

Malignant epithelioid hemangioendothelioma of the liver, spreading through the hepatic veins

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Summary. A case of malignant epithelioid hemangioendothelioma of the liver mimicking veno-occlusive disease is reported. The histological, ultrastructural, and immunohistochemical features of the present case indicate striking similarities to epithelioid hemangioendothelioma (EHE) of the soft parts described by Weiss and Enzinger. Tumour metastasis to the lung gave a picture closely resembling intravascular bronchiolo-alveolar tumour (IVBAT) of the lung. EHE of the liver is considered to be a unique type of hepatic endothelial neoplasm behaving as a low grade malignant tumour with a veno-occlusive process which has rarely been described, and had previously been classified as other diseases or neoplasms.

Key words. Epithelioid hemangioendothelioma – Liver – IVBAT – Venocclusive disease

Introduction

Epithelioid hemangioendothelioma (EHE), which was first described by Weiss and Enzinger (1982), is a soft tissue tumour characterized by the presence of histiocytoid or epithelioid endothelial cells with frequent cytoplasmic vacuoles and myxohyaline stroma. We present here a case of malignant endothelial tumour of the liver, which showed the same characteristics as those of EHE. The tumour spread in a particular fashion through the hepatic veins, entering into collapsed hepatic lobules from their central parts. In addition, the histology of its metastasis in the lung revealed a close relationship between EHE and intravascular, bronchiolo-alveolar tumour of the lung (IVBAT) (Dail and Liebow 1975). EHE may occur in the liver, and should be classified as an independent category of endothelial neoplasm.

Case report

Seventeen years before her death at age 38 in 1983, a then 21 year old housewife took oral contraceptives for 21 days. Five years before her death, during pregnancy, she received medication with a hormone to prevent abortion for three weeks. She had 2 pregnancies and deliveries. She had been seeing a local doctor regularly since proteinuria was discovered at the age of 27. In 1982 fever and abdominal distension occurred and she first visited the Metropolitan Komagome Hospital, at which time ascites, an epigastric tumour and abnormalities of liver function were noted. She was given oral diuretics and was admitted to the Hospital for further evaluation. Physical examination revealed that an epigastric mass was persistent, but the ascites had disappeared. Laboratory findings were as follows: Alb 3.2 g/dl, T.Bil 0.8 mg/dl, GOT 60 IU/l (normal, 8–26), GPT 44 IU/l (normal, 2–24), ALP 406 mU/ml (normal, 23–76), CEA 1.2 ng/ml (normal, less than 2.5), AFP 2.4 ng/ml (normal, less than 20), HBsAg (–), HBsAb (–). There was no abnormality in chest roentgenogram. Abdominal CT scan disclosed shrinkage of the right lobe of the liver with decreased density and hypertrophy of the left lobe with focal areas of decreased density at its periphery. Mild splenomegaly was also revealed. The scintiscan of the liver (technetium-99M-sulfur colloid) showed radioactivity exclusively in the enlarged left lobe of the liver. The selective angiography of the coeliac artery showed a corkscrew-like configuration of the right hepatic arteries and distension of the left arteries. The portal vein was obstructed at the orifice of its right branch. A malignant tumour of the right hepatic lobe was strongly suspected and open biopsy of the liver was performed. The right lobe was not observed due to adherence to the peritoneum. The peripheral part of the left lobe was discolored and shrunken, and the residual part of the lobe was enlarged with normal hepatic color. Diagnosis, determined by biopsy, was an unusual form of angiosarcoma. Ascites which had recurred was controlled by diuretics and the patient was discharged four months later. She was in favorable condition before a gradual increase of ascites in 1983. She was re-admitted because of nasal bleeding and haematemesis. Despite vigorous therapy, repeated haematemesis occurred together with overt hepatic failure. She died 16 months after her first admission.

Materials and methods

The wedge biopsy specimen from the shrunken peripheral part of the left lobe of the liver was fixed in 17% neutral buffered formalin and routinely embedded in paraffin. Sections cut at 3 micron were stained with haematoxylin and eosin (H-E), Masson trichrome, Elastica van Gieson (EvG), periodic acid – Schiff (PAS) with or without diastase, alcian blue and colloidal iron with or without hyaluronidase, Congo red, and toluidine blue (PH 1.0).

Small cubes of the tumour were fixed in phosphate buffered 3% glutaraldehyde, post-fixed in 2% OsO₄, routinely processed and examined by H500 electron microscope (Hitachi).

For immunohistochemistry, the unlabeled antibody peroxidase-antiperoxidase (PAP) method of Sternberger et al. (1970) was applied to formalin-fixed and paraffin-embedded tissue. Rabbit anti-Factor VIII-related antigen (FVIII R:AG) antibody was obtained from Dakopatts (Copenhagen, Denmark).

Autopsy was performed at 2 h after death. Sections of each organ were fixed in 17% formalin and processed in the same manner as biopsied material.

Results

Liver biopsy

Light microscopy. Biopsied specimens from the shrunken peripheral part of the left lobe disclosed that central parts of the hepatic lobules had been replaced by the tumour with myxohyaline stroma, obliterating the central veins (Fig. 1). Spindle or irregularly dendritic-shaped cells with eosinophilic cytoplasm were scattered in the hyaline matrix with many acellular vacuoles. The cytoplasmic vacuolization of the pleomorphic cells appeared as an

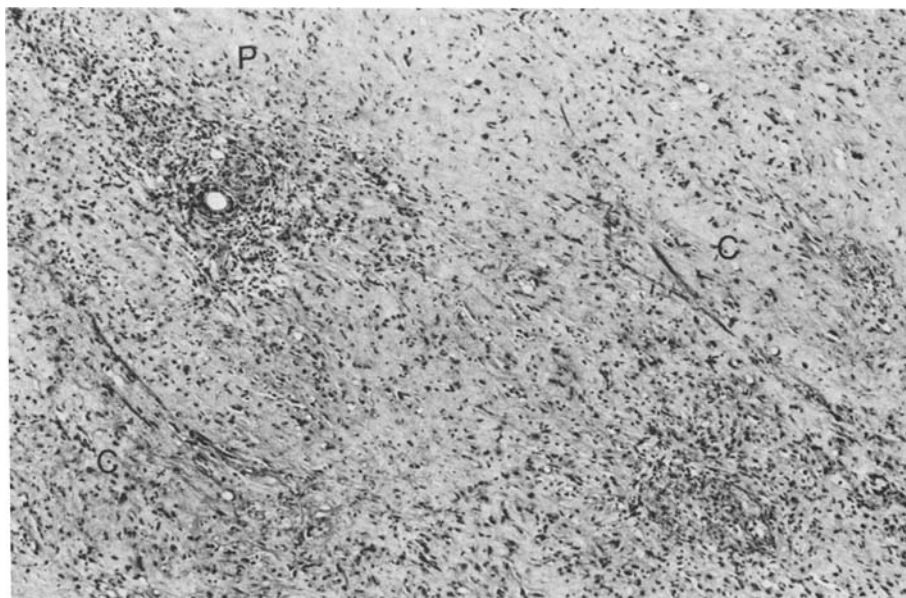


Fig. 1. Wedge biopsy from the discolored lesion of the left lobe of the liver. The central areas of the hepatic lobules were replaced by the tumour with myxohyaline stroma. The central veins (C) was buried in it. P portal areas. ($\times 20$, HE)

aggregation of capillary lumina, suggesting vasoformation (Fig. 2a). In some areas, the tumour consisted of anastomosing cords of cells embedded in myxoid matrix. Some cells contained myxomatous material both in cytoplasm and cytoplasmic vacuoles, somewhat like mucus-containing signet ring cell carcinoma. Occasionally, rather polyhedral cells with cytoplasmic vacuoles protruded into the dilated capillary lumina and formed papillary structures. (Fig. 2c).

The interlobular bile ducts and arteries in the portal areas remained intact, though focal hyperplasia of bile ducts and slight infiltration of lymphocytes were observed. The portal veins were occluded and surrounded by rather spindle-shaped cells. The sublobular veins were also occluded by recanalized thrombus-like structures with polyhedral cells in recanalized capillary lumina (Fig. 2d). These pleomorphic cells showed mitotic figures with frequency less than 1/10 HPF ($\times 200$).

The myxomatous stroma was stained with colloidal iron, as well as alcian blue. The positive staining was digested by hyaluronidase. The hyaline stroma displayed a positive staining reaction for PAS without digestion by diastase. Both stromas were stained blue with Masson, but negatively stained with Congo red. These stromas did not show metachromasia with toluidine blue (pH 1.0).

Immunohistochemistry. Factor VIII-related antigen (FVIII R:AG) has been widely used as an endothelial cell marker (Jaffe et al. 1973; Mukai et al. 1980; Sehested et al. 1981). FVIII R:AG was found to be definitely localized in the

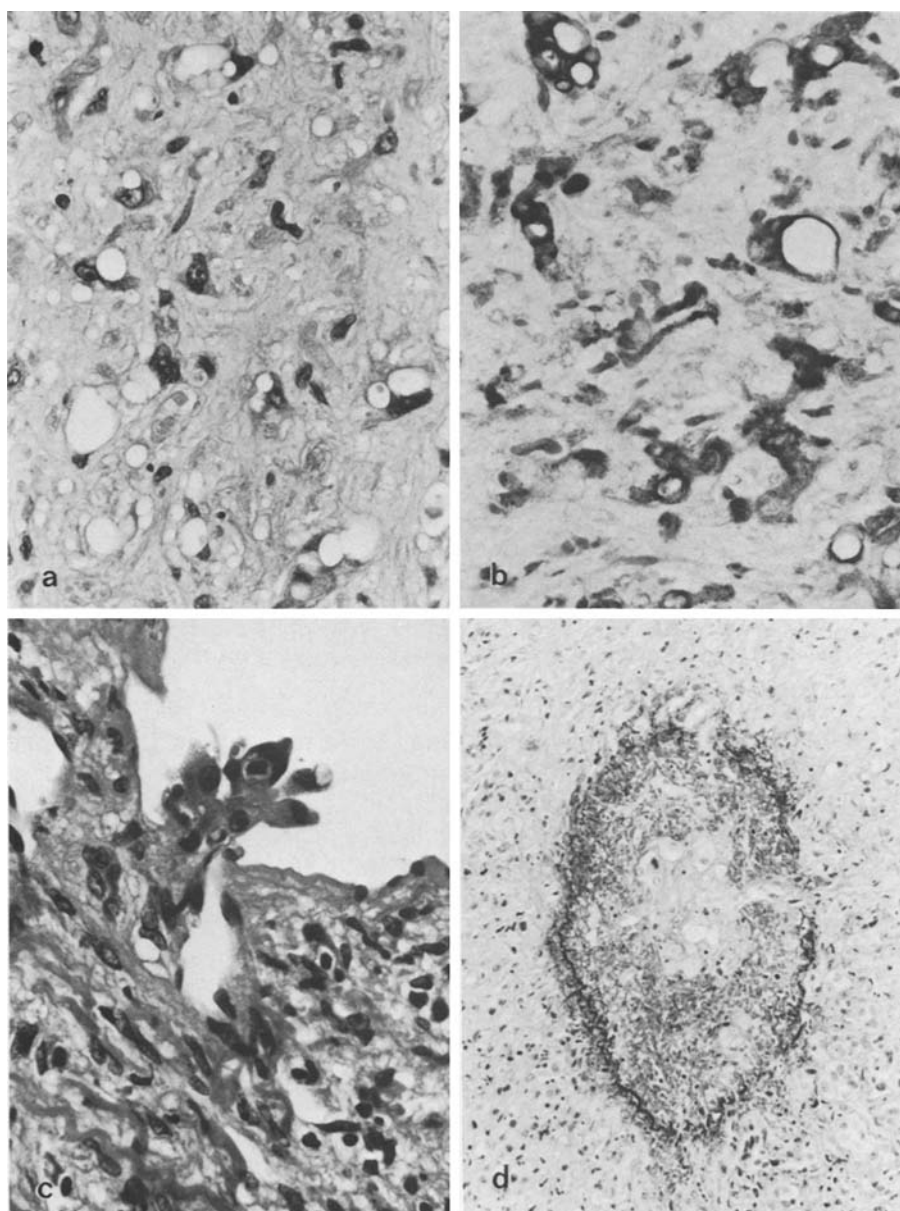


Fig. 2a. Pleomorphic cells were scattered in the hyaline stroma. Note the cytoplasmic vacuolization, suggesting vasoformation ($\times 160$, HE). **b** Factor VIII-related antigen was localized diffusely and granularly in the cytoplasm of pleomorphic cells. Note the morphological continuity from the cytoplasmic vacuoles to capillaries. ($\times 160$, PAP). **c** Several cells aggregated in papillary fashion and protruded into the capillary lumen from its wall. The cytoplasmic vacuolation was also noted in the polyhedral cells ($\times 160$, HE). **d** A sublobular vein was occluded by a thrombus like structure with polyhedral-shaped cells in recanalized capillaries. ($\times 50$, EvG)

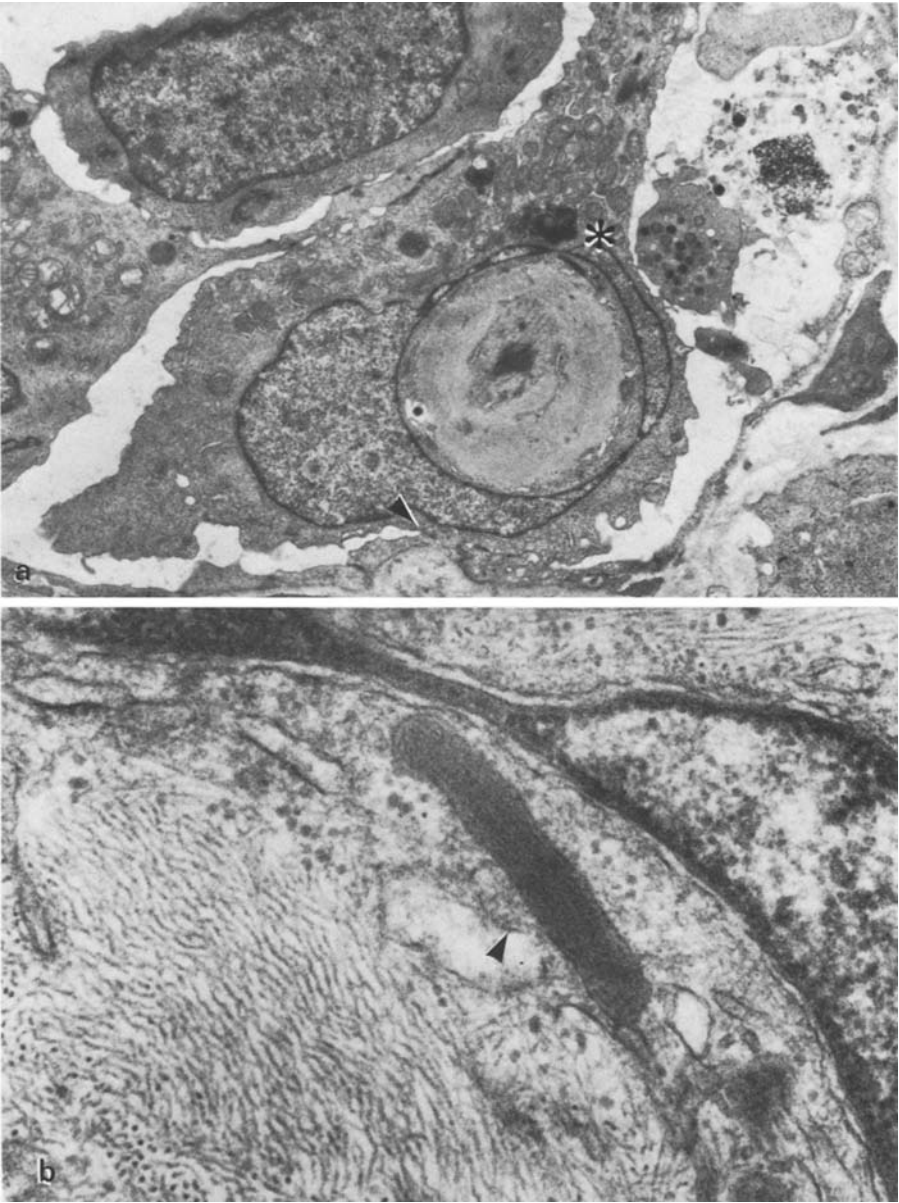


Fig. 3a Polyhedral-shaped cells in the dilated capillary. They contained rich subnuclear filaments. Intercellular junctions were evident among them and between them and flat endothelial cells (*arrow*). A Weibel-Palade body was demonstrated (*). ($\times 2,000$). **b** High magnification view of the Weibel-Palade body in Fig. 3a. (*arrow*) ($\times 23,000$)

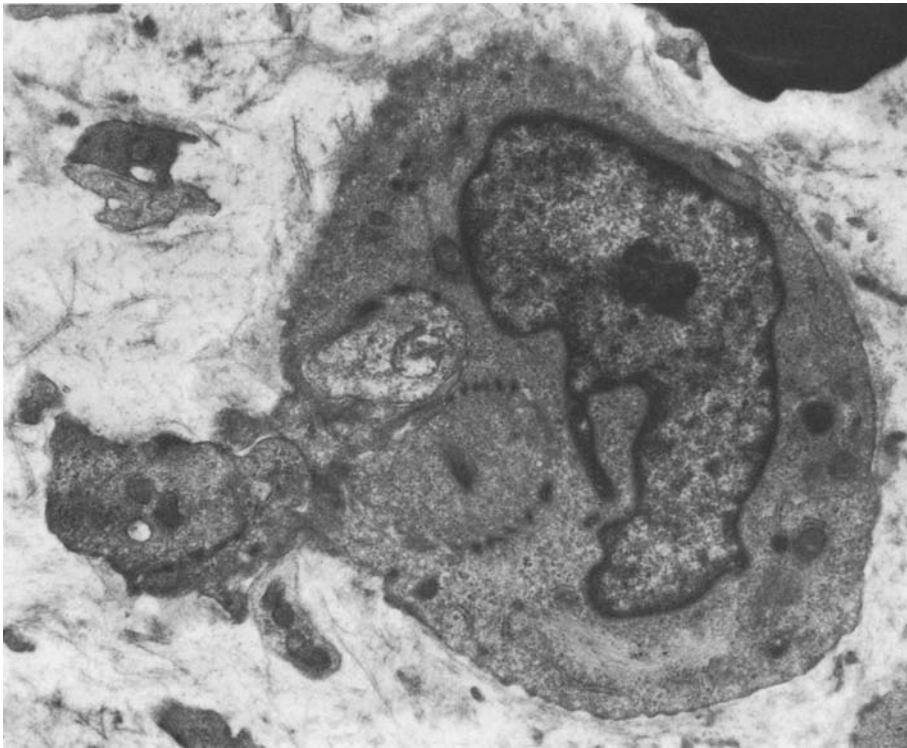


Fig. 4. In the stroma corresponding to myxohyaline stroma, irregular shaped cells contained rich cytoplasmic intermediate filaments and pinocytotic vesicles at the surface. They were invested by the discontinuous basal lamina. ($\times 3,300$).

cytoplasm of all above-described “pleomorphic cells”. It was clear that the cytoplasmic vacuole-laden cells, in which FVIII R:AG was revealed, assumed the continuity of the structure of the aggregation of capillaries (Fig. 2b).

Electron microscopy. The ultrastructure of “pleomorphic cells” appeared to agree with the characteristics of endothelial cells. The polyhedral-shaped cells protruded into the dilated capillary lumina. The cells had nuclear infoldings and subnuclear cytoplasmic filaments (Fig. 3a). In the stroma of the myxohyaline areas, there were spindle or dendritic cells which also contained substantial subnuclear intermediate filaments, some with dense body-like structures (Fig. 4). There were many pinocytotic vesicles at their periphery. Mitochondria, rough endoplasmic reticulum, and Golgi apparatus were present in various amounts. Desmosome-like intercellular junctions were evident. Cytoplasmic vacuoles were also evident, suggesting intracytoplasmic canalization, similar to the seamless endothelial cells in the vasoformative process in embryos (Wagner 1980) (Fig. 5). Cells in the stroma including seamless endothelial cells were invested by continuous or discontinuous basal lamina, partly laminated. Some fibroblasts surrounded the neoplastic cells



Fig. 5. The cell had 4 intracytoplasmic vacuoles without intra or intercellular junction on this plane, suggesting intracytoplasmic canalization, similar to seamless endothelial cells in embryos. Basal lamina invested the cell, with partial lamination. ($\times 2,200$)

and their protrusion extended toward the basal lamina. A few Weibel-Palade bodies were clearly identified in the tumour cells (Fig. 3b).

Autopsy

Gross findings. The liver was distorted in shape. The right lobe was shrunken and firm, and the left lobe nodular. On the cut surface (Fig. 6), a yellowish white tumour with reticular reddened lesions occupied the whole right lobe with continuous infiltration into the left lobe. Irregularly shaped nodules were present at the peripheral region of the left lobe. The residual part of the

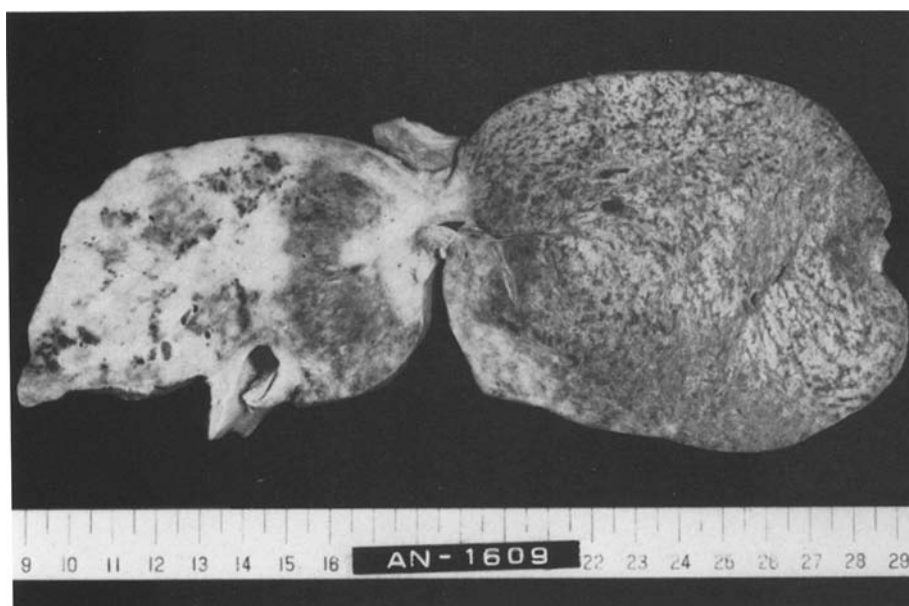


Fig. 6. The cut surface of the liver. The right lobe was shrunk, and replaced by the myxoid yellowish tumour. Intrahepatic metastatic foci were identified in the enlarged left lobe with distorted lobular structure

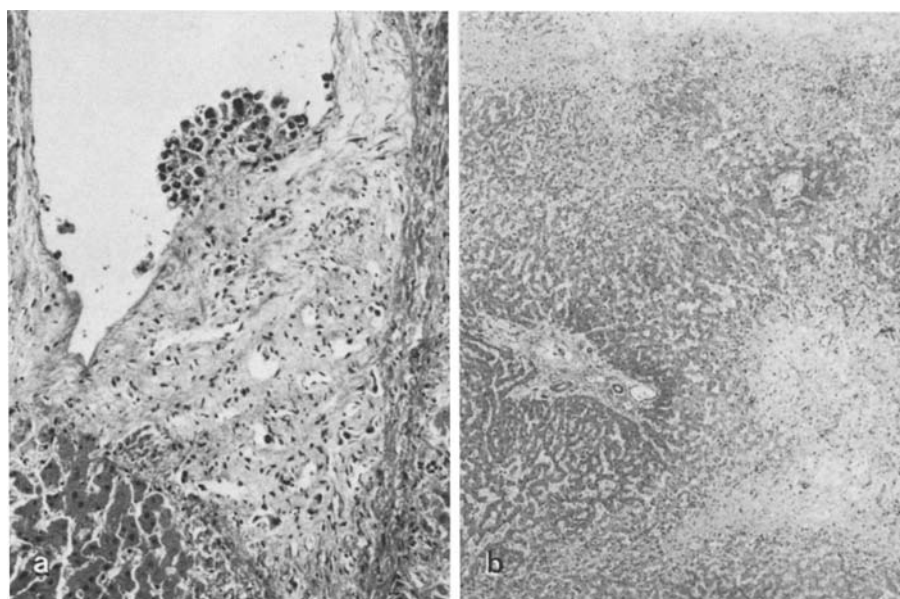


Fig. 7a. Tufts of neoplastic cells attached to the thrombus like structure of the tumour in a tributary of left hepatic vein. ($\times 40$ HE). **b** Collapse of sinuses and fibrosis bridged central areas in the left lobe. ($\times 10$ HE)

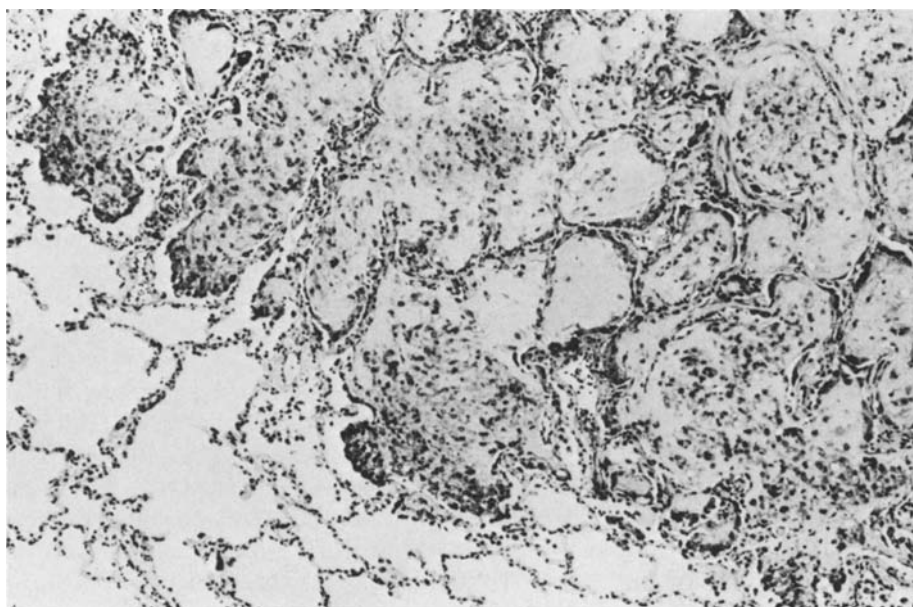


Fig. 8. A metastatic tumour in the lungs showed micropolypoid nodules in the bronchiolo-alveolar space, which was so similar to the IVBAT. ($\times 20$ HE)

left lobe showed distortion of lobular structures. The right and middle hepatic veins were occluded by the tumour at their orifices and tumour invasion existed in the wall of intrahepatic inferior vena cava. The right portal vein was similarly occluded and infiltration from the hepatic hilum to the right adrenal gland was found. Many metastatic nodules were identified in both lungs and the pericoeliac lymph nodes.

Histopathological findings. The tumour was histologically identical to that of the biopsied specimens. Tufts of tumour cells were attached to the recanalized thrombus-like structure of the tumour in the tributaries of the left hepatic vein (Fig. 7a). In the left lobe, tumour occlusion was observed in the sublobular and central veins, resulting in either dilatation of sinuses of the central areas or disappearance of hepatocytes and collapse of sinuses. Bridging fibrosis in the central areas of the hepatic lobules with focal regeneration was observed (Fig. 7b). Neoplastic cells were identified in the collapsed lesion and dilated sinuses. The tumour was therefore thought to have spread through the hepatic veins and replaced collapsed liver tissue with myxohyaline stroma.

The metastatic nodules of the lungs shared the same histological features with so-called IVBAT of the lung (Fig. 8). Micropolypoid tumour occupied the alveolar and bronchiolar lumina without any destruction of the bronchiolo-alveolar structure. The histology of the central myxohyaline part of the metastatic nodules was the same as that of the central area of the hepatic lesions. It was evident that myxomatous stroma was not merely ascribed to

desmoplastic reaction but to secretion by the tumour itself. Tumours became more cellular at the periphery and were composed of polyhedral-shaped cells, similar to neoplastic cells in dilated capillaries in the liver. There were almost no mitotic figures. Metastatic nodules were extremely like IVBAT. Immunohistochemically, FVIII R:AG was found to be localized in these neoplastic nodule cells, as it was in the biopsied specimens of the liver. Where the pulmonary veins were occluded by the tumour, the distal lung tissue showed dilatation of capillaries of alveoli, bronchovascular sheath and interlobular septae. Some tumour cells were seen within dilated capillaries.

Discussion

Macroscopically, shrinkage of hepatic parenchyma with marked replacement by myxomatous yellowish white tumour was so striking that it was difficult to consider it to be vascular in origin. Rather, it was reminiscent of sclerosing cholangiocellular carcinoma. But the vasoformative structure associated with cytoplasmic vacuoles corresponding to seamless endothelial cells, was demonstrated by histological examination. Furthermore, ultrastructural findings including the presence of Weibel-Palade bodies, relatively specific to endothelial cells (Waldo et al. 1977), as well as cytoplasmic localization of FVIII R:AG were also indicative of the endothelial origin of the tumour. Though abundant cytoplasmic filaments are not usually found in endothelial cells, similar filaments have been observed in various neoplastic endothelial cells (Rosai et al. 1976; Waldo et al. 1977).

Both the polyhedral-shaped endothelial cells with plump eosinophilic cytoplasm in dilated capillaries, and dendritic or spindle endothelial cells in myxohyaline stroma with prominent cytoplasmic vacuolization, were compatible with histiocytoid (Rosai et al. 1979) or epithelioid (Enzinger and Weiss 1983) endothelial cells described in vascular tumours of the soft parts. Enzinger and Weiss (1983) separated these vascular tumours comprising characteristic endothelial cells into epithelioid hemangioma including angiolymphoid hyperplasia with eosinophils and epithelioid hemangioendothelioma (EHE). The histological appearance of their EHE seems to be identical to that of our case in the liver, because the former is also composed of epithelioid endothelial cells with cytoplasmic vacuoles and myxohyaline matrix, and shows an angiocentric location, mainly in intermediate or large veins. Further, they described not only the ultrastructural features of EHE, such as pinocytotic vesicles, Weibel-Palade bodies and prominent cytoplasmic filaments, but also found seamless endothelial cells in EHE. Thus, we consider that the tumour in the present case is a counterpart of EHE of the liver, or a different, independent type of endothelial neoplasm in the liver, which has thus far been rarely reported.

The lung metastatic nodules found in this case were histologically quite similar to those of IVBAT described by Dail and Liebow (1975). Recently, many reports have revealed an endothelial nature of IVBAT using ultrastructural studies (Corrin et al. 1979; Weldon-Linne et al. 1981) and immunohistochemical localization of FVIII R:AG (Bhagavan et al. 1982). Dail et al.

(1983) changed their previously suggested name for this tumour, with its implication of bronchiolo-alveolar cell origin, to the merely topographical name of intravascular, bronchiolar and alveolar tumour. Interestingly, they described 2 cases with large liver tumours in 20 cases of IVBAT, suggesting that the liver tumours might have been primary. Moreover, according to Dail et al., there are several reported cases of liver tumours, under various terminologies, whose metastases to the lungs resembled IVBAT (Ludwig et al. 1975; Echevarria et al. 1978). In some cases, tumours were clearly shown to be localized only in intrathoracic portions. However, IVBAT does not necessarily mean primary pulmonary neoplasm. IVBAT may be metastasis of the lung from EHE of other organs.

In addition to IVBAT-like nodules, there was a partial veno-occlusive process with prominent dilatation of capillaries in our case. The veno-occlusive process, which has rarely been described in IVBAT, may be related to dyspnoea of which some patients with long-standing IVBAT have complained.

The tumour spread in a particular fashion through the hepatic veins and replaced the hepatic lobule from the central vein; the left hepatic lobe showed central fibrosis within the limits that the tumour had spread. The veno-occlusive process clinically showed a great resemblance to an occlusive disease of the liver, the Budd-Chiari syndrome (Mitchell et al. 1982). Recently, Gledhill and Kay (1984) reported a case of IVBAT with hepatic metastasis, whose biopsy of the liver was originally diagnosed as hepatic veno-occlusive disease. They interpreted IVBAT as primary neoplasm, but the tumours of the liver were larger (maximum diameter 6.0 cm) than those of the lung (up to 1 cm on chest roentgenogram). Although the possibilities of multicentric origin could not be ruled out, their case might be similar to ours, a malignant EHE of the liver spreading through the hepatic veins with IVBAT-like lung metastasis.

It seems worthy to note that the patient had taken oral contraceptives for a short duration many years before. Monroe et al. (1981) reported a case of hepatic angiosarcoma in an oral contraceptive user for 8 years. However, the histological appearance they presented was not definitely accordant with the typical structure of angiosarcoma, but rather resembled features shown in our case. There have been many case reports that oral contraceptives may damage hepatic vasculature, leading to a condition like Budd-Chiari syndrome (Nime et al. 1979; Alpert 1976; Ecker et al. 1966). In light of the fact that the shortest period of the drug use was 2 weeks (Ecker et al. 1966), we could not simply deny the possibility that oral contraceptives might have a role in the genesis of the peculiar endothelial neoplasm we found. Further findings are needed to elucidate the relationship between oral contraceptives and EHE, and to compile additional confirmation of malignant EHE of the liver.

EHE, first described by Weiss and Enzinger (1982) is considered to show the biological behavior of a so-called borderline lesion or low-grade malignancy. They reported that 20 out of 31 patients were alive and well with no evidence of disease following excision of tumours, and 6 patients developed

distant metastasis. It is indisputably evident that EHE in the present case was malignant in nature in view of the metastases to the peri-coeliac lymph nodes and lungs, although mitotic figures of the tumours were almost non-existent and the clinical course of the patient was longer, as compared with that of the angiosarcoma of the liver which had been reported by Ishak (1976). Hence, pathologists and clinicians must be fully aware that EHE in the liver may occur with the behavior of a low-grade malignant tumour associated with a veno-occlusive process.

Acknowledgements. The skillful assistance of Yumiko Shiozawa, Yukiko Hayashi and Yoshiyuki Kasuga is greatly acknowledged. The Authors also wish to thank Dr. N. Hirota and Prof. T. Yokoyama (Department of Pathology, Jichi Medical School) for reviewing the manuscript.

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Accepted July 5, 1984