al. (1979) to represent «histiocytoid hemangioma» of the heart and pericardium has now been reinterpreted as a peculiar form of nodular mesothelial hyperplasia (Luthringer et al., 1990).

The epithelioid endothelial cell

Epithelioid endothelial cells are characterized by polygonal outline, abundant eosinophilic hyaline cytoplasm, and a central oval or indented nucleus with or without grooving (Fig. 1). The abundance of hyaline cytoplasm is due to accumulation of intermediate filaments, notably vimentin (Angervall and Kindblom, 1991) (Fig. 2). Solitary or multiple cytoplasmic vacuoles
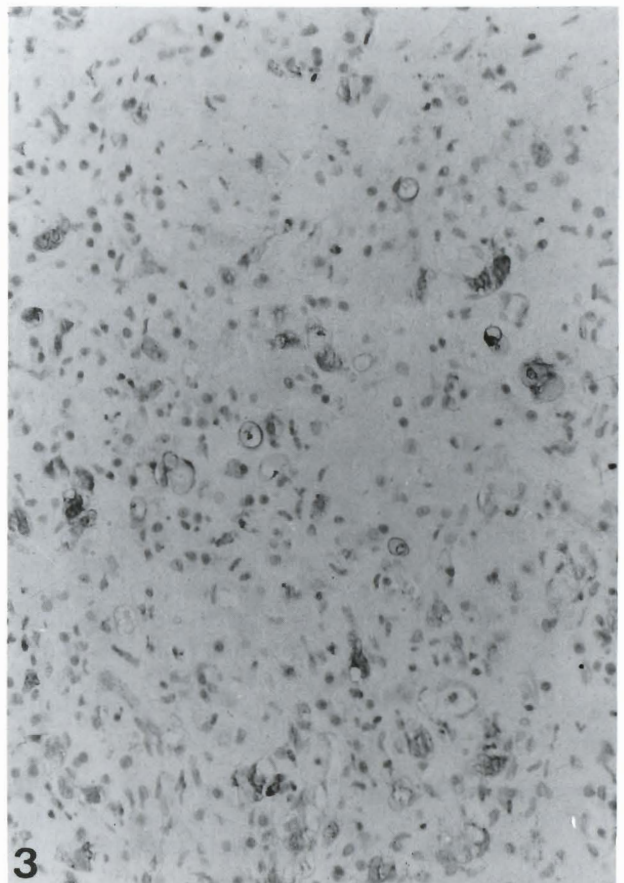

Fig. 2. Epithelioid hemangioendothelioma showing strong immunostaining of the tumor cells for vimentin. Note the characteristic growth pattern in the form of cords. Immunoperoxidase. x 150

Fig. 3. Immunostaining for Factor VIII-related antigen shows diffuse cytoplasmic positivity with accentuation around the cytoplasmic vacuoles in the tumor cells of epithelioid hemangioendothelioma. Immunoperoxidase. x 188
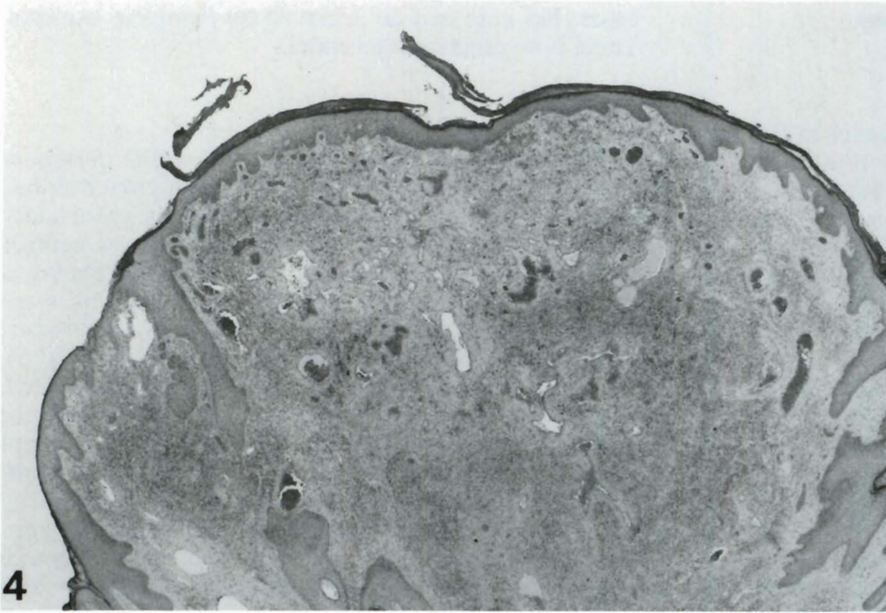
Fig. 4. Epithelioid hemangioma of the skin with non-circumscribed borders and epithelial collarette formation, resembling a pyogenic granuloma. H&E. x 15
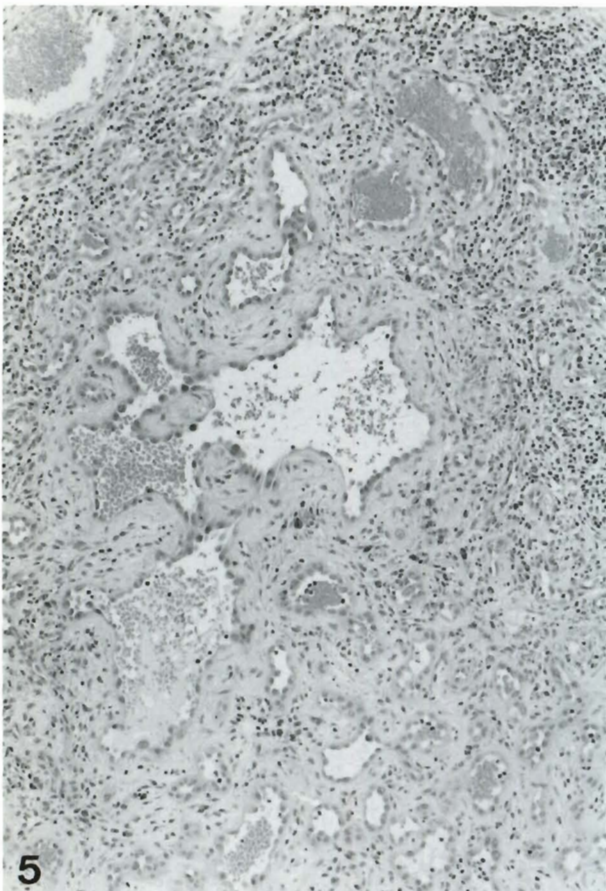

Fig. 5. Epithelioid hemangioma. Proliferated blood vessels with irregular lumina and papillary tufts lined by hobnail endothelial cells. Note the prominent mixed inflammatory infiltrate with eosinophils in the background. H&E. x 75

are common, and represent early vascular lumina formation (Fig. 1). Staining for factor-VIII related antigen and other endothelial markers (such as *Ulex europaeus*, CD34) reveals diffuse cytoplasmic positivity, often with accentuation in the vacuoles (Angervall and Kindblom, 1991; Traweek et al., 1991; Weiss and Enzinger, 1982) (Fig. 3). Cytokeratin, mostly low-molecular weight form, has frequently been demonstrated in epithelioid angiosarcoma, sometimes in epithelioid hemangioendothelioma, and potentially in epithelioid hemangioma (Battifora, 1990; Eusebi et al., 1990; Gray et al., 1990; Van Haelst et al., 1990; Fletcher et al., 1991; Maiorana et al., 1991). It is important to be aware of the possible occurrence of cytokeratin-immunoreactivity, lest these epithelioid tumors may be mistaken for carcinoma or other epithelial neoplasms.

The epithelioid endothelial cells have all the ultrastructural features of endothelial cells, such as basal lamina, pinocytotic vesicles and Weibel-Palade bodies (Rosai et al., 1979; Enzinger and Weiss, 1988). In contrast to the normal endothelium, alkaline phosphatase activity is absent or weak, and acid phosphatase and non-specific esterase can often be demonstrated (Castro and Winkelmann, 1974; Eady and Wilson-Jones, 1977; Rosai et al., 1979; Rosai, 1982).

Epithelioid hemangioma

Epithelioid hemangioma has been reported in the literature under a plethora of terms, such as angiolymphoid hyperplasia with eosinophilia, atypical or pseudopyogenic granuloma, inflammatory angiomatous nodule, papular angioplasia, inflammatory arteriovenous hemangioma, and intravenous atypical vascular proliferation, reflecting differences in opinion on its nature (Chan et al., 1989). It resides on the benign end of

the spectrum of epithelioid vascular tumors.

Clinical features

Epithelioid hemangioma typically occurs in the skin of the head and neck (particularly temporal and periauricular regions), but may also occur in the distal extremities, trunk and deep structures such as muscle, artery, bone, tongue and lymph node (Wilson-Jones and Bleehen, 1969; Rosai and Akerman, 1974; Barnes et al., 1980; Hidayat et al., 1983; Olsen and Helwig, 1985; Morton et al., 1987; Suster, 1987; Chan et al., 1989, 1992; Dannaker et al., 1989; Razquin et al., 1991). Of interest, one case has been reported to arise within an ovarian mature teratoma (Madison and Cooper, 1989).

This tumor occurs over a wide age range (mean 35 years), more commonly in males (Chan et al., 1989; Fetsch and Weiss, 1991). A small proportion (<20%) of cases may have eosinophilia in the peripheral blood. These lesions are solitary or occur as clusters in the same anatomic location. The superficial lesions appear as reddish skin papules or nodules that may ulcerate or bleed. Local recurrence occurs in about one-third of cases, but cure can be achieved by complete excision. There is no metastatic potential.

Pathology

The cutaneous lesions are located in the dermis or subcutis. The dermal ones are often non-circumscribed (Fig. 4), whereas the subcutaneous ones are usually circumscribed. A lobular growth pattern can sometimes be found. The most prominent and diagnostic feature is exuberant proliferation of capillary- to medium-sized blood vessels lined by oval, cuboidal or hobnail endothelial cells which may form papillary tufts (Fig. 5). Occasionally the proliferated vessels are thick-walled, and their smooth muscle coats often show myxoid change. Some blood vessels may be barely canalized (Fig. 7). The endothelial cells possess abundant eosinophilic hyaline cytoplasm (Figs. 1, 8). The nuclei are oval with fine chromatin and indistinct nucleoli. Nuclear pleomorphism is minimal to mild, although occasional nuclei may appear enlarged and hyperchromatic. Mitotic figures are rarely seen. Cytoplasmic vacuoles can often be identified in some
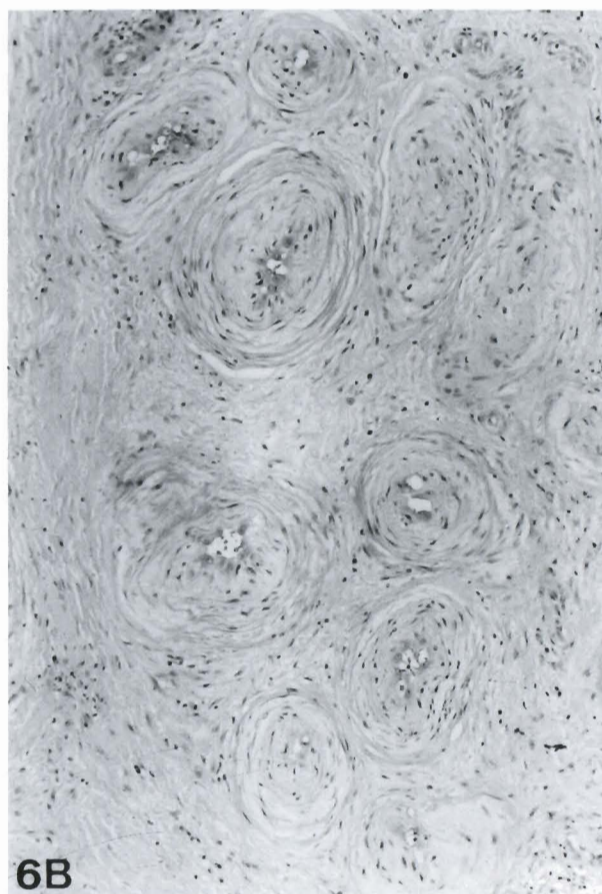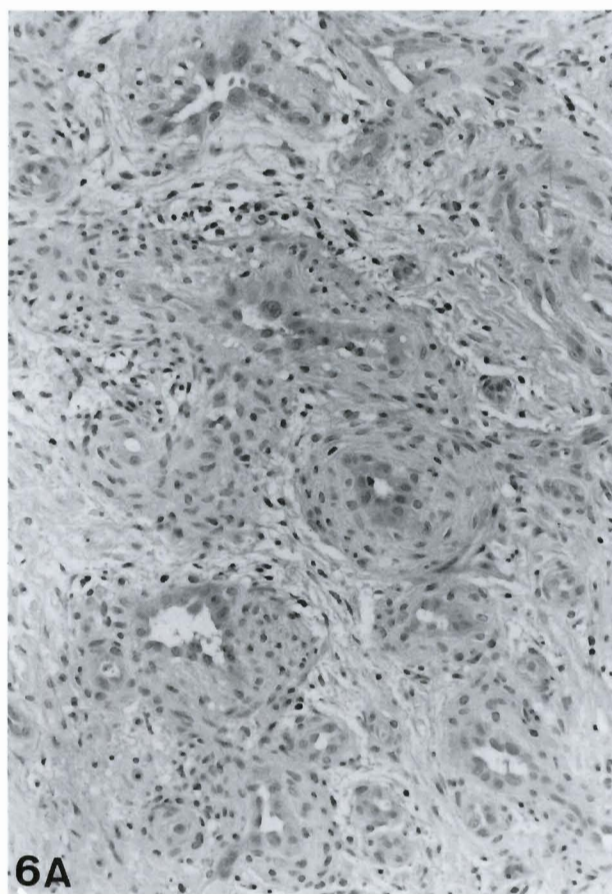
Fig. 6. Epithelioid hemangioma with proliferation of thick-walled vessels. **(A)**. Smooth muscle cells surround the vascular spaces. **(B)**. Concentric layering of the wall results from myxoid change. H&E, (A) x 150; (B). x 75

cells (Fig. 1). The vascular channels appear to be formed by fusion of the cytoplasmic vacuoles, and often take up a scalloped contour in the lumina (Fig. 8). Very focal occurrence of solid sheets, small clusters or cords is also acceptable within the morphologic spectrum of epithelioid hemangioma; these patterns are seen mostly around the walls of the larger pre-existing blood vessels (Fig. 9). In some cases, however, portions of the lesion may lack epithelioid features, that is, the lining endothelium appears flat (Fig. 10).

Involvement of or origin from a muscular artery or vein is common, with the vessel being lined by epithelioid endothelial cells, which frequently break through the intima, elastic lamina and muscle coat, becoming continuous with the surrounding proliferated vessels (Fig. 11). The intima and muscle coat are typically thickened by abundant myxoid matrix. Rarely, the entire lesion is located intravascularly (Rosai and Akerman, 1974).

A variable inflammatory infiltrate consisting of eosinophils, lymphocytes, plasma cells and mast cells, with or without lymphoid follicle formation, is often present (Figs. 5, 7, 10). It may form a dense cuff around the lesion, resulting in an appearance not unlike a lymph node (Fig. 12); this phenomenon occurs much more commonly in subcutaneous than dermal lesions (Olsen and Helwig, 1985). However, in some cases, the inflammatory component is completely lacking (Fig. 6).

The histologic features of lesions occurring in sites other than the skin are basically identical, but the amount of inflammatory infiltrate is highly variable.

Differential diagnosis

Epithelioid hemangioma differs from epithelioid hemangioendothelioma in being composed mostly of well formed blood vessels, lacking the chondromyxoid matrix containing isolated or cords of endothelial cells, and frequent presence of an inflammatory component (Table 1). It is most important not to misinterpret the poorly canalized vessels seen in some epithelioid hemangiomas for the cellular cords of epithelioid hemangioendothelioma (Fig. 7); they can be recognized by the presence of two rows of endothelial cells and
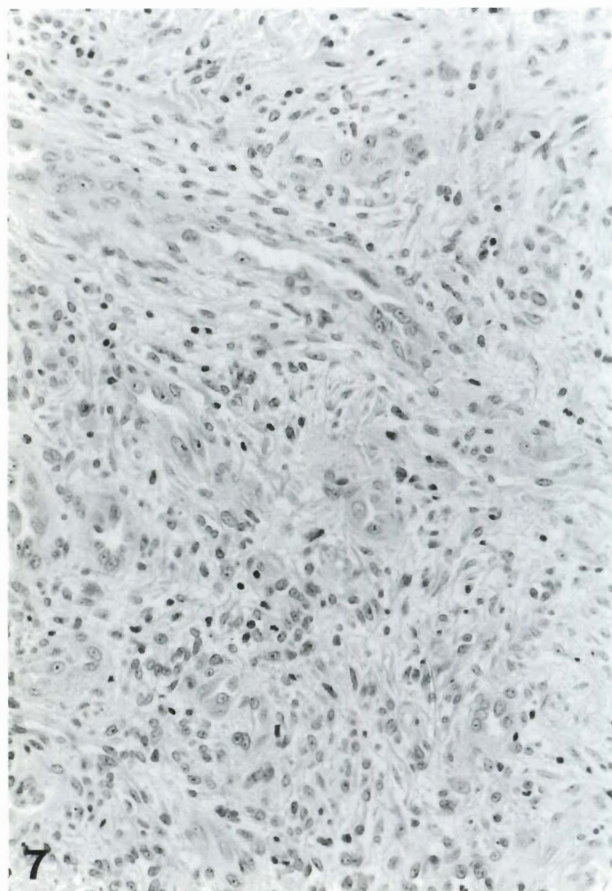

Fig. 7. Epithelioid hemangioma, with barely canalized vessels (lower field) next to well canalized vessels. H&E. x 188
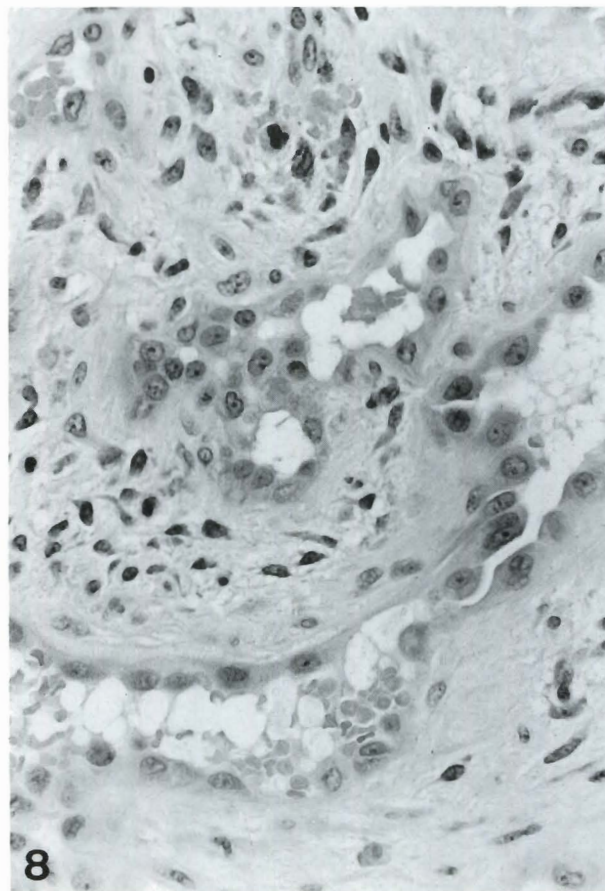

Fig. 8. Epithelioid hemangioma. The vascular lumina are apparently formed by fusion of cytoplasmic vacuoles of the individual endothelial cells, resulting in a scalloped contour. H&E. x 300

highlighted by reticulin staining.

It is now clear that epithelioid hemangioma is distinct from Kimura's disease, an idiopathic allergic-inflammatory condition often confused with epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia) in the literature (Kung et al., 1984; Googe et al., 1987; Urabe et al., 1987; Kuo et al., 1988; Chan et al., 1989; Hui et al., 1989). Epithelioid hemangioma occurs in all races, whereas Kimura's disease occurs predominantly in Oriental males. The most important distinguishing feature is the nature of the proliferated vessels. In Kimura's disease, the proliferated vessels are merely high endothelial venules lined by *pale*, plump endothelial cells which lack the dense hyaline cytoplasm and vacuoles typical of epithelioid vascular neoplasms, and there is no involvement of muscular vessels (Fig.

Table 1. Histologic features helpful in distinguishing between the different types of epithelioid vasculat tumors.

	EPITHELIOID HEMANGIOMA	EPITHELIOID HEMANGIOENDOTHELIOMA	EPITHELIOID ANGIOSARCOMA
GROWTH PATTERN	Well formed vessels	Cords of vacuolated cells; solid or nested growth	Predominantly solid growth; dissecting maze-like vascular channels occasionally
NUCLEAR ATYPIA	Mild only	Mild, occasionally moderate	Significant nuclear pleomorphism
MITOTIC FIGURES	Rare	Rare to moderate numbers	Frequent
STROMAL ELEMENTS*	Inflammatory infiltrate (lymphocytes, eosinophils) common	Cartilage-like myxoid-hyaline matrix common	No specific accompanying feature

*The stromal changes, although characteristic of the different types of epithelioid vascular tumors, are not essential for diagnosis.
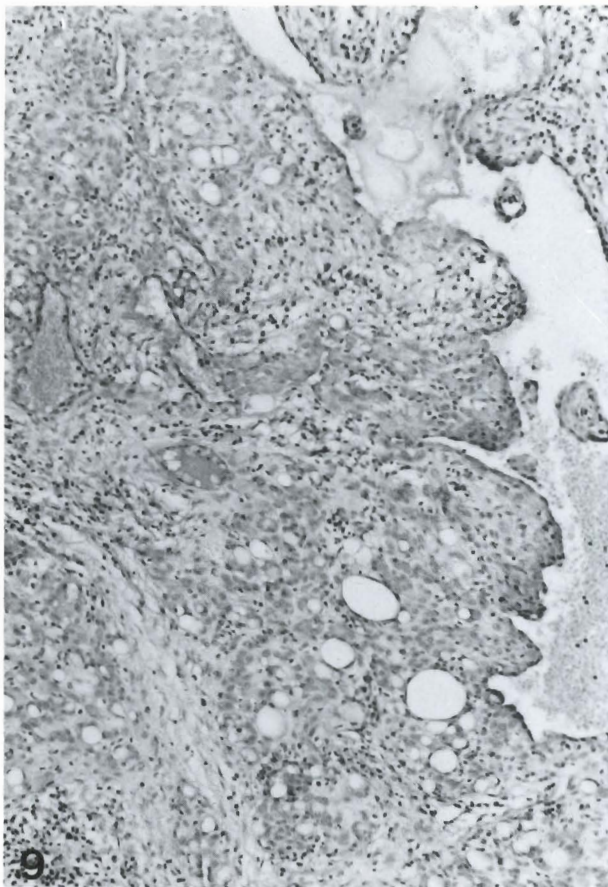

Fig. 9. Epithelioid hemangioma, with focal solid growth of epithelioid endothelial cells around a large vascular space. Note the prominent cytoplasmic vacuolation with fusion of vacuoles. H&E. x 93

Fig. 10. Epithelioid hemangioma. In this field, the vessels are lined by endothelial cells that lack epithelioid morphology. Note the heavy background inflammation which is eosinophil-rich. H&E. x 94

13). On the other hand, sclerosis, a prominent feature of Kimura's disease, is often insignificant in epithelioid hemangioma.

Bacillary angiomatosis, a reactive vascular proliferation occurring in immunocompromised hosts in response to infection by the Rickettsia *Rochalimaea henselae*, should not be mistaken for epithelioid vascular neoplasm because it is highly responsive to antibiotics but may be fatal if left untreated (Tsang and Chan, 1992; Welch et al., 1992). Morphologically, bacillary angiomatosis differs from epithelioid hemangioma in that although the proliferated endothelial cells in the former are commonly referred to as being «epithelioid» (as reflected by the original designation «epithelioid angiomatosis»), they possess pale to clear cytoplasm attributable to paucity of intermediate filaments. The inflammatory infiltrate in bacillary angiomatosis is predominated by neutrophils, and there is an interstitial deposit of eosinophilic/amphophilic material formed by clumps of bacilli. Furthermore, bacillary angiomatosis does not involve the luminal lining and wall of muscular vessels. This diagnosis can

be confirmed by demonstration of the bacilli using the Warthin-Starry or Giemsa stain (Chan et al., 1988; Tsang and Chan, 1992; Tsang et al., 1992), or by immunohistochemical studies (Reed et al., 1992).

Pathogenesis

Some authors have raised the possibility that epithelioid hemangioma is reactive or repair in nature based on the documentation in some cases of vascular damage (such as fibrointimal proliferation, discontinuity of internal elastic lamina and mural disruption), a history of antecedent trauma, a prominent inflammatory component, and association with an underlying arteriovenous malformation (Fetsch and Weiss, 1991). However, presence of vascular disruption cannot be considered strong evidence to support the non-neoplastic nature of epithelioid hemangioma, because this phenomenon can also be observed in epithelioid hemangioendothelioma, which is universally accepted as a neoplastic condition. It is probable that epithelioid hemangiomas represent a mixture of benign vascular

Fig. 11. Epithelioid hemangioma showing involvement of a muscular artery. **(A)**. The muscle coat is broken up focally (arrow) by the proliferated small vessels. **(B)**. These small vessels have apparently sprouted out from the artery, the intima of which is also lined by similar epithelioid endothelial cells. H&E, (A) x 30, (B) x 75

neoplasms and reactive vascular proliferations (Rosai, 1982).

Two reports have incriminated vaccination in the development of «angiolymphoid hyperplasia with eosinophilia» (Hallam et al., 1989; Akosa et al., 1990). It is our view, a view also shared by Allen (1991), that the endothelial cells in these cases lack the epithelioid morphology typical of epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia). These examples are more compatible with so-called injection site granuloma (Fawcett and Smith, 1984).

Epithelioid angiosarcoma

It is not uncommon to encounter occasional epithelioid tumor cells in otherwise classical cutaneous angiosarcomas. However, angiosarcomas composed entirely or predominantly of epithelioid tumor cells have only been characterized recently (Fletcher et al., 1991; Tsang et al., 1991). Not only are they found in sites where conventional angiosarcomas occur, such as the skin and thyroid, they also show a high propensity to

Fig. 12. Epithelioid hemangioma of the subcutis exhibiting a prominent rim of lymphoid tissue with germinal centers, mimicking a lymph node. H&E, x 15

occur in the deep somatic soft tissues (Eusebi et al., 1990; Marrogi et al., 1990; Fletcher et al., 1991; Maiorana et al., 1991). It is important to be aware of such occurrence because these tumors may be mistaken for metastatic carcinoma.

Based on the limited number of reported cases, it is currently unclear whether distinction between epithelioid and conventional angiosarcoma is warranted apart from the fact that the former appears to have a higher propensity to occur in the deep soft tissues. No strict morphologic criteria for distinguishing between them have been established. Since both tumors are highly aggressive and share many clinicopathologic similarities, it is possible that they may represent different ends of a morphologic spectrum of angiosarcoma in which variable proportions of epithelioid tumor cells can occur. On the other hand, some epithelioid angiosarcomas show histologic features bordering on epithelioid hemangioendothelioma (Chan et al., 1992).

Clinical features

The cutaneous epithelioid angiosarcomas present no differently from conventional angiosarcomas, whereas the deep ones present as rapidly enlarging masses in the limb and around the limb girdle (Fletcher et al., 1991). One case has been reported to arise in an arteriovenous fistula (Byers et al., 1992). Epithelioid angiosarcomas can also occur in the viscera, such as the thyroid and adrenal (Eusebi et al., 1990; Livaditou et al., 1991). They occur mostly in old individuals, with a striking male predominance. Metastasis is not uncommonly found at presentation. From the limited available information, it appears that epithelioid angiosarcomas are highly aggressive, widely metastasizing, rapidly fatal tumors.

Pathology

The hallmark of epithelioid angiosarcoma is infiltrative, destructive growth composed of moderately to markedly pleomorphic, large, polygonal tumor cells possessing abundant eosinophilic cytoplasm (Figs. 14, 15). The tumor cell nuclei are oval with prominent amphophilic to basophilic nucleoli, which are often connected with the nuclear membrane by a strand of chromatin. The vasoformative nature of the tumor is betrayed by the presence of red blood cells within some cytoplasmic vacuoles (Fig. 15A) and a vague ovoid nested pattern representing primitive vascular columns, which are better outlined by reticulin stain (Fig. 16). Focally, the tumor may show frank vascular differentiation with irregular, blood-filled spaces or anastomosing vascular channels with a papillary pattern (Figs. 15B, C). Very rarely, well formed vascular spaces simulating glandular structures can occur (Fig. 17). Mitotic figures are frequently seen and often abnormal. Necrosis is common. Rare features include intravascular growth and sclerosis.

Immunohistochemically, epithelioid angiosarcomas often show a degree of immunoreactivity for endothelial markers exceeding that expected from their degree of vascular differentiation. They are also frequently immunoreactive for cytokeratin (Eusebi et al., 1990; Fletcher et al., 1991; Byers et al., 1992).

Differential diagnosis

Epithelioid angiosarcoma can be distinguished from epithelioid hemangioendothelioma by the prominent cellular anaplasia, less frequent cytoplasmic vacuoles, lack of a chondromyxoid matrix, and rarity of cord-like growth of endothelial cells (Table 1).

It is important not to mistake epithelioid angiosarcoma for carcinoma (Banerjee et al., 1992). The presence of cytoplasmic vacuoles containing red blood cells and areas showing definite vasoformative features should be looked for in any unusual epithelioid tumor occurring in the skin or deep soft tissues. Immunohistochemical studies are helpful, but it should be remembered that immunoreactivity for cytokeratin alone should not be equated with a diagnosis of carcinoma.

Epithelioid sarcoma may be mistaken for epithelioid angiosarcoma by virtue of its epithelioid morphology and pseudovascular morphology when it dissects collagen fibres. However, it typically occurs in the distal extremities of young individuals, shows necrotizing granuloma-like nodules and less prominent anaplasia, and lacks immunoreactivity for endothelial markers. A note of caution is that epithelioid sarcoma also characteristically stains with CD34 (Traweek et al., 1991).

Epithelioid hemangioendothelioma

Epithelioid hemangioendothelioma is perhaps the best known member in the family of epithelioid vascular neoplasms. This term was first coined by Weiss and Enzinger (1982) for a distinctive vascular tumor occurring in the soft tissues, occupying an intermediate position in terms of morphology and behaviour in the spectrum of vascular neoplasms, and which may be mistaken for carcinoma. Shortly after delineation of this entity, it was realized that identical tumors have been
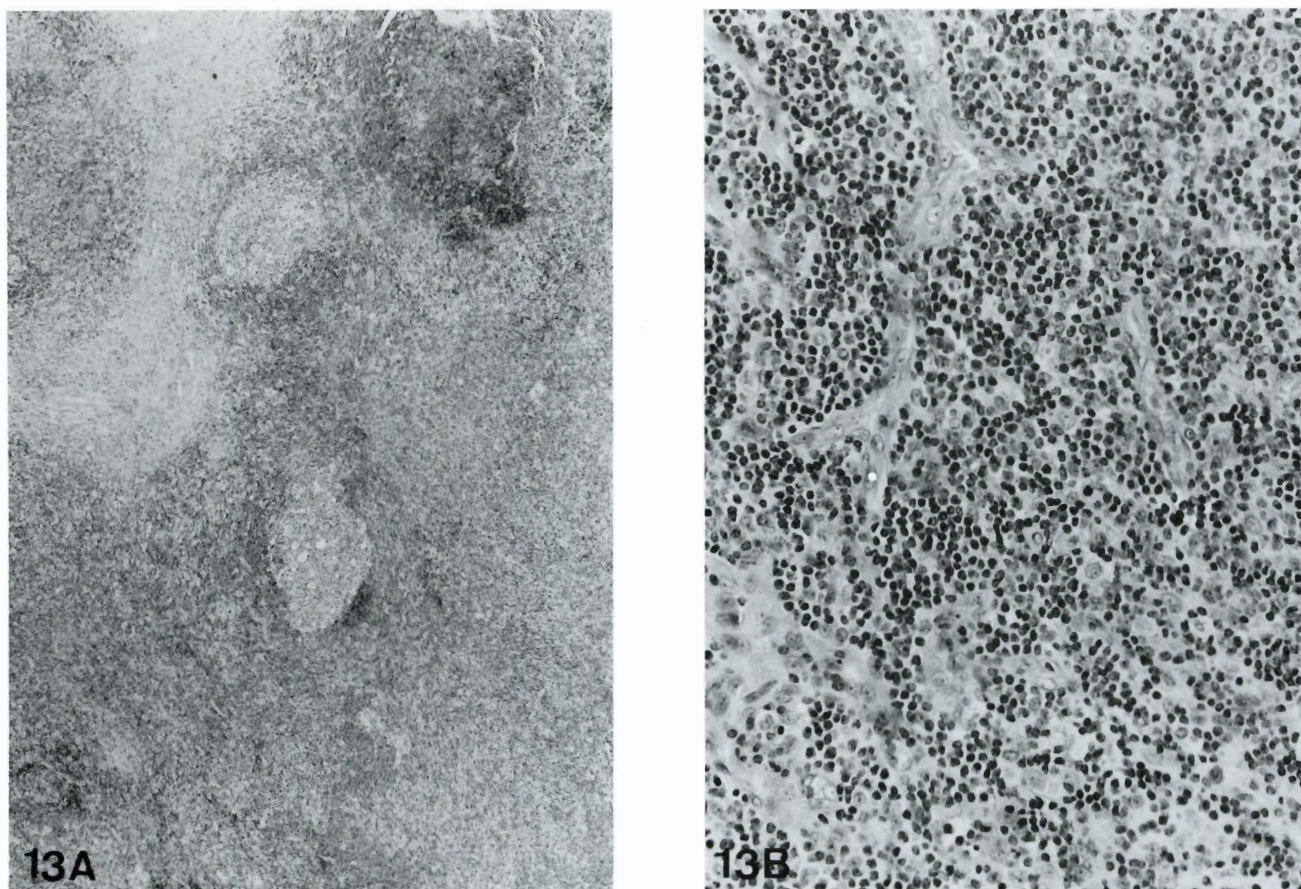

Fig. 13. Kimura's disease. **(A)**. Note the reactive lymphoid hyperplasia in a background of sclerosis (left upper field). **(B)**. There is mixed inflammatory infiltrate including eosinophils; the proliferated high endothelial venules are lined by pale endothelial cells. (B). H &E (A) x 30; (B) x 188
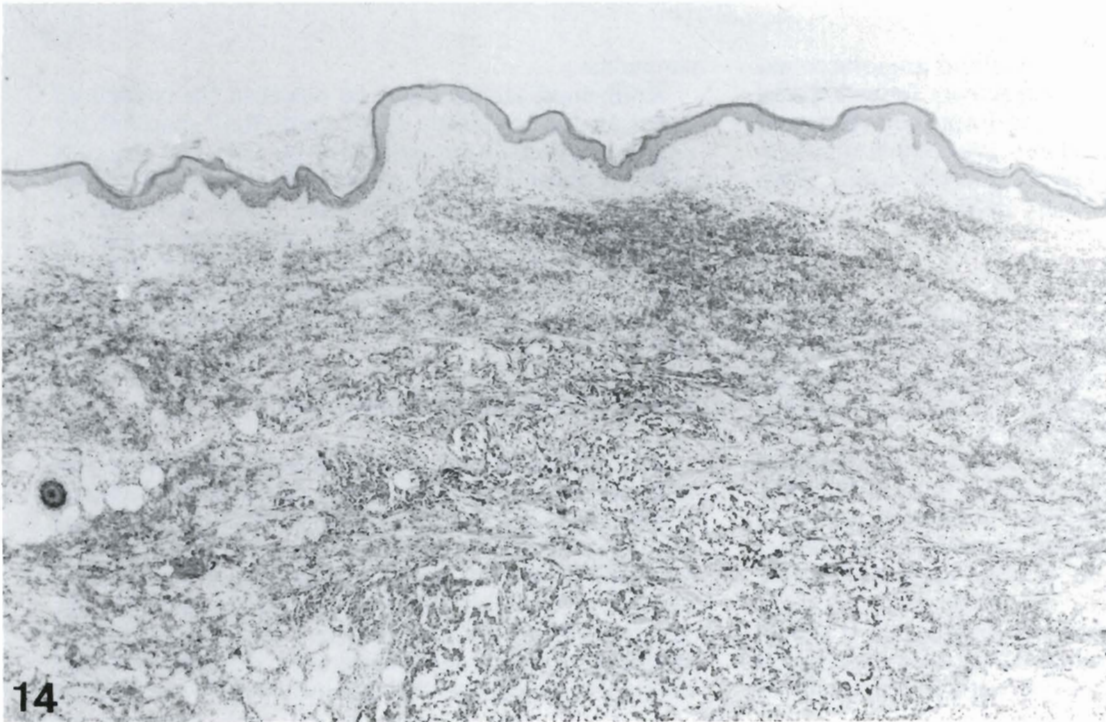
Epithelioid vascular tumors

Fig. 14. Epithelioid angiosarcoma of the skin. The growth infiltrates the dermis and subcutis extensively, dissecting between collagen fibers and creating anastomosing cleft-like spaces, no different from those seen in conventional angiosarcoma. H&E. x 40
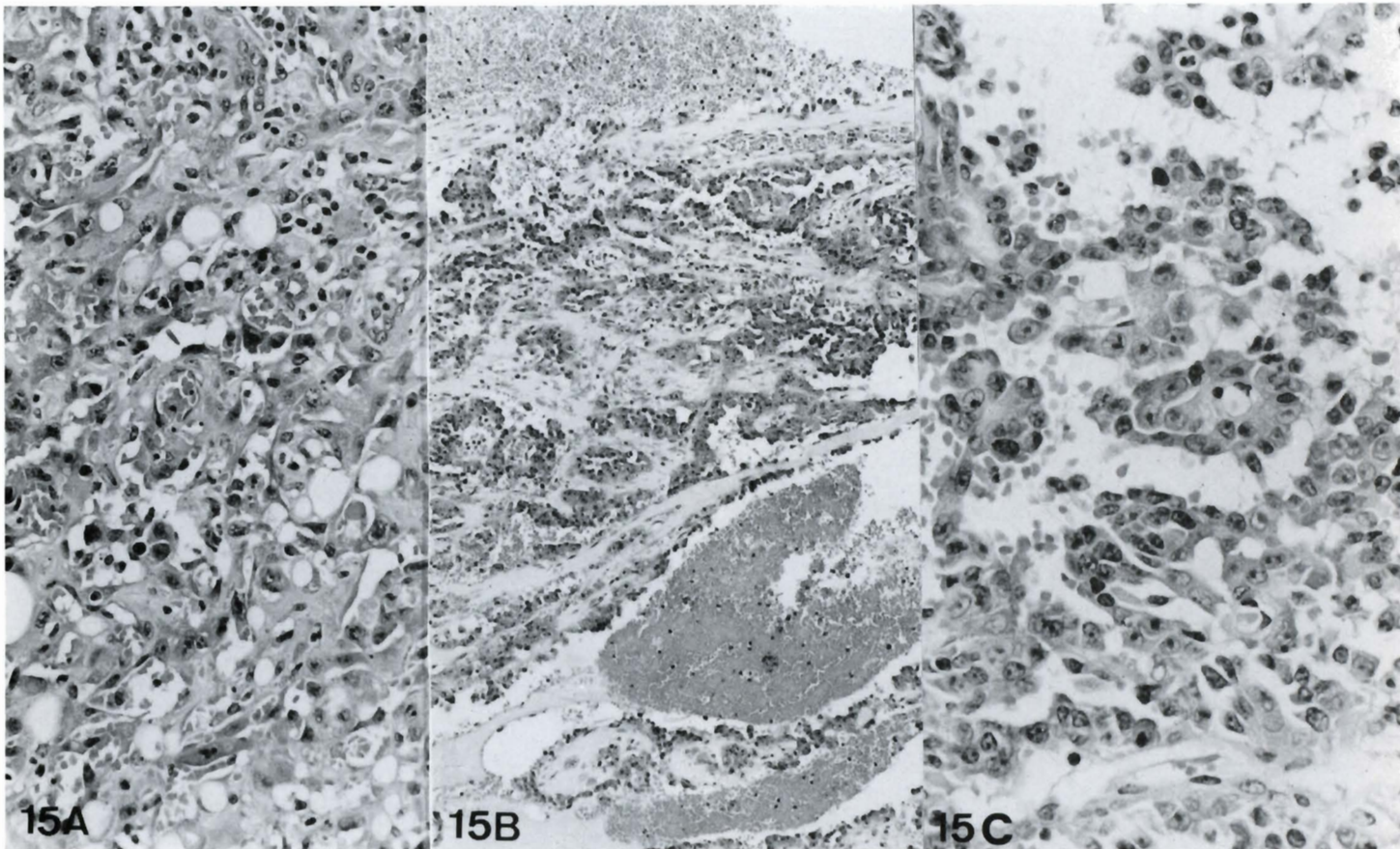

Fig. 15. Epithelioid angiosarcoma. **(A).** The tumor grows in solid sheets with primitive blood channels formed by fusion of cytoplasmic vacuoles. **(B).** Irregular anastomosing clefts and ectatic spaces. **(C).** Cellular papillary tufts. Note the prominent nuclear hyperchromatism and pleomorphism. H&E. (A) x 186; (B) x 50; (C) x 300
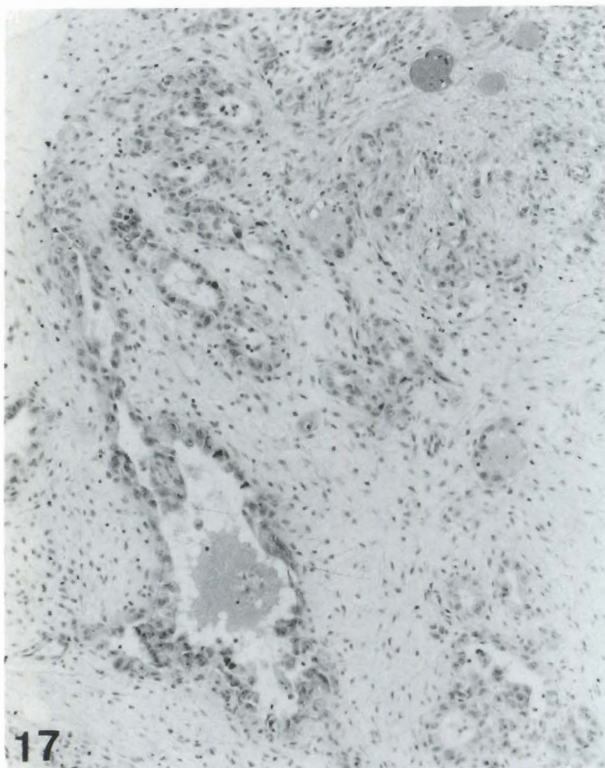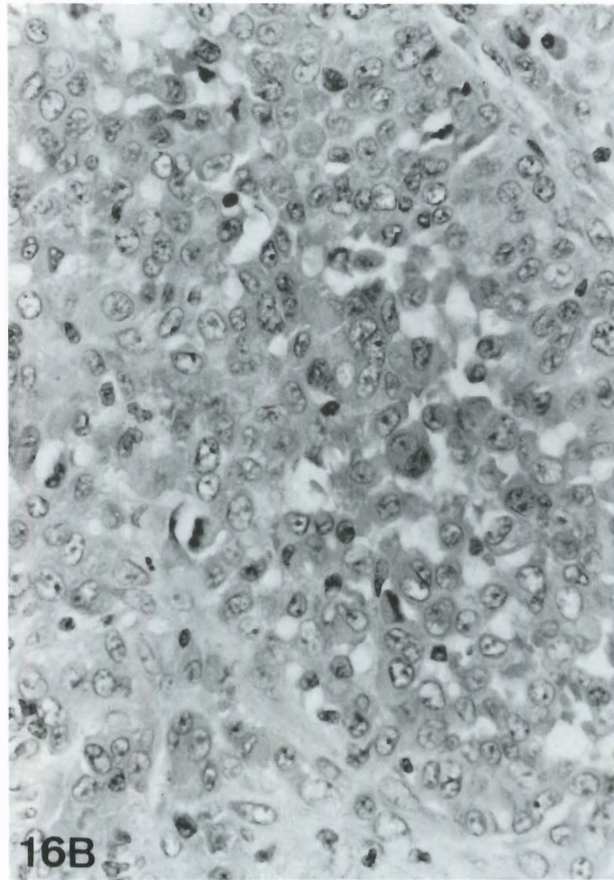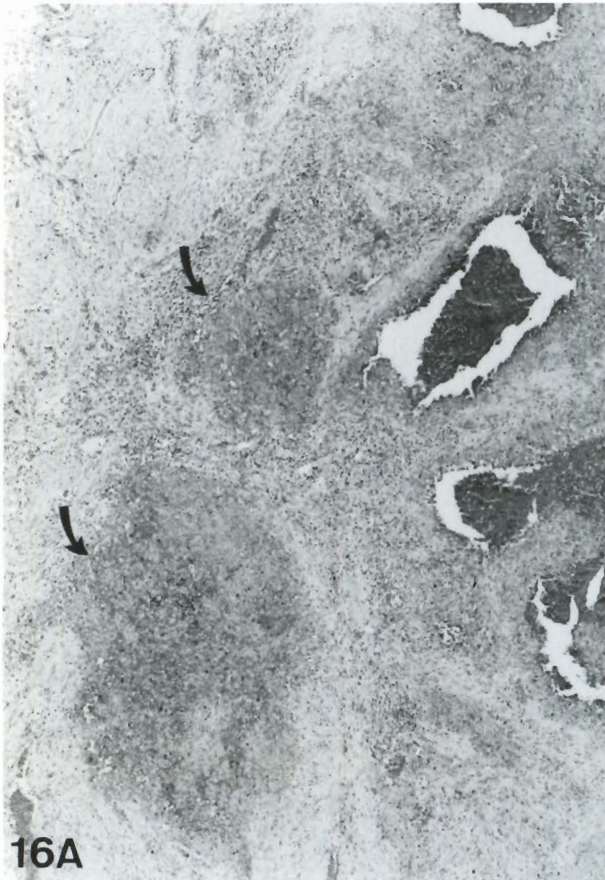
Fig. 16. Epithelioid angiosarcoma. **(A)**. Vascular differentiation in this growth is manifested by formation of solid ovoid nests representing primitive vascular columns (arrows) and blood-filled spaces. **(B)**. The tumor cells are moderately pleomorphic and possess abundant cytoplasm. H&E, (A) x 30; (B) x 300

described, albeit often misinterpreted as epithelial or chondroid tumors, in various sites of the body, notably the lung, liver and bone (Weiss et al., 1986).

Clinical features

Epithelioid hemangioendothelioma occurs over a wide age range, and the peak incidence is in the third decade. It is rare in childhood with the exception of skeletal tumors. There is a striking female predominance for tumors occurring in the liver and lung, but otherwise men and women are equally affected. The principal sites of occurrence include: 1) soft tissues, 2) lung, 3) liver, and 4) bone (Weiss and Enzinger, 1982; Dail et al., 1983; Ishak et al., 1984; Tsuneyoshi et al., 1986). However, it can occur in almost any site, for example,

Fig. 17. Epithelioid angiosarcoma of deep soft tissue. This tumor shows well-formed vascular channels resembling glandular spaces. The lining cells are markedly pleomorphic with focal papillary tuft formation. H&E. x 75
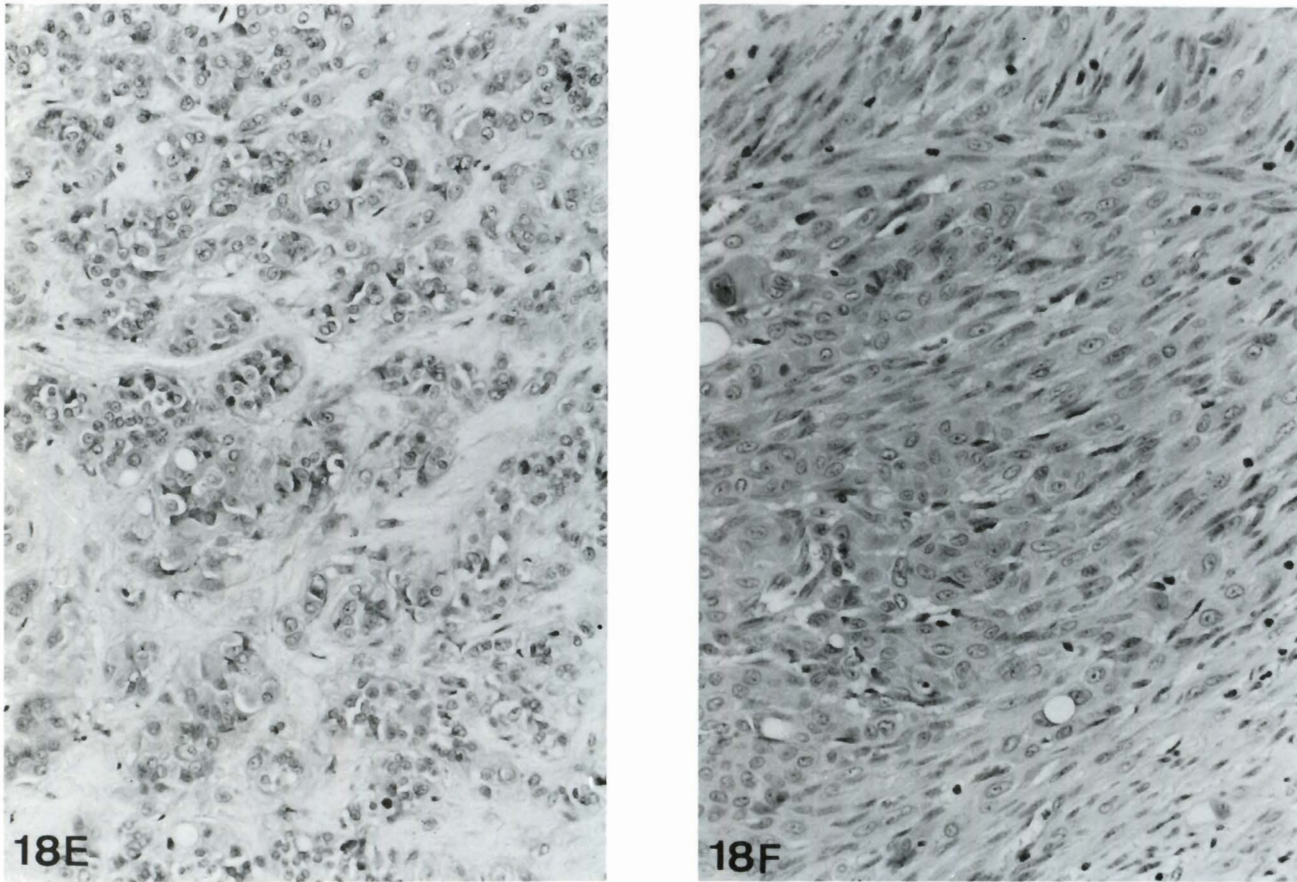
18A

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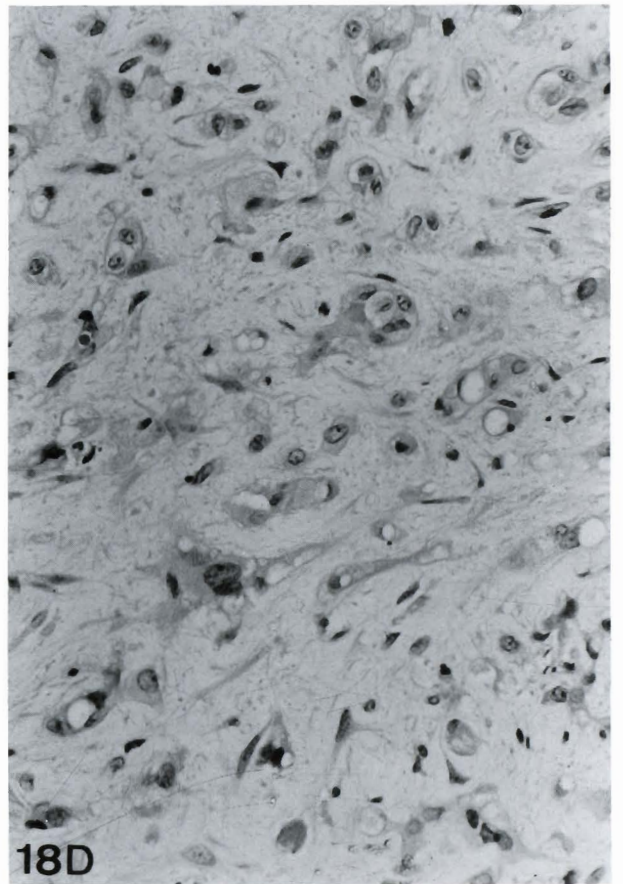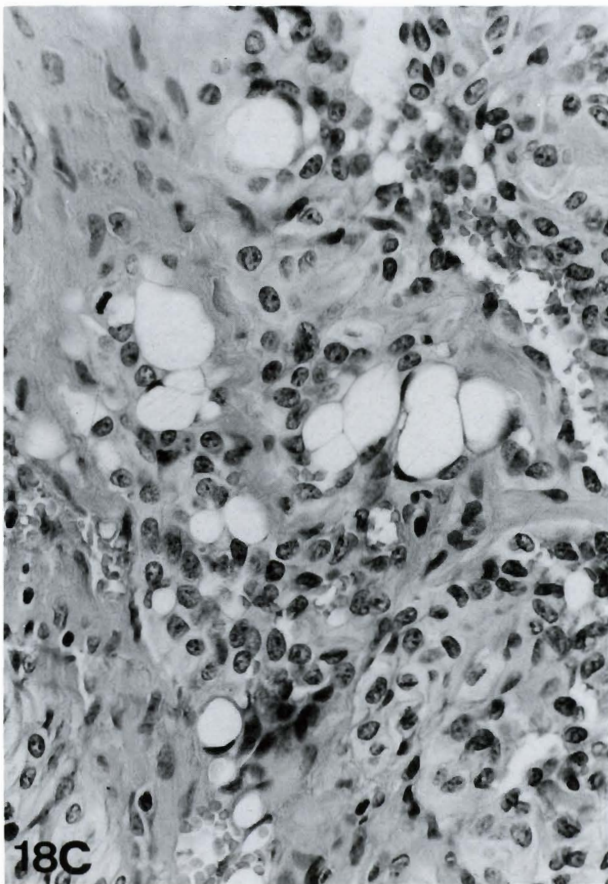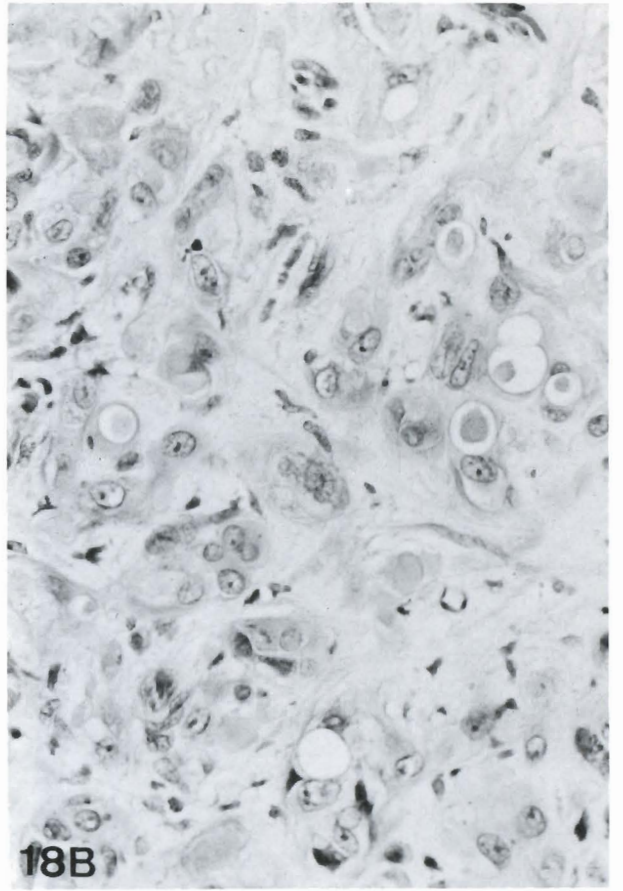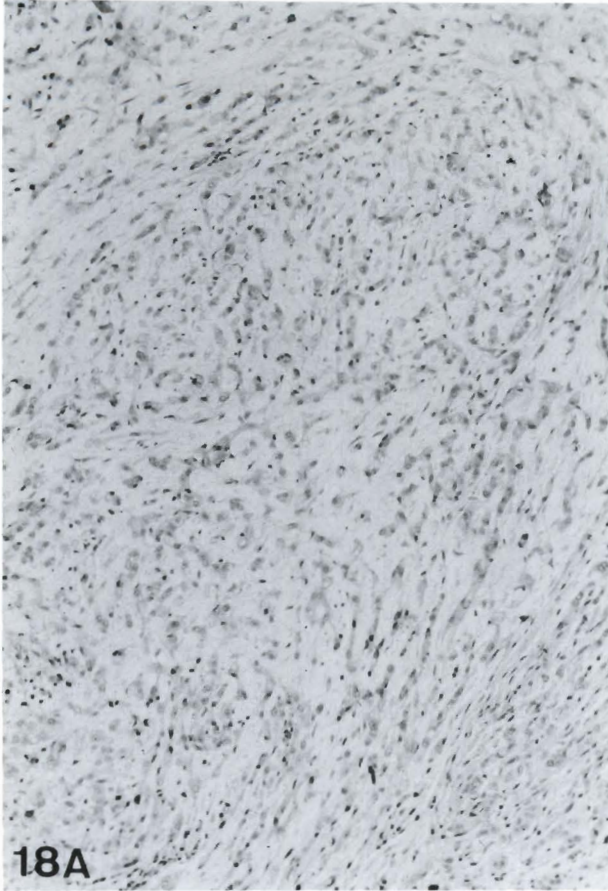
Fig. 18. The variable cytoarchitectural features of epithelioid hemangioendothelioma. **(A)**. Stellate to polygonal cells grow in single-filed cords within a myxoid stroma. **(B)**. Polygonal cells with prominent cytoplasmic vacuoles containing red blood cells; some also assume a signet-ring appearance. **(C)**. Fusion of vacuoles creates larger lumina separated by delicate cytoplasmic septa. **(D)**. The tumor cells appear stellate or plump spindled in some lesions. **(E)**. Growth in solid nests. **(F)**. Spindle cell fascicles. H&E, (A) x 95; (B) x 300; (C) x 300; (D) x 300; (E) 150; (F) x 188

lymph node, brain, gastrointestinal tract and mediastinum (Ellis and Kratochvil, 1986; Kepes et al., 1986; Yousem and Hochholzer, 1987; Lee et al., 1988; Chan et al., 1992; Chow et al., 1992). The soft tissue tumors often present as deep or superficial masses which are not uncommonly painful, and they commonly arise from a vein causing edema or thrombophlebitis of the affected region. The etiology of this tumor is not known, but one case has been reported to follow radiation, and one air gun pellet injury (Akosa and Ali, 1989; Nadha Sarma, 1992). The pulmonary lesions, which are usually multiple or bilateral, are either discovered incidentally on chest X-ray or cause respiratory symptoms at presentation (which is associated with a worse prognosis). Rarely, they can present with diffuse pleural thickening mimicking malignant mesothelioma, or a lymphangitic pattern mimicking lymphangitis carcinomatosa (Yousem and Hochholzer, 1987). The hepatic lesions may present with abdominal discomfort, jaundice, hepatosplenomegaly, hemoperitoneum, or veno-occlusive disease-like picture. The involvement is often multicentric and extensive. Some cases have been linked to use of oral contraceptives (Dean et al., 1985). The skeletal growths, which are commonly multicentric, present with pain and/or pathologic fractures in the skull, axial skeleton, and long bones. They appear on X-ray as osteolytic, expansile masses.

Pathology

The morphologic spectrum of epithelioid hemangioendothelioma is broad. However, several basic patterns characterize this entity, and are found in variable proportion in an individual case:

1) Vascular differentiation at the cellular level

The neoplastic endothelial cells commonly occur singly or in short, single-filed cords in a background of myxo-hyaline matrix (Figs. 2, 18A). They are polygonal or stellate, with variable amounts of hyaline cytoplasm, and are frequently vacuolated (blister cells) (Figs. 18B-
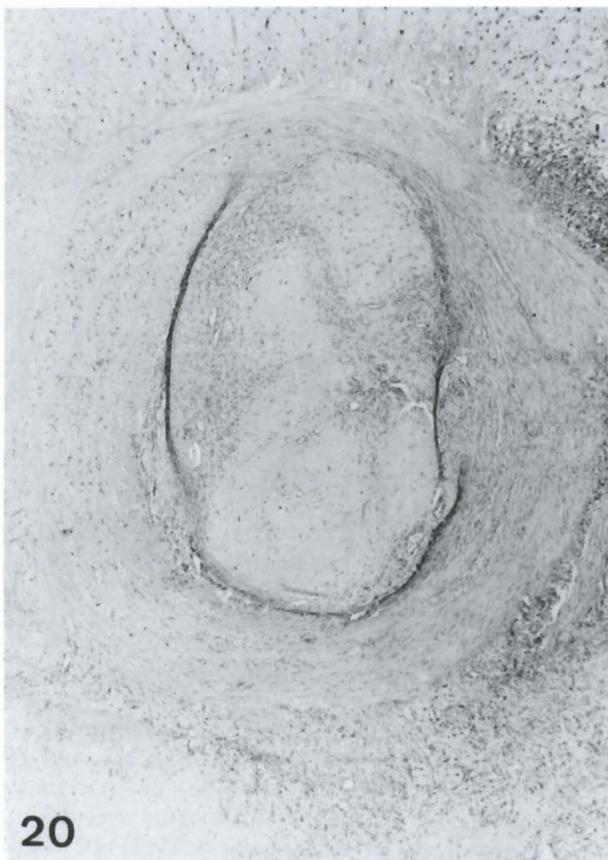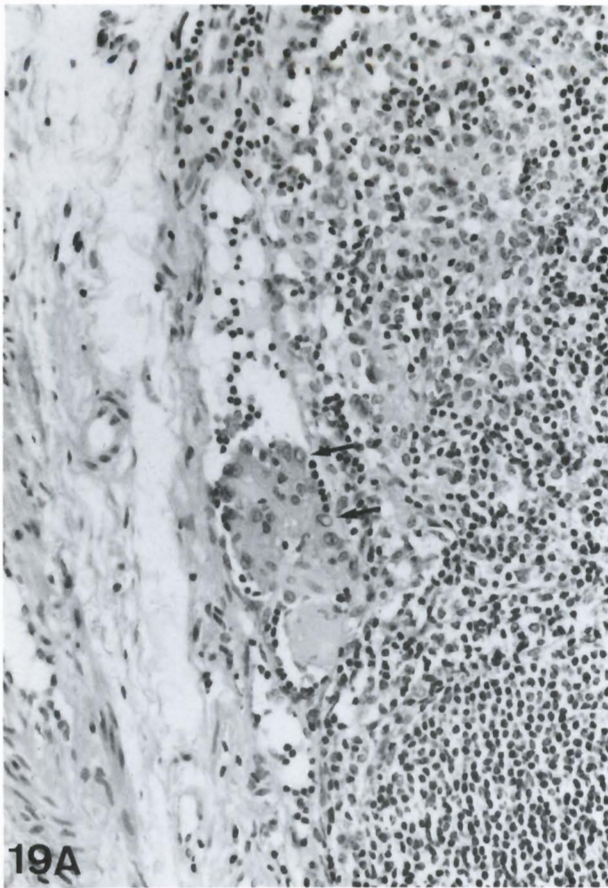
Fig. 19. Epithelioid hemangioendothelioma. (A). Growth within the subcapsular sinuses of lymph node typically takes the form of papillary tuft covered by polygonal cells with a hyalinized core. Note the nuclear pseudoinclusions (arrows). (B). This tumor extends into a large blood vessel in the form of a polypoid mass with a cellular periphery and a hyalinized, acellular core. H&E, (A) x 183; (B) x 30

D). Larger vacuoles tend to compress the nucleus into a crescent, resulting in a signet ring appearance (Figs. 18B, C). Fusion of the vacuolated cells creates larger vacuoles which may contain thin septa formed by strands of cell membrane and cytoplasm (Fig. 18C). The presence of erythrocytes or lysed blood in the vacuoles will confirm the endothelial nature of these cells (Fig. 18B). Cellular pleomorphism is mild to moderate, and mitotic figures are usually few. Nuclear pseudoinclusions are commonly present (Fig. 19A). Well canalized vascular channels are in general absent or very focal. Sometimes, the epithelioid endothelial cells may form nests, solid sheets (Fig. 18E) and spindle cell fascicles (Fig. 18F) with little intervening stroma.

2) Intravascular and intralymphatic growth

Epithelioid hemangioendothelioma shows a marked propensity to spread along pre-existing blood and lymphatic vessels. The epithelioid appearance of the proliferated endothelial cells is particularly well

Fig. 20. Epithelioid hemangioendothelioma of soft tissue. Angiocentric growth resulting in obliteration of the parent vessel by hyaline matrix containing scattered tumor cells. Note the centrifugal infiltration of tumor cells into the surrounding tissue. H&E. x30
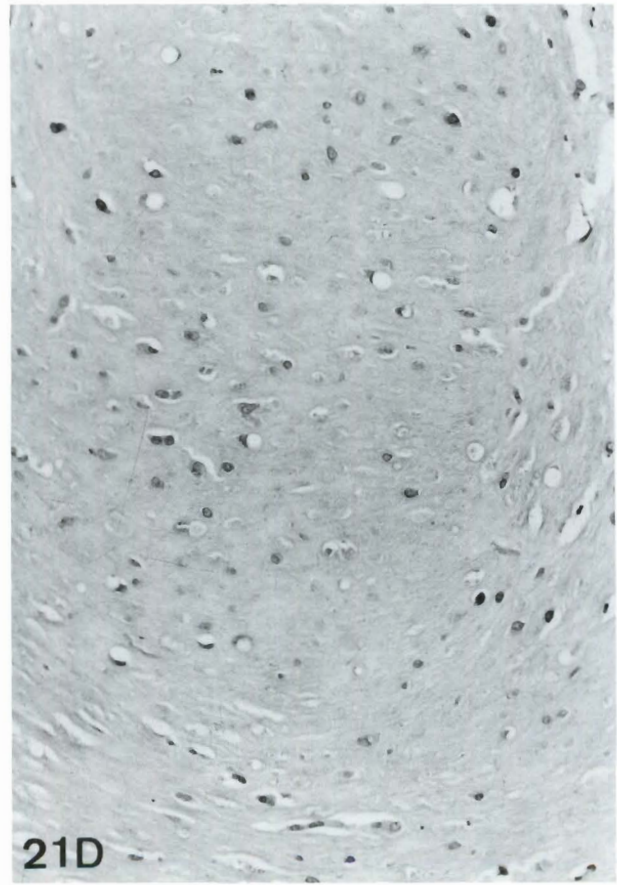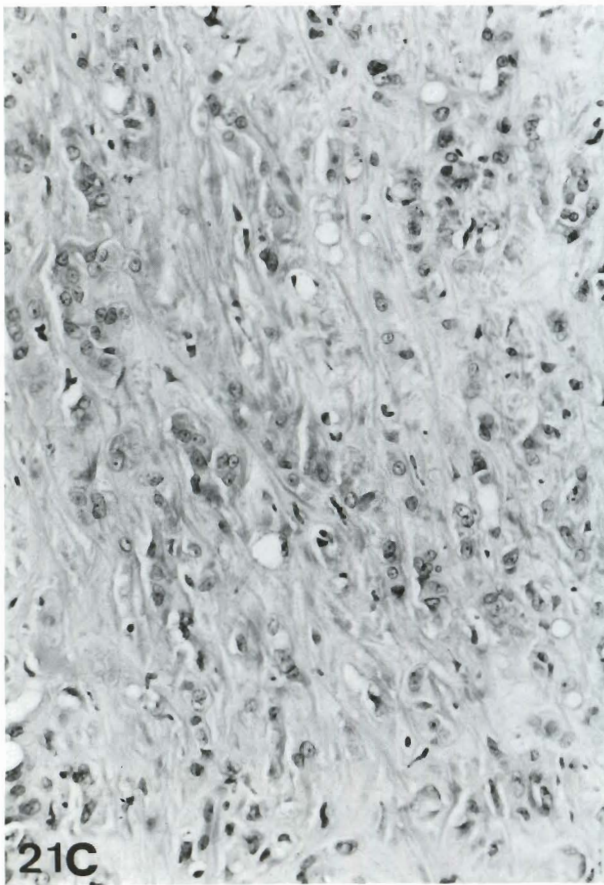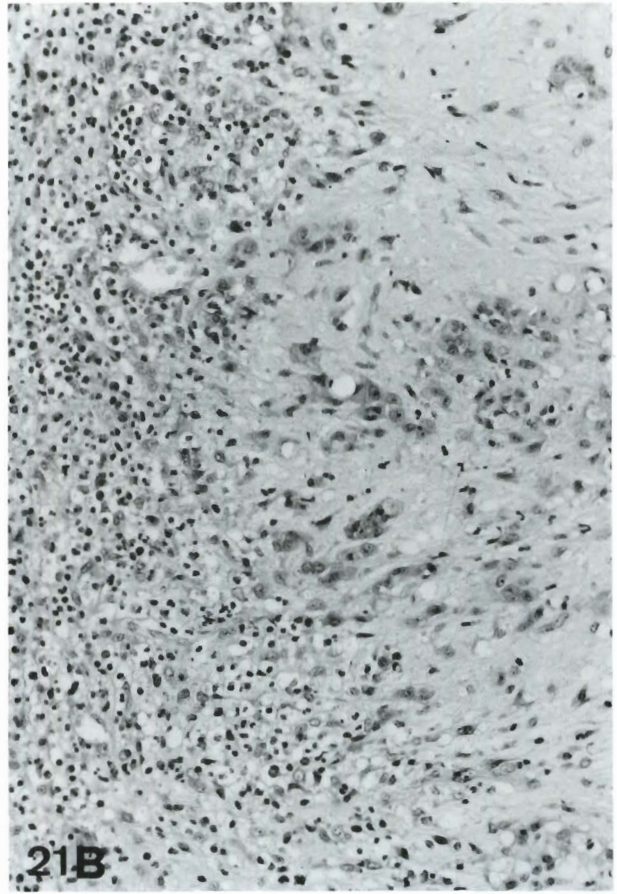
21A

21B

21C

21D

Fig. 21. Epithelioid hemangioendothelioma. **(A)**. A tumor of the brain showing spindly and stellate tumor cells in a myxoid background; a diagnosis cannot be rendered from this field. **(B)**. Other parts of the tumor shown in (A) show vacuolated plump cells associated with prominent eosinophilic infiltration, and a diagnosis can be made from this field. **(C)**. The stroma of epithelioid hemangioendothelioma commonly undergoes progressive hyalinization and sclerosis. **(D)**. Advanced sclerosis renders the lesion very difficult to diagnose, although the cytoplasmic vacuoles provide an important diagnostic clue. H & E, (A) x 188; (B) x 150; (C) x 188; (D) x 150

appreciated when the growth extends into these pre-existing spaces, forming papillary tufts covered by cuboidal or hobnail cells with or without a hyalinized core (Fig. 19). The intravascular papillary growth is often best appreciated in the peripheral portion of the tumors.

3) Angiocentricity

This is a particularly prominent feature in the soft tissue epithelioid hemangioendotheliomas, being found in about half of the cases. The tumor typically arises from and expands a pre-existing vessel with the tumor cells infiltrating centrifugally through the vessel wall into the surrounding tissue (Fig. 20). The outline of the vessel is preserved, but the lumen is frequently thrombosed by necrotic debris.

4) Hyaline to chondromyxoid matrix

Epithelioid hemangioendotheliomas are typically rich in matrix containing hyaluronic acid and sulphated mucopolysaccharides although this is not an invariable feature (Figs. 18A, D, 21A, B). They frequently appear myxoid to chondroid on conventional sections, and show hyaluronidase-resistant alcian-blue positivity. It is important not to equate this histochemical profile with cartilaginous differentiation, since normal endothelial cells are known to produce sulphated mucopolysaccharides (Enzinger and Weiss, 1988). There is a tendency to undergo regressive hyalinization and calcification, masking the neoplastic nature of the lesion as a result of paucity and «strangulation» of tumor cells in the matrix (Figs. 21C, D). These regressed foci may not be diagnosable, and it is important to search for more
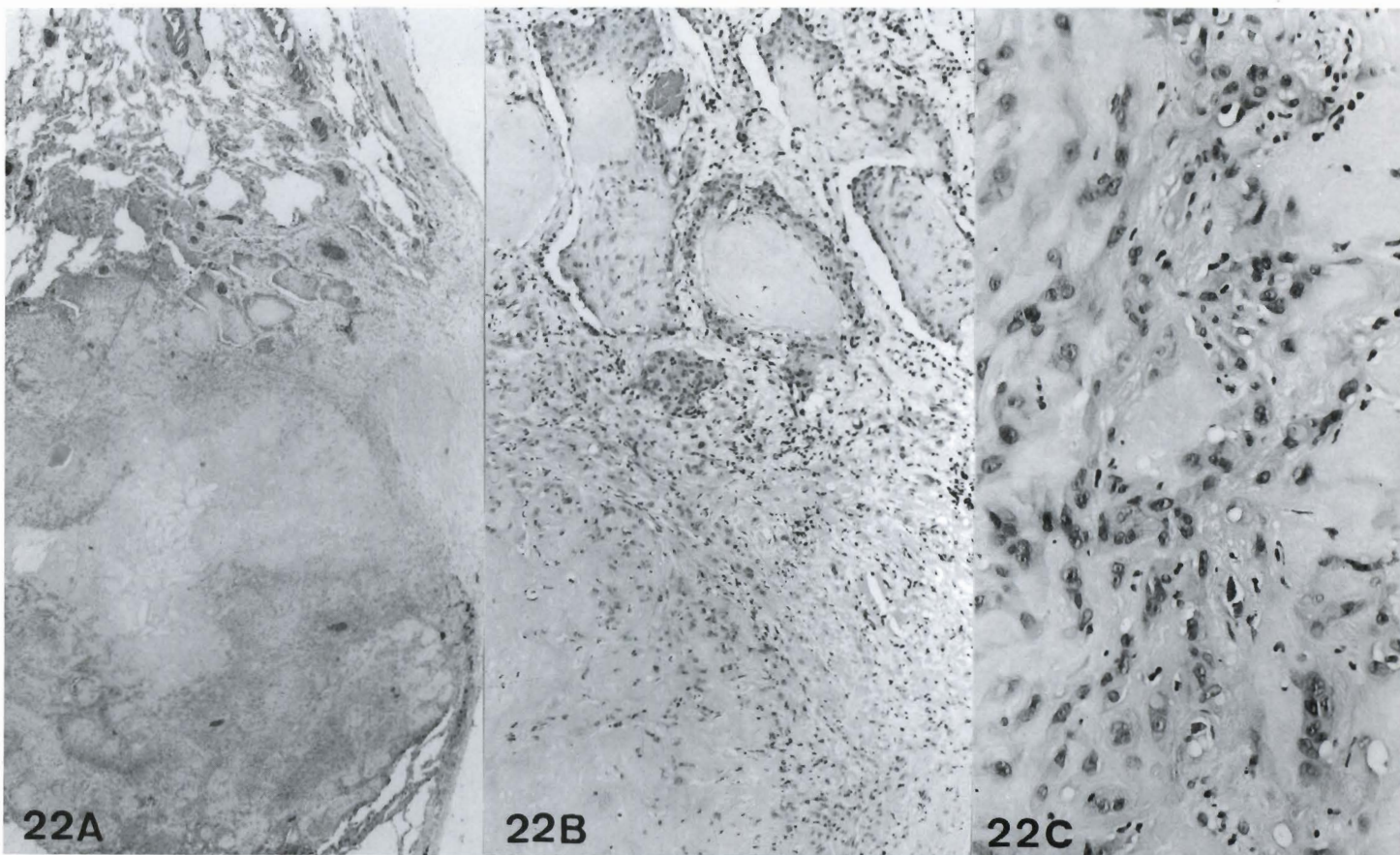
Fig. 22. Epithelioid hemangioendothelioma of the lung. **(A)**. The tumor shows a sclerotic, acellular center and a cellular periphery with papillary formations. **(B)**. The papillae are hyalinized and covered by hobnail tumor cells. **(C)**. In the intermediate zone, tumor cells with occasional vacuoles grow in cords within a myxohyaline matrix, highly characteristic of epithelioid hemangioendothelioma. H&E, (A) x 19 (B) x 75; (C) x 188

diagnostic areas (Fig. 21D). An inflammatory component is usually lacking, but occasional cases can be rich in eosinophils, neutrophils and/or lymphocytes (Ishak et al., 1984; Ellis and Kratochvil, 1986; Chan et al., 1992) (Fig. 21B). Exceptionally, there are intermingled osteoclast-like giant cells (Lamovec et al., 1990).

Epithelioid hemangioendotheliomas involving the lung and liver have characteristic morpho-architectural features that may be of help in their recognition. In the lung, they are typically multifocal, and grossly the tumor nodules possess a firm, opaque center and a fleshy, semi-translucent periphery. The appearance can be strikingly chondroid on gross and microscopic examination (Dail et al., 1983). The central regression results in a characteristic gradient of cellularity from the sclerotic, occasionally calcified center towards the cellular periphery (Fig. 22). Furthermore, in the periphery, the tumor spreads from one alveolar space to another through the pores of Kohn, with preservation of the pulmonary architecture, forming characteristic casts of the distal airspaces (Figs. 22A, 23). The intra-alveolar growths are covered by epithelioid endothelial cells and often have hyalinized cores (Fig. 22B). It was this growth pattern that had led to the original misinterpretation of this tumor as a special variant of bronchial epithelial tumor («intravascular bronchiolo-alveolar tumor») (Corrin et al., 1979; Dail et al., 1983). However, the above distinctive features may be lacking in some pulmonary epithelioid hemangioendotheliomas; such tumors may appear no different from their soft tissue counterparts.

In the liver, the tumor is typically multifocal, insinuating into the sinusoids and replacing large areas of the liver parenchyma (Fig. 24). The terminal hepatic venules and portal vein branches are often thrombosed by myxohyaline matrix containing isolated tumor cells infiltrating into the vessel wall and adjacent parenchyma (Fig. 24B). Involvement of the arterial branches is rarely seen. The Glisson's capsule may also be involved. The hepatocytes may be extremely atrophic and barely recognizable as a result of replacement by tumor.

Lesions showing extensive hyalinization had often been mistaken in the past as sclerosing cholangiocarcinoma. The sclerosis can sometimes be so prominent that it may lead to an erroneous diagnosis of massive hepatic fibrosis or hepatic veno-occlusive disease.

Differential diagnosis

The clinicopathologic features of epithelioid hemangioendothelioma occurring in the liver, lung and bone of adults are particularly suggestive of metastatic carcinoma. However, metastatic carcinoma usually show greater degree of cellular anaplasia and do not exhibit genuine vascular differentiation (Banerjee et al., 1992). Table 2 lists the histologic clues for recognition of epithelioid hemangioendothelioma. The cytoplasmic vacuoles are mucin-negative, and immunohistochemical studies can resolve the problem in most instances. We caution, however, that cytokeratin positivity may occur in epithelioid hemangioendotheliomas.

Epithelioid hemangioendothelioma occurring in the bone and soft tissue may be mistaken for myxoid chondrosarcoma, particularly when the hyaluronidase-

Table 2. Histologic clues for recognition of epithelioid hemangio-endothelioma.

HISTOLOGIC CLUES (3 or more of the following features)
    Plump cells with eosinophilic hyaline cytoplasm
    Cytoplasmic vacuoles
    Arrangement of cells in cords
    Chondromyxoid matrix
    Papillary tufts of plump cells within lymphovascular spaces (more commonly seen in peripheral portion of tumor)

CONFIRMATORY EVIDENCE
    Identification of erythrocytes within cytoplasmic vacuoles or primitive tumor-cell lined channels
    Immunohistochemical evidence of vascular differentiation, e.g. Factor VIII-related antigen, Ulex europaeus, CD 34
    Ultrastructural evidence of endothelial differentiation (Weibel-Palade bodies)

Fig. 23. Epithelioid hemangioendothelioma of the lung, showing the characteristic cartilage-like growth, forming «casts» of the alveolar spaces. H&E. x 75
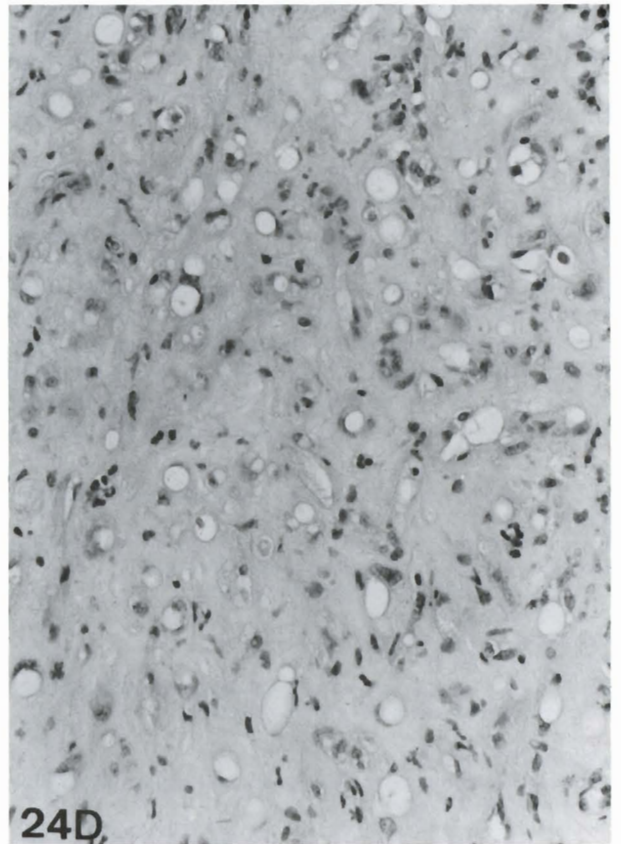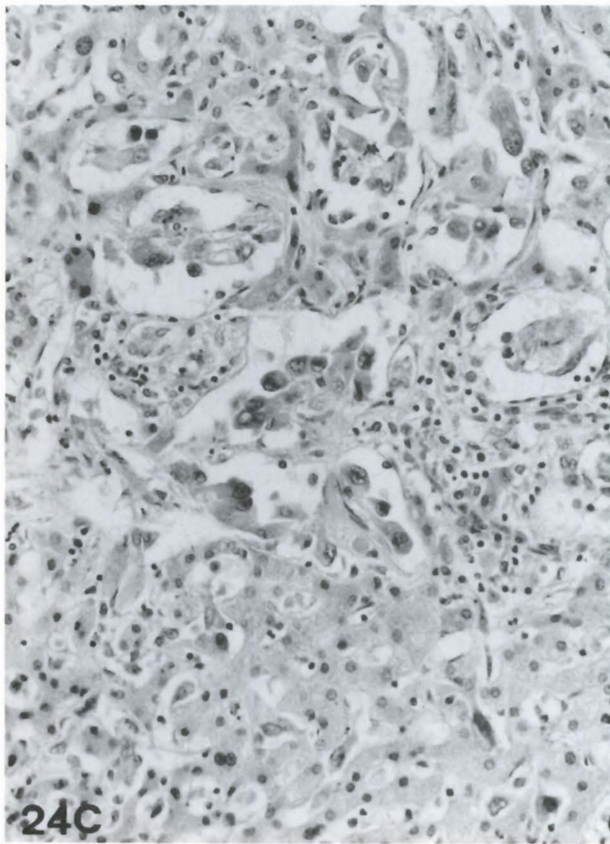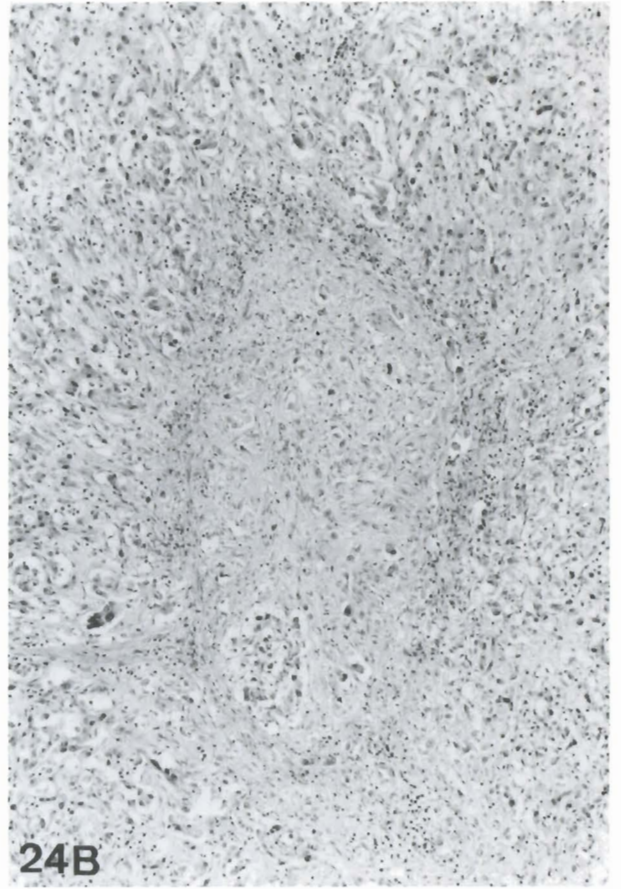
Fig. 24. Epithelioid hemangioendothelioma of liver. **(A)**. Extensive growth replacing most of the hepatic parenchyma with some preserved liver cells in the upper field. **(B)**. The terminal hepatic vein is obliterated by tumor. **(C)**. The tumor cells insinuate along the sinusoids, compressing and causing atrophy of the hepatocytes. Some papillary tufts are formed. **(D)**. The tumor is composed of isolated vacuolated cells scattered in a hyaline matrix. H&E, (A) x 30; (B) x75; (C) and (D) x 188

resistant alcian-blue staining is taken into consideration. However, it lacks the distinct lobulation of cartilaginous tumors, and vacuolated cells are not a feature of myxoid chondrosarcoma. Furthermore, myxoid chondrosarcoma shows immunoreactivity for S-100 protein but not endothelial cell markers.

Tumors and tumor-like conditions of mesothelial cells, including adenomatoid tumor, nodular mesothelial hyperplasia of heart and malignant mesothelioma, can mimic epithelioid hemangioendothelioma. Adenomatoid tumor shows particularly striking histologic resemblance to epithelioid hemangioendothelioma and epithelioid hemangioma, due to the presence of polygonal pink-staining cells with frequent vacuoles and occasional tubule formation (Fig. 25). Distinction between these two entities can be very difficult, although the occurrence around the genital tract strongly favors the diagnosis of adenomatoid tumor. However, some examples of «adenomatoid tumor» of the testis have recently been reinterpreted as epithelioid vascular tumor (Banks and Mills, 1990). Although cellular vacuolation is characteristic of epithelioid vascular tumors, large

Fig. 25. Adenomatoid tumor. This field, which features vacuolated epithelioid cell-lined spaces, is practically indistinguishable from epithelioid vascular tumor. However, the larger cystic spaces containing mucin (arrow) serve to distinguish this tumor from the latter. H&E. x 150

cystic spaces, such as those found in most adenomatoid tumors, are not present. Identification of basophilic-staining mucin in some of the tubules or cystic spaces also favors the diagnosis of adenomatoid tumor (Fig. 25). Immunohistochemical studies are most helpful for the problematic cases, because adenomatoid tumors are positive for cytokeratin and negative for endothelial markers.

Nodular mesothelial hyperplasia occurring in the pericardium and endocardium, previously called «endocardial benign angioreticuloma», has been misinterpreted as epithelioid vascular neoplasm (Rosai et al., 1979; Luthringer et al., 1990). It typically occurs as incidentally discovered small nodules in the hearts of patients who have undergone cardiac catheterization. It is composed of polygonal mesothelial cells with interspersed large empty spaces, probably representing air introduced during the catheterization.

Mesotheliomas with predominantly epithelial growth can mimic epithelioid hemangioendothelioma by virtue of the cord-like growth and cytoplasmic vacuolation. Serosal location of the tumor, cellular pleomorphism, complex tubulo-papillary or sarcomatoid component if present, should distinguish mesothelioma from epithelioid hemangioendothelioma. Immuno-histochemical and electron microscopic studies are invaluable in the evaluation of difficult cases.

Epithelioid malignant schwannoma may show focal areas indistinguishable from epithelioid hemangio-endothelioma (Laskin et al., 1991). The cells may grow in isolation or short cords, with occasional cytoplasmic vacuoles (Fig. 26). However, the overall growth pattern, the lack of definite vascular differentiation, relationship with a nerve or associated neurofibromatosis if present, and the S-100 protein immunoreactivity can help to identify the neural differentiation of these tumors.

Cords of vacuolated plump cells are also characteristically present in chordoma and round cell liposarcoma. The lobulated growth and large multivacuolated, S-100 protein-positive, factor VIII-related antigen-negative physaliferous cells allow one to make the correct diagnosis in the former. In round cell liposarcoma, nuclear pleomorphism and hyper-chromatism are usually more prominent, the cytoplasmic vacuoles contain fat instead of red cells and there may be a delicate plexus of straight branching capillaries (Fig. 27). Furthermore, a history of or coexisting myxoid liposarcoma strongly favors the diagnosis of liposarcoma. Immunohistochemical staining for endothelial markers is useful in the differential diagnosis.

Spindle and histiocytoid (epithelioid) hemangio-endothelioma should probably be considered a morphologic variant of epithelioid hemangio-endothelioma instead of a separate entity (Silva et al., 1986; Chan et al., 1992; Suster, 1992). So far, only three cases have been reported in the literature, two presenting in lymph node and one in the spleen. Histologically, it is characterized by solitary or multinodular growth of short
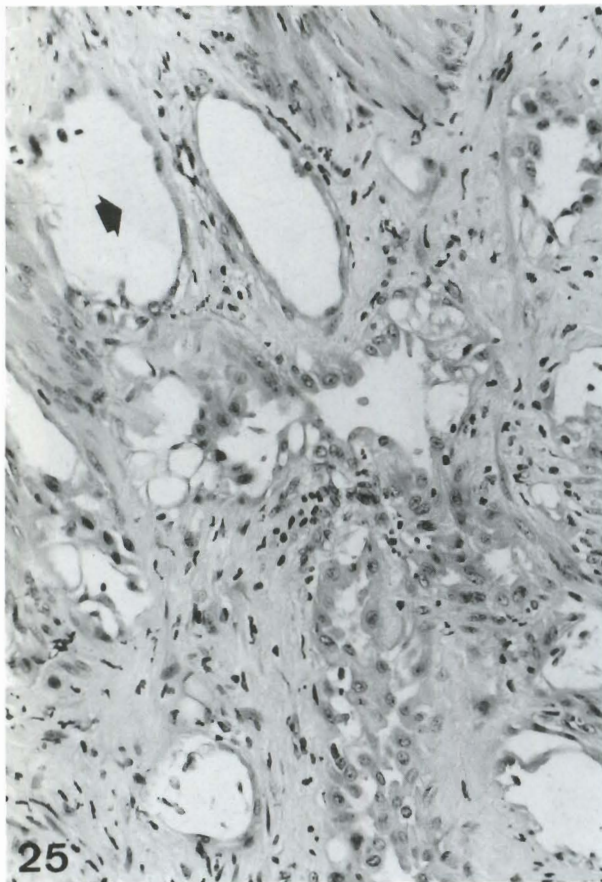
intersecting fascicles of spindle cells interspersed by polygonal cells with abundant eosinophilic cytoplasm. Cytoplasmic vacuoles may or may not be present.

Other vascular tumors may also mimic epithelioid hemangioendothelioma. Prominent edema and myxoid change in capillary hemangioma (such as those occurring in the nasal cavity) may lead to compression of the proliferated vessels into thin cell cords dispersed in a myxoid background, reminiscent of epithelioid hemangioendothelioma (Fig. 28). However, careful examination will reveal that each cord is in fact composed of a double layer of apposed endothelium with occasional lumina in between, and surrounded by pale-staining pericytes which can be highlighted by actin immunostaining (Fig. 28). Spindle cell hemangio-endothelioma is another «borderline malignant» vascular tumor occurring mostly in the subcutis of limbs of young patients (Weiss and Enzinger, 1986; Tsang et al., 1991). They differ from epithelioid hemangioendothelioma by the presence of narrow ramifying vascular spaces among spindle cells and a prominent cavernous component. Although there are interspersed vacuolated endothelial cells, epithelioid endothelial cells are lacking.

Interestingly, a case of epithelioid hemangio-endothelioma coexisting with spindle cell hemangio-endothelioma has been reported in a patient with chronic lymphedema (Zoltie and Roberts, 1989). It is most important not to mistake the hepatic epithelioid hemangioendothelioma for angiosarcoma, because the latter is a much more aggressive neoplasm. Angiosarcoma lacks the epithelioid cellular component and hyaline matrix, and often shows more significant nuclear pleomorphism.

Behaviour and prognosis

In general, epithelioid hemangioendotheliomas are indolent and compatible with long term survival (Weiss et al., 1986). In the soft tissue, local recurrence after complete excision is uncommon; in one series, about one-third of cases develop metastasis (Weiss and Enzinger, 1982). The metastases are commonly confined to regional lymph nodes and may be amenable to surgical excision. Distant metastases can occur in the lung, liver, and bone.

Those occurring in the bone are associated with an

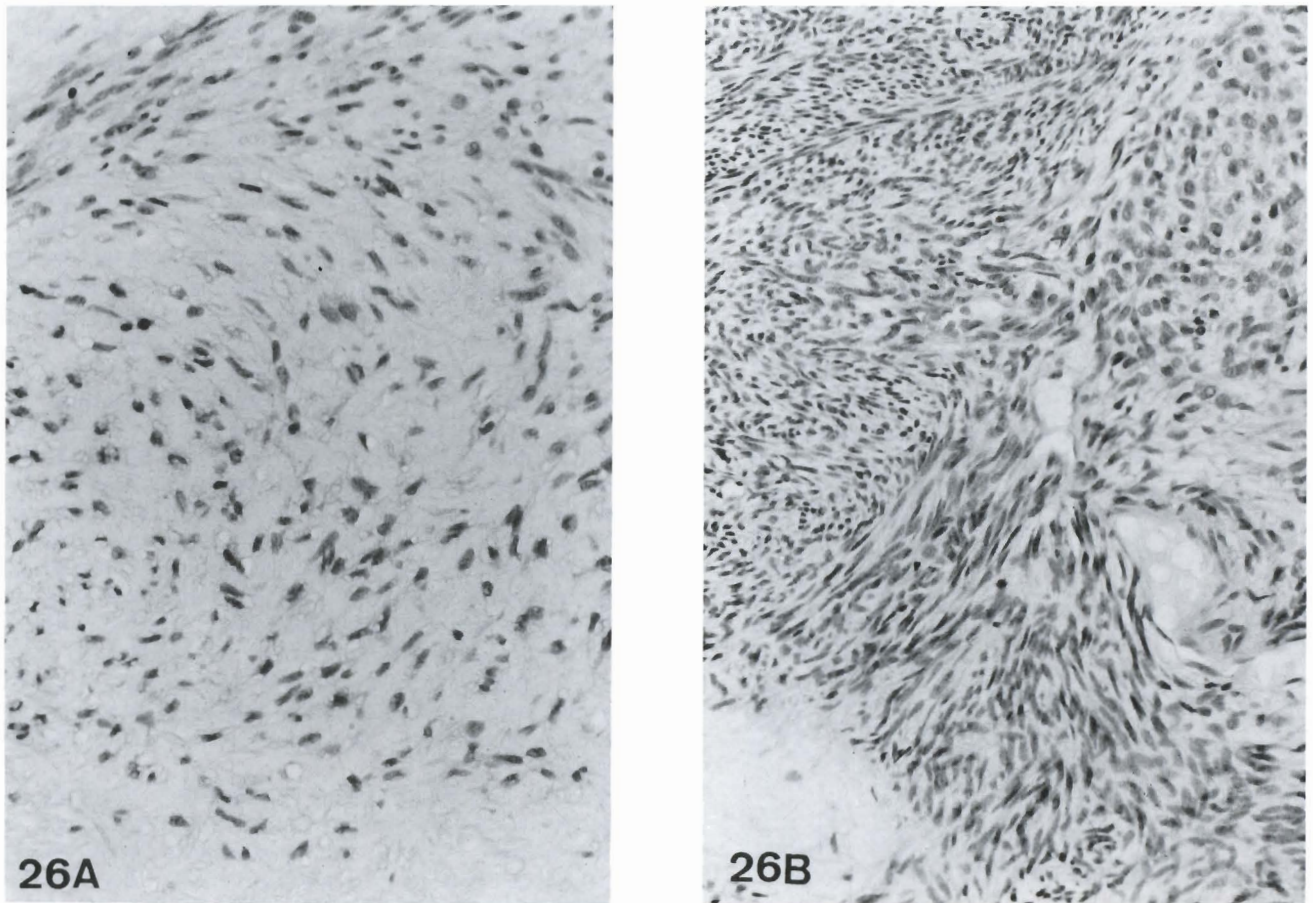**Fig. 26.** Epithelioid malignant Schwannoma. **(A).** Areas of this growth resemble epithelioid hemangioendothelioma by virtue of the short cords of vacuolated plump spindle cells dispersed in a myxoid matrix. **(B).** Other areas of the tumor show the typical pattern of malignant Schwannoma, with cellular fascicles of spindle cells possessing hyperchromatic, buckled nuclei. H&E, (A) and (B) x 188

indolent course and most patients experience long survival although distant metastasis may rarely occur (Weiss et al., 1986).

On the other hand, due to the multifocal nature and insinuating growth, epithelioid hemangioendotheliomas occurring in the lung and liver are rarely resectable, and usually pursue an indolent, but relentless downhill course. Although some patients with extensive disease may survive many years even in the absence of specific treatment, most eventually succumb to respiratory and hepatic failure due to extensive tumor growth (Weiss et al., 1986). Liver transplantation offers the best chance of cure for the unresectable hepatic tumors (Marino et al., 1988).

Histologic features may be of some help in predicting the behaviour of an individual case. Weiss and Enzinger (1982) divided epithelioid hemangioendothelioma of soft tissues into malignant and benign forms based on the presence of significant atypia, mitotic activity (>1 mitotic figure/10 high power fields), focal spindling of tumor cells and necrosis. These features are associated with more aggressive clinical course and higher incidence of metastasis (53% of cases with these

features, versus 17% for those without). However, these criteria are not foolproof because tumors without these features may also behave in an aggressive fashion. After repeated recurrences, epithelioid hemangioendothelioma can progressively acquire these «malignant» features and the associated prognostic adversity. There are however no clear-cut criteria to distinguish the malignant variant of epithelioid hemangioendothelioma from epithelioid angiosarcoma.

Borderline cases and approach to diagnosis

The constellation of features discussed above should permit distinction of the three categories of epithelioid vascular tumors in most instances (Table 1). However, we view them as three defined points on a continuous spectrum only; there are neoplasms which may defy classification into these categories. Some tumors may show infiltrative solid growth of epithelioid tumor cells with occasional vacuoles and moderate nuclear atypia, but lacking cord-like growth and hyaline matrix; such cases may be considered to lie at the borderline between epithelioid hemangioendothelioma and angiosarcoma (Fig. 29). On the other hand, there are cases in which cords or sheets of vacuolated epithelioid endothelial

Fig. 27. Round cell liposarcoma. Cords of vacuolated tumor cells lie in a myxoid stroma. The delicate plexus of capillaries as seen in the lower field clinches the diagnosis. H&E. x 150
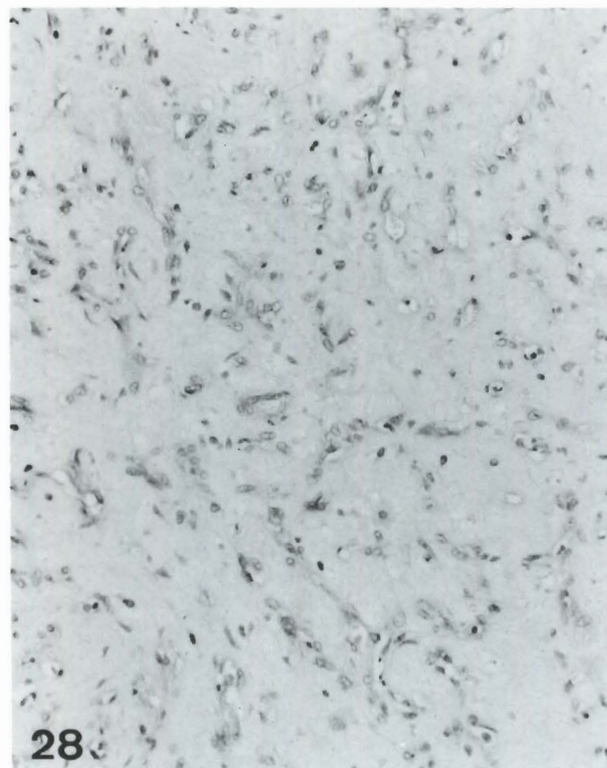

Fig. 28. Hemangioma with myxoid change. Cords of compressed capillaries are dispersed in a myxoid background, mimicking epithelioid hemangioendothelioma. However, each «cord» is in fact composed of a endothelium-lined channel surrounded by pale-staining pericytes. H&E. x 150
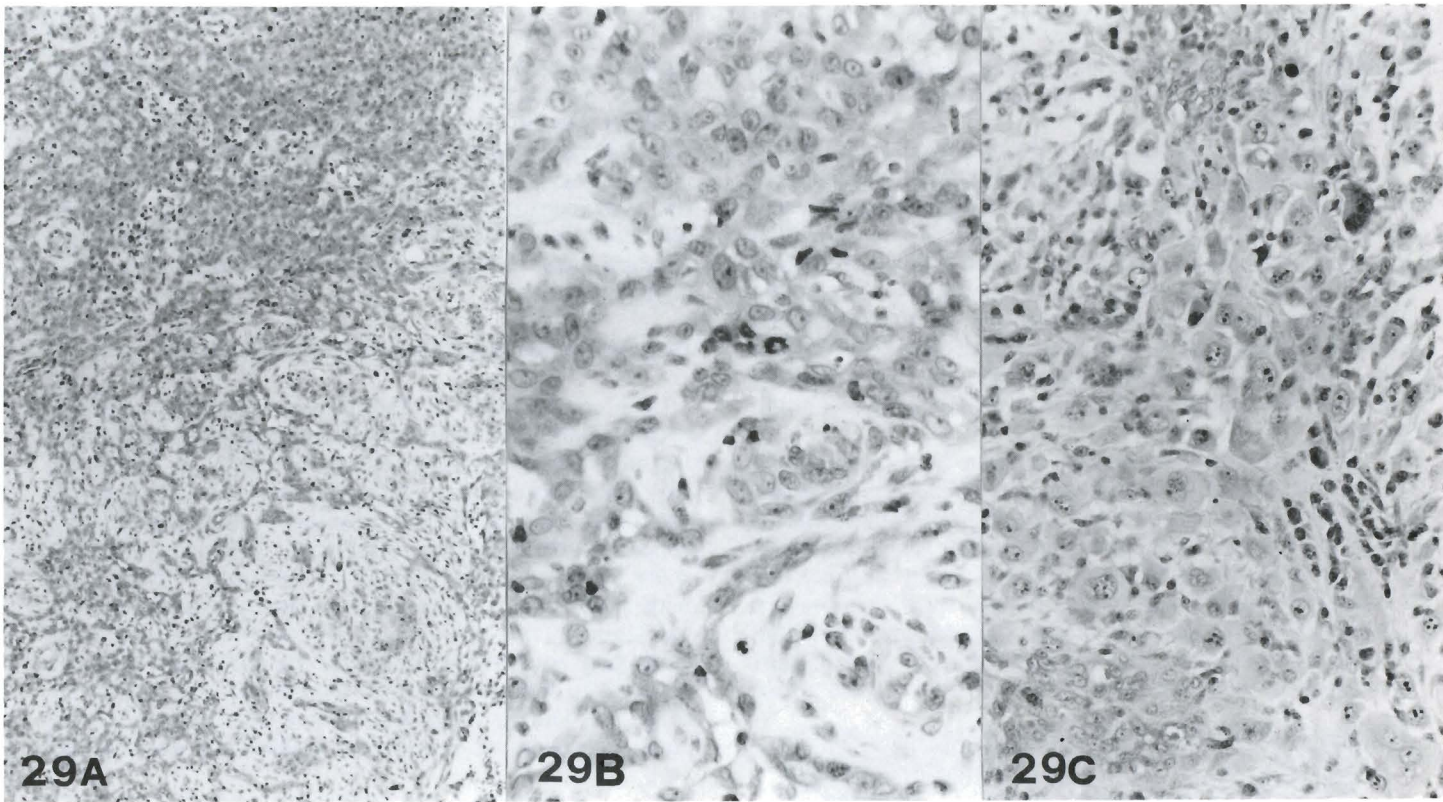
Fig. 29. Epithelioid vascular tumor, borderline between epithelioid hemangioendothelioma and angiosarcoma. **(A)**. The tumor shows predominantly solid growth, but very focally the tumor cells are arranged in anastomosing cords within a myxoid background. **(B)**. Higher magnification showing tumor cells with moderate pleomorphism and occasional mitotic figures. **(C)**. In the tumor that recurs after 2 years, the tumor cells are much larger and pleomorphic, and possess giant, bizarre, hyperchromatic nuclei. This tumor is now a frankly malignant epithelioid angiosarcoma. H&E, (A) x 96; (B) x 300; (C) x 186
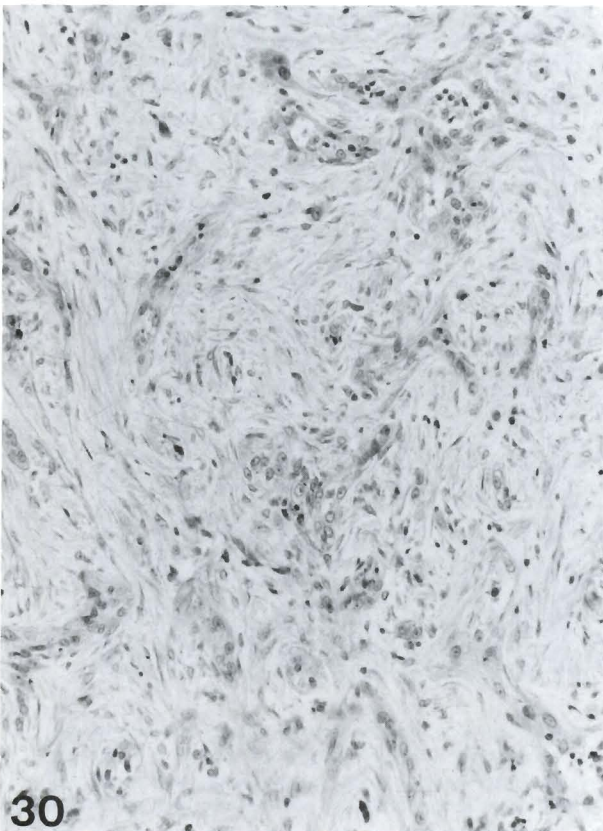
cells are admixed with well canalized blood vessels, sometimes accompanied by a rich eosinophilic infiltration; we consider such cases to show overlapping features of epithelioid hemangioma and hemangio-endothelioma (Figs. 30-32). We have also observed the evolution of a tumor from an indeterminate category to a frankly malignant tumor (Fig. 29).

In the categorization of epithelioid vascular tumors as being benign, borderline or malignant, the whole histological picture should be taken into account (Table 1). A lobulated growth pattern, if present, favors a benign diagnosis. The degree of vascular differentiation is the most important consideration. Vascular differentiation can take place at different levels: well

Fig. 30. Epithelioid vascular tumor of lung, borderline between epithelioid hemangioendothelioma and hemangioma. The cord-like growth is typical of epithelioid hemangioendothelioma, but many of the «cords» actually represent collapsed vascular channels well lined by endothelial cells, indicating a more advanced degree of vascular differentiation than that normally seen in epithelioid hemangio-endothelioma. H&E. x 150
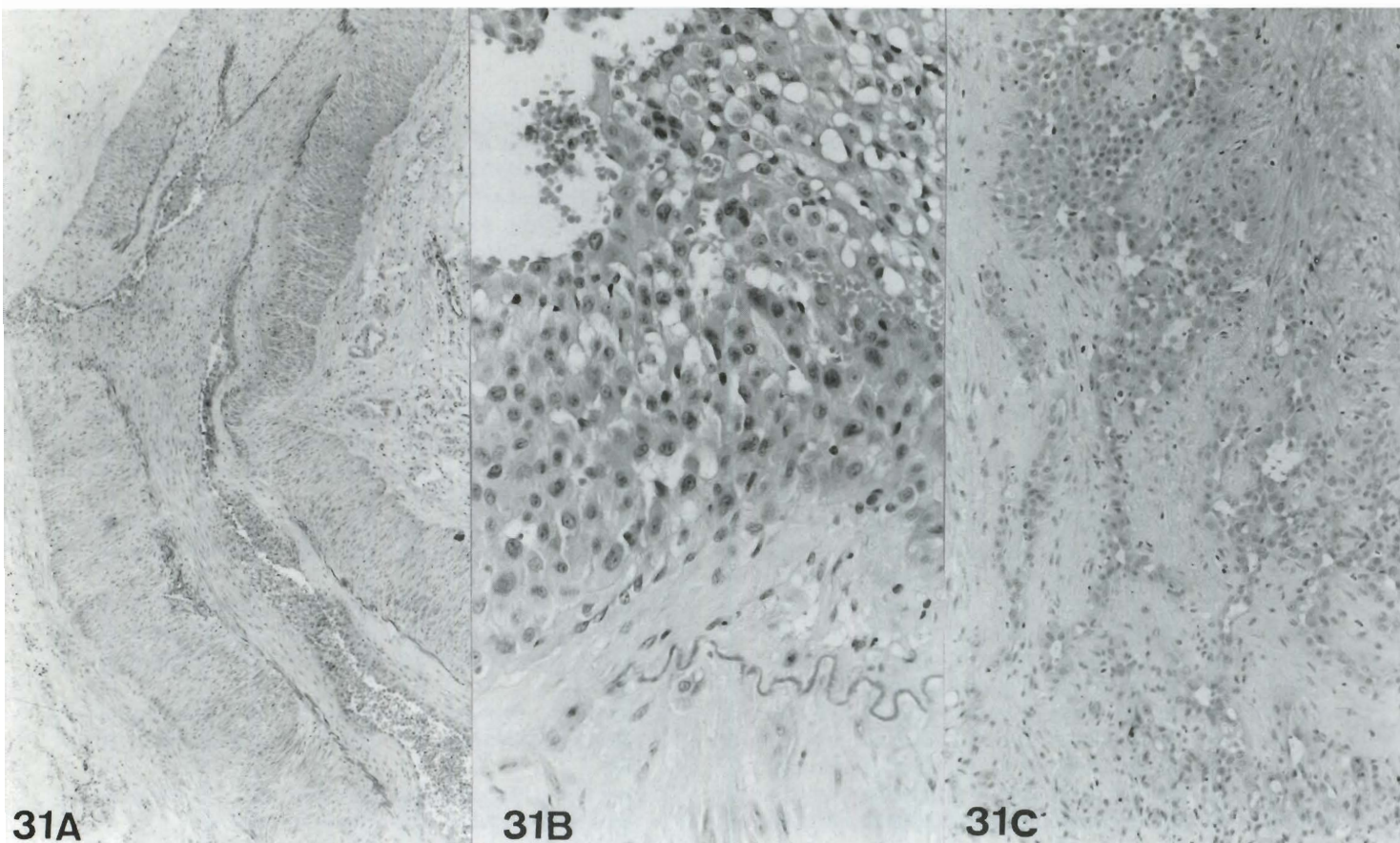
31A   31B   31C

Fig. 31. Epithelioid vascular tumor of the stomach, borderline between epithelioid hemangioma and hemangioendothelioma. This case was previously reported as an example of epithelioid hemangioendothelioma (Lee et al., 1988). **(A)**. The proliferated epithelioid endothelial cells involve a muscular artery, lining the lumen and breaking through its wall, a pattern reminiscent of epithelioid hemangioma. **(B)**. Areas with solid growth of vacuolated cells. **(C)**. Other areas show solid growth, cords and some fairly well developed vascular channels. This tumor thus exhibits variable degrees of vascular differentiation. H&E, (A) x 38; (B) x 186; (C) x 96

canalized vessels represent the most mature degree of vascular formation, cytoplasmic vacuolation in isolated cells or cell cords represents early vascular differentiation at the cellular level, whereas solid sheets or cellular columns represent poor vascular differentiation (Figs. 31, 32). The presence of dissecting, anastomosing, maze-like vascular channels such as those seen in conventional angiosarcoma is always indicative of malignancy (Fig. 14). However, consideration should also be given to the degree of cellular atypia and mitotic activity in the final designation.

The stromal changes are of secondary importance in influencing the categorization of epithelioid vascular tumors, and only in selected circumstances. Eosinophils

Fig. 32. Epithelioid vascular tumor of soft tissue, borderline between epithelioid hemangioendothelioma and hemangioma. This tumor shows mainly solid growth of vacuolated tumor cells (right field), but there are occasional foci with advanced vascular differentiation in the form of ectatic spaces (left field), resembling those seen in a cavernous hemangioma. H&E. x 94

are usually prominent in the benign epithelioid vascular tumors, and become sparse or absent for tumors lying on the intermediate and malignant ends of the spectrum. On the other hand, a hyaline-myxoid matrix is typically associated with epithelioid vascular tumors of borderline malignancy. Therefore, in an epithelioid vascular tumor of indeterminate categorization, the presence of a rich infiltrate of eosinophils may prompt one to slightly downgrade it towards the benign end. Similarly, for an indeterminate epithelioid vascular tumor, the presence of an abundant hyaline-myxoid matrix may indicate a greater relationship with epithelioid hemangio-endothelioma.

In conclusion, the majority of the epithelioid vascular tumors can be classified as one of the three defined subtypes. For cases that show overlapping features, it is important to provide an estimation of their relative position on the spectrum, for example, «epithelioid vascular tumor, borderline between epithelioid hemangioendothelioma and angiosarcoma» (Fig. 29) or «epithelioid vascular tumor borderline between epithelioid hemangioma and hemangioendothelioma, but probably nearer the benign end» (Fig. 31). However, prediction of behaviour of such tumors is even more difficult due to the paucity of reported cases and the discordance between morphology and behaviour in some epithelioid vascular tumors of intermediate malignancy.

Addendum

Since submission of this manuscript for publication, Allen et al. (1992) have published a review on the controversial aspects of histiocytoid hemangiomas. Some of their views are significantly different from ours, and the interested readers may refer to their paper.

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