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Fatal epithelioid haemangioendothelioma presenting in the lung and liver

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Summary. Three patients with epithelioid haemangioendothelioma (EHE) are described. Two patients presented with pulmonary infiltrates and one with a hepatic tumour. All had a metastatic disease ending fatally, and all were autopsied. The diagnosis was confirmed either by immunohistological or ultrastructural analysis. All three tumours were cytokeratin-negative and vimentin-positive, while only two contained cells reacting with the antibody of factor VIII-related antigen. Electron microscopy of the third tumour revealed features indicating endothelial differentation. A short literature review is also presented demonstrating that the outlook of EHE is worse than previously thought.

Key words: Epithelioid haemangioendothelioma – IVBAT – Immunohistochemistry – Ultrastructure

Introduction

Dail and Liebow described in 1975 a peculiar lung tumour which they designated as intravascular bronchioloalveolar tumour (IVBAT) (Dail and Liebow 1975). Subsequent EM studies revealed that the tumour cells had features compatible with endothelial cells (Corrin et al. 1979; Azumi and Churg 1981; Weldon-Linne et al. 1981a; Bhagavan et al. 1982 and Dail et al. 1983). The hypothesis of an angiogenic nature of IVBAT was strongly supported by the demonstration of factor VIII-related antigen in the tumour cells (Weldon-Linne et al. 1981b; Bhagavan et al. 1982; Corrin et al. 1983 and Dail et al. 1983). Echevarria (1981) was the first to suspect that IVBAT is not confined to the lungs. Soon thereafter, a series of 41 patients who had tumours in the soft tissues was published (Weiss and Enzinger 1982). They coined the term epithelioid haemangioendothelioma (EHE) and stated that similar tumours occur in the lungs and in the liver where they had been previously diagnosed as sclerosing cholangiocarcinomas (Weiss and Enzinger 1982). The next development was the publication of 32 patients with hepatic EHE by Ishak et al. in 1984. They remarked that "In our series the tumour nodules in the lung metastases in three patients were indistinguishable from those arising primarily in that organ". Recently, Dean et al. (1985) described five young women, who had all taken oral contraceptives, with hepatic EHEs, which behaved aggressively. We report here three patients, who had hepatic or pulmonary EHEs, with autopsy findings and review the pertinent literature briefly.

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Case histories

Patient 1 was a 57-year-old man, who had ascites, pathological liver function tests and general physical deterioration. Liver biopsy yielded hypocellular fibrotic and necrotic tissue; fibroma or hamartoma were suspected. Ultrasonography revealed a tumour of 10 cm in diameter below the liver. Computerized tomography showed a non-homogenous liver with a dorso-caudal expansion dislocating the right kidney and pancreas. The patient had a small infiltrate in the right lung, which had been followed for years. He died in hepatic coma.

In the autopsy the enlarged liver was found to be almost completely replaced by necrotic and fibrotic white tissue. The gallbladder was surrounded but not infiltrated by the tumour. In the spleen there was a tumour of three cm in diameter, and in the right lung a one-centimeter nodule was found.

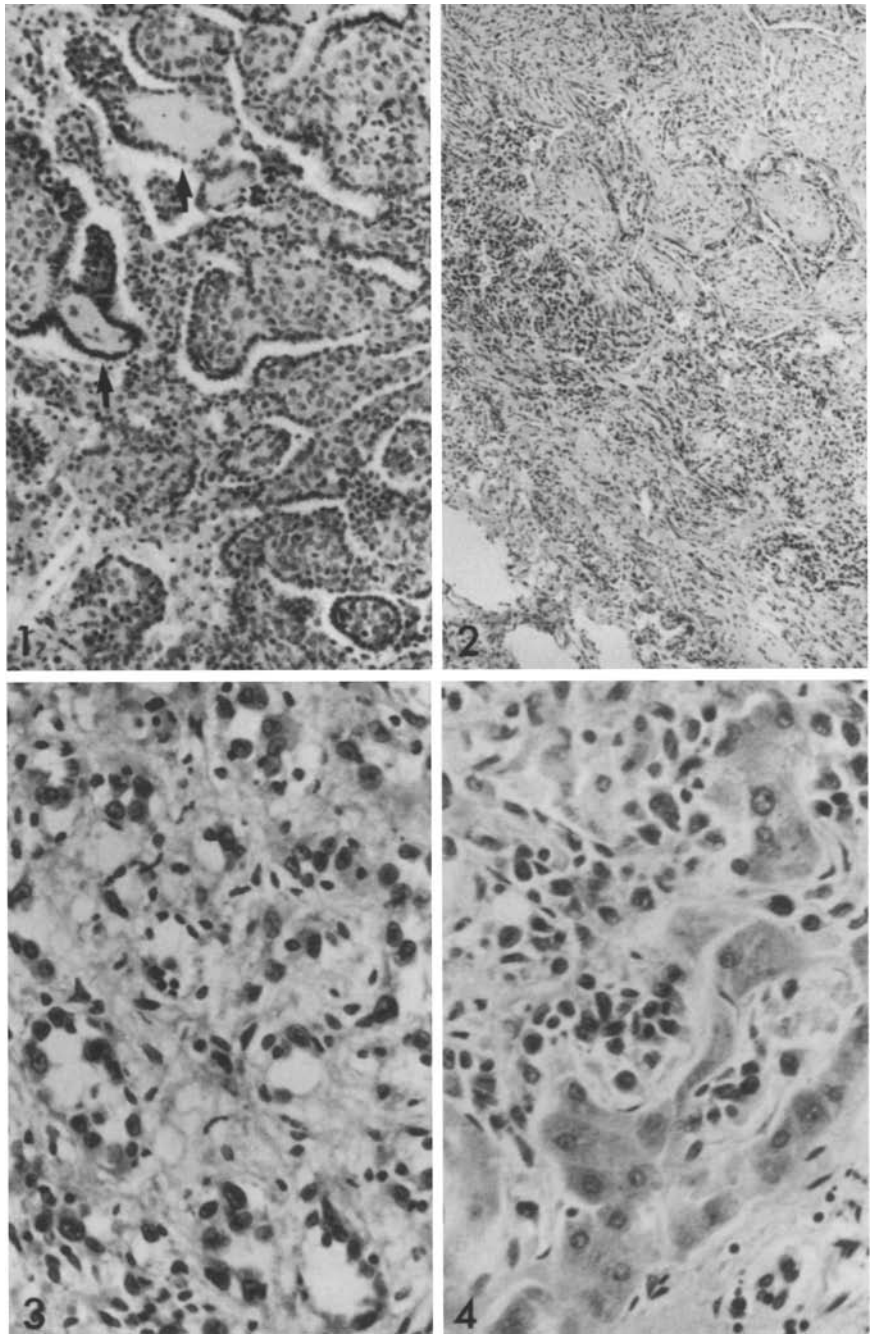

Fig. 1. Pulmonary epithelioid haemangioendothelioma in the patient 2. Air spaces are filled with polypoid, cellular nodules covered by hypertrophied pneumocytes. A couple of nodules are sclerosed (*arrows*). van Gieson, ×105

Fig. 2. Pulmonary epithelioid haemangioendothelioma in the patient 3. The margin between the lung and tumour shows progressively sclerosing intra-alveolar nodules. van Gieson, ×45

Fig. 3. Epithelioid haemangioendothelioma in the spleen of the patient 1. Mildly atypical tumour cells are lining empty-looking vascular spaces. van Gieson, ×260

Fig. 4. Groups of small, hyperchromatic tumour cells are invading and destroying hepatic parenchyma of the patient 1. van Gieson, ×260

Table 1. The immunohistological and electron microscopic findings

Patient	F VIII RAG[a]	Cytokeratin	Vimentin	S-100	EM
1	+++	−	+	−	ND[b]
2	(±)	−	+	−	++
3	+	−	+	−	ND

[a] Factor VIII related antigen
[b] Not done

Patient 2 was a 19-year-old woman. Her disease began with back pain almost two years before chest X-ray revealed a tumour in the left lung. At surgery a 2.5 cm tumour located peripherally in the left lower lobe was found. The tumour was yellowish and firm. Several hilar and mediastinal lymph nodes were involved as was the parietal pleura on the diaphragm. The surgeon removed all macroscopic tumour tissue along with the left

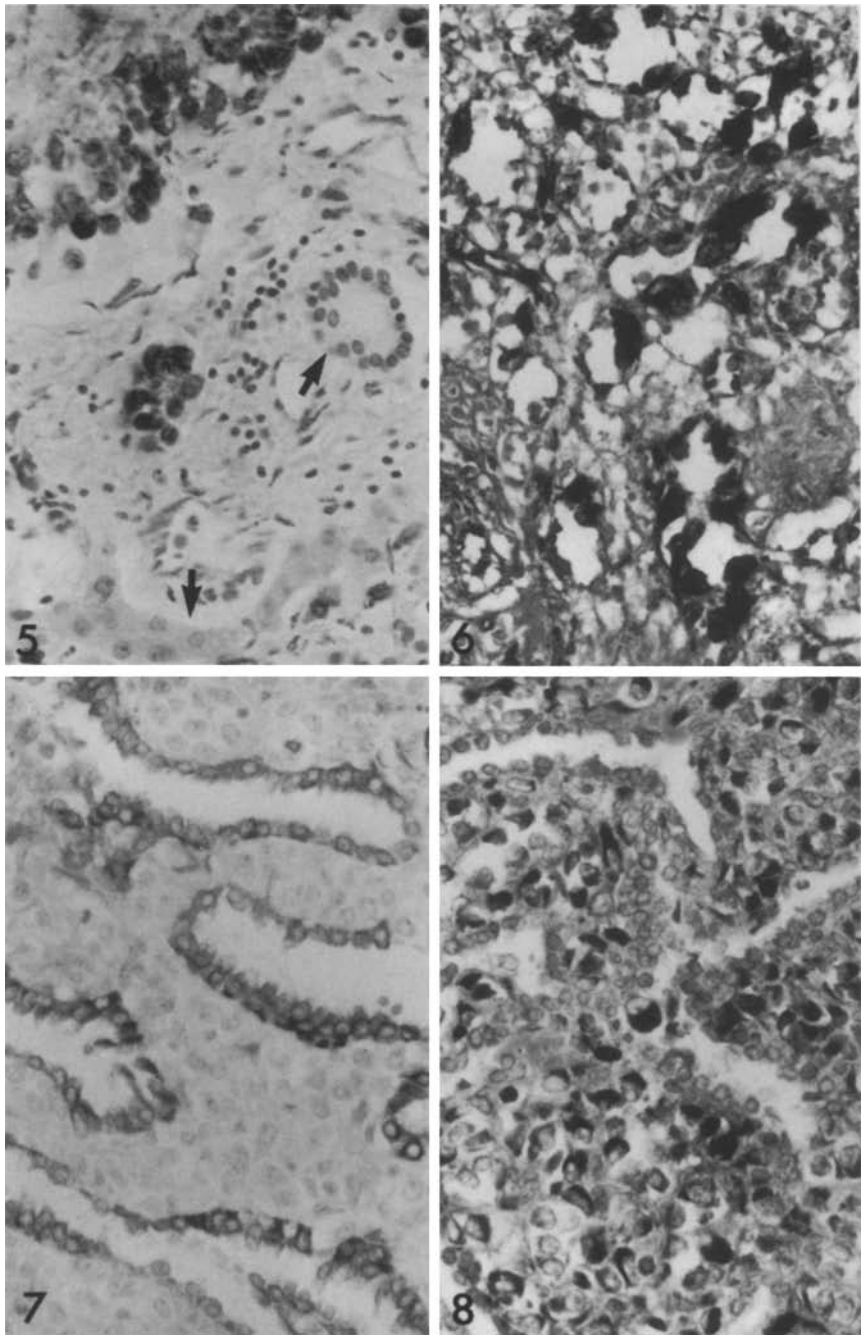

Fig. 5. Patient 1. Tumour cells in the liver are strongly immunoreactive with monoclonal antifactor VIII-related antigen, while hepatocytes (*arrow*) and cells of a bilary duct (*arrow*) are not. Counterstain with haematoxylin, ×260

Fig. 6. The cells lining neoplastic vascular spaces in the spleen of the patient 1 are decorated with the polyclonal antibody of factor VIII-related antigen. Counterstain with haematoxylin, ×260

Fig. 7. All the tumour cells are negative when immunostained with monoclonal anticytokeratin. Only reactive pneumocytes are stained (the lung of the patient 2). Counterstain with haematoxylin, ×260

Fig. 8. Most of the tumour cells are immunostained with monoclonal anti-vimentin (the lung of the patient 2). Counterstain with haematoxylin, ×260

lower lobe. The patient developed compression fractures of a cervical and lumbar vertebra soon after the surgery. In spite of irradiation and cytotoxic therapy she died less than six months later.

At autopsy widespread dissemination of the tumour in the spinal column was observed. Small solitary metastases were also found in the left kidney and lung.

Patient 3 was a 93-year-old man, who had a cough and signs of respiratory failure. Atrial fibrillation and ventricular extrasystoles were found out in the medical examination. Chest X-ray revealed several round infiltrates in both lungs, right pleural effusion and enlarged heart. Treatment with digitalis and diuretics was started. In pleural puncture the effusion fluid was bloody, but no tumour cells were identified. In the bronchoscopy an extrabronchial compression was seen in the right lower lobe bronchus, but the biopsy was free of tumour tissue. Sputum cytology was also normal. The prostate was nodular, but fine-needle biopsy contained only normal epithelial elements. His general condition

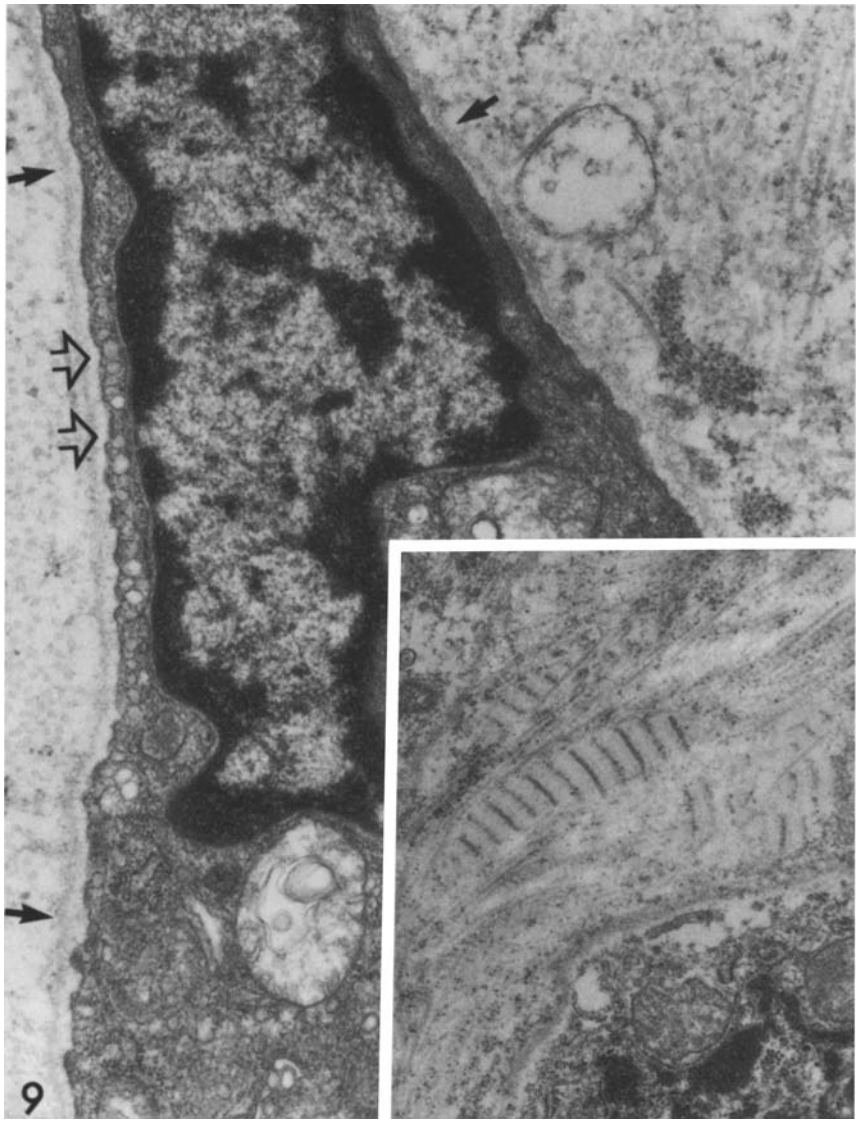

Fig. 9. Electron micrograph of a tumour cell from the patient 2. Note continuous basal lamina (*dark arrows*) and a segment of cell membrane with numerous pinocytotic vesicles (*open arrows*), ×22,000. *Inset*: intercellular matrix is rich in collagen with long-spacing bodies, ×21,500

deteriorated quickly, and a deep thrombosis was diagnosed in the left leg. The patient died on the same day, and pulmonary embolism was suspected.

The autopsy confirmed the suspicion of massive pulmonary embolism. Other relevant findings included multiple tumours of 0.5–2 cm in diameter in the lungs, pleura, mediastinal lymph nodes, pericardium and myocardium. A small tumour nodule was also found in a thrombosed vein close to the prostate.

Material and methods

Tumour tissue was fixed in phosphate-buffered neutral formalin. The paraffin sections were stained by van Gieson, haematoxylin and eosin, PAS with and without diastase treatment, Alcian blue and Gomori reticulin. Small pieces of tumour were also taken into glutaraldehyde from a mediastinal lymph node of the patient 2. It was processed, cut and stained according to the standard procedure for electron microscopy. Ultrathin sections were studied with a Jeol Jem 100 C electron microscope.

Immunohistological staining was carried out either by using peroxidase-antiperoxidase method for polyclonal antibodies or biotinavidin system (Vectastain®, Vector Laboratories, Burlingame, Ca, USA) for monoclonal antibodies. The sources of antibodies were as follows: monoclonal anti-cytokeratin (PKK1) and monoclonal anti-vimentin were from Labsystems Co., Helsinki, Finland, polyclonal anti-factor VIII-related antigen was from Immunolok, Inc., Carpinteria, Ca, USA, monoclonal anti-factor VIII-related antigen was from BioGenex Laboratories, Dublin, Ca, USA, and anti-S-100 protein was from Dako Laboratories, Santa Barbara, Ca, USA. Negative controls were accomplished by replacing the primary antiserum with normal serum or albumin at corresponding dilutions.

Results

Light microscopy.

The histological appearance of the tumour tissue was somewhat variable depending on the tissue where it was found. In the lungs it was very characteristic: the tumour was formed by polypoid nodules filling the alveoli. The nodules were covered by hypertrophied pneumocytes (Fig. 1). The proportions of cellular and sclerosed areas varied from tumour to tumour (Fig. 2). The tumour cells were usually small and uniform, but occasional mitoses were found. More atypia was seen in some tumours of the patient 3, who had also a few overtly sarcomatoid nodules. Vascular spaces were infiltrated strikingly often.

The vasoformative capacity was evident only in the spleen of the patient 1 (Fig. 3). The liver of the same patient was largely infiltrated by the tumour. Most of tissue was necrotic and fibrotic, almost acellular, but in some areas remaining hepatic cords were infiltrated by tumour cells (Fig. 4).

Immunohistology

Table 1 summarizes the immunohistological and ultrastructural findings. Both monoclonal and polyclonal antibody to factor VIII-related antigen was used. In the first patient most tumour tissue was strongly stained by both antibodies (Figs. 5 and 6), although some cell groups, often lying intravascularly, were completely negative. In the second patient a few tumour cells were stained by the polyclonal antibody, but practically no positive cells were seen by monoclonal antibody to factor VIII-related antigen. The tumours of the third patient were variably positive with the polyclonal antibody, but only a few cells showed immunoreactivity, when the monoclonal antibody was used.

The tumour cells were invariably cytokeratin negative (Fig. 7), but reacted well with anti-vimentin (Fig. 8). Stainings with anti-S-100 protein were negative as were the controls.

Electron microscopy

Tumour cells were usually covered by a continuous basal lamina. Some segments of cell membrane contained numerous pinocytotic vesicles (Fig. 9). No cell junctions, pseudolumina or intracellular vacuolization could be seen. The cytoplasm contained occasionally abundant intermediate filament collections, but no actin-type filaments with fusiform densities were found. Weibel-Palade bodies were seen only in the endothelial cells of normal capillaries. The intercellular matrix contained plenty of collagen, which was occasionlly arranged as long-spacing collagen bodies (Fig. 9, inset).

Discussion

On the basis of histological, immunohistochemical and ultrastructural findings we believe that the tumours represent epithelioid haemangioendotheliomas. The tumour cells of the patient 2 were negative when monoclonal antibody to factor VIII-related antigen was used. According to the literature the proportion of tumour cells which are immunoreactive with the antibody of factor VIII-related antigen is highly variable, and differences depending on the antibody batch used have been noted (Dail et al. 1983). The negative stainings with anti-cytokeratin and positive stainings with anti-vimentin are consistent with the endothelial differentiation.

The electron microscopic structure of tumour cells was also indicative of endothelial differentiation. Numerous intermediate filaments, pinocytotic vesicles, continuous basal lamina and long-spacing collagen are all features frequently encountered in these tumours (Corrin et al. 1979; Azumi and Churg 1981; Weldon-Linne et al. 1981; Bhagavan et al. 1982; Dail et al. 1983; Corrin et al. 1983 and Meister et al. 1985). Additional characteristic findings in EHE have been intercellular junctions, intracellular lumina and, occasionally, Weibel-Palade bodies, which could not be found in the present tumour. Basal lamina and long-spacing collagen are features seen in tumours of Schwann cell origin. Schwannomas show, however, usually extensive entanglement of cytoplasmic processes. Furthermore cells of differentiated Schwann cell tumours contain S-100 protein which was absent from the present tumours.

Another differential diagnostic problem is so-called sclerosing haemangioma of the lung (Liebow and Hubbel 1956). It has been shown to be factor VIII-related antigen-negative (Dail et al. 1983) and vimentin-negative (Haimoto et al. 1985). The latter group came to the conclusion that sclerosing haemangioma most probably represents neoplasia derived from type I pneumocytes. Sclerosing haemangioma contains usually much extravasated blood, and it is generally considered as a benign neoplasm. Pulmonary angiosarcoma does not seem to be a differential diagnostic difficulty (Yousem 1986). The vasoformative capability of EHE is almost non-existent. Only in the spleen lesion of the patient 1 neoplastic vascular spaces could be discerned.

Table 2. Summary of the reports about epithelioid haemangioendotheliomas

Report	Number of cases	Average age (years)	Male to female ratio	Location	Follow-up
Arnold et al. 1986	1	55	1:0	lymph node	3.5 years, NED[a]
Azumi and Churg 1981	1	48	1:0	lung	DOD[b], metastases
Bhagavan et al. 1982	3	43	1:2	lung	1–9 years, little progression
Corrin et al. 1979	3	29	0:3	lung	Not available
Corrin et al. 1983	2	51	1:1	lung	Metastases in 1 patient
Dail et al. 1983	20	35	4:16	lung	Metastases in 8 of 17 patients
Dean et al. 1985	5	33	0:5	liver	Metastases in 4 patients
Echevarria 1981	1	62	0:1	liver	Metastases
Echevarria et al. 1978	2	53	1:1	liver	DOD, metastases
Ferrer-Roca 1980	1	49	0:1	lung	7 years, no progression
Ishak et al. 1984	32	50	12:20	liver	Metastases in 9 patients
Ludwig et al. 1975	2	46	1:1	liver	DOD, metastases
Meister et al. 1985	1	78	1:0	scalp	10 months, a local recurrence
Mirra and Kameda 1985	1	12	0:1	bone	11 years, metastases
Morgan et al. 1972	1	21	0:1	liver	1.5 years, DOD, metastases
Reed 1982	1	45	0:1	bone	12 years, metastases
Sherman et al. 1981	1	28	0:1	lung	2 years, asymptomatic
Weiss and Enzinger 1982	41	appr.45	23:17	soft tissue	Metastases in 6 of 31 patients
Weldon-Linne et al. 1981	1	55	0:1	lung	No progression
Wenisch and Lulay 1980	1	56	0:1	lung	Metastases
Present study	3	56	2:1	lung 2, liver 1	DOD, metastases in all patients

[a] No evidence of disease
[b] Dead of disease

Table 2 gives a summary of the reports concerning EHEs. The investigations of haemangioendothelioma of bone by Hartmann and Stewart 1962 and Volpe et al. 1985 as well as the studies of histiocytoid haemangiomas by Rosai et al. 1979 and atypical haemangioendotheliomas by Angervall et al. 1985 are not included, although some of the patients might qualify. In the literature there are now at least 124 cases of EHEs that are reasonably well documented. These include the patients reported by Ludwig et al. (1975) and one of the patients reported by Morgan et al. 1972. The case of Farinacci et al. (1973) was included in the series of Dail et al. (1983), and that of Monroe et al. (1981) in the series of Ishak et al. (1984). Spencer (1985) states that he has seen several cases of IVBAT, but he does not give any details. The bone tumours designated as malignant myxoid angioblastoma by Reed (1982) and myxoid angioblastomatosis by Mirra and Kameda (1985) are also included, but that designated as angioglomoid tumor by Tang et al. (1976) is not convincing enough to meet the criteria of EHE. The diagnostic difficulties of EHE are well documented by the Table 2 in the article of Dail et al. (1983). It lists 13 different original diagnoses submitted for their 20 cases.

The sex distribution is 61% females and 39% males, and among pulmonary tumours women outnumber men even more. The average age is about 45 years with a range from 12 to 93 years. The distribution of the published cases between the lungs, liver and soft tissue is approximately equal. Echevarria (1981) was the first to suspect the systemic nature of this tumour, but Weiss and Enzinger (1982) deserve the honour of realizing first the fact that all these tumours represent the different facets of the same disease.

Follow-up information is available from 105 patients. Metastases have been described in 41 patients, which means 39% of those with sufficient follow-up information. In addition to that a few patients died of respiratory failure caused by multiple, widespread bilateral pulmonary nodules. Thus, it is evident that EHE is a malignant neoplasm, though it grows usually slowly and may occasionally remain stationary for years. Some investigators, e.g. Mirra and Kameda (1985) have questioned the cancerous nature of the disease and suggested that it is a multicentric hamartomatous or developmental process. We do not accept this interpretation, though the multicentric origin of pulmonary nodules is hard to disprove. The atypicality and uncontrolled proliferation of tumour cells as well as the lymphogenous spread are features consistent with a malignancy.

The characteristic slow progression of the tumour makes the therapy a big problem. No therapy is suggested for those IVBAT patients who are

symptomless (Dail et al. 1983). When EHE is in the soft tissue, the removal of all tumour tissue is indicated (Weiss and Enzinger 1982).

The aetiology of the disease is unknown. An interesting suggestion was made by Dean et al. (1985) who described five female patients with hepatic EHEs. All had used oral contraceptives. In the series of Ishak et al. (1984) there were two patients with known history of oral contraceptives. The patient of Sherman et al. (1981) was also currently using these preparations. Unfortunately in earlier reports little attention has been paid to this fact, but because a sizable proportion of IVBAT patients are young women, it would be worthwhile clarifying the use of oral contraceptives. This can not, however, be the sole reason, since all the patients had not used these drugs.

The tumour has been labelled with many names, which reflects the diagnostic difficulties. The adjectives used include sclerosing, epithelioid and myxoid. Taking the angioblastic nature into consideration, the term angioblastoma seems to be most recommendable. We feel, however, that because epithelioid haemangioendothelioma is now in general use, there is no reason to increase the confusion by suggesting new designations for the time being.

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Addendum

Since the submission of the manuscript we have encountered one more patient with EHE. She was a 25-year-old nurse, who had used oral contraceptives in her teens. She had haemoptysis during pregnancy followed by back pain. X-ray studies showed lytic lesions in the skeleton. Biopsy from the iliac bone revealed minute foci of tumour formed by oval, sometimes vacuolated cells in myxoid and fibrous stroma. The cells were cytokeratin-negative, vimentin-positive, and a remarkable number contained factor VIII-related antigen. Two relevant articles on the topic have appeared: Ellis GL, Kratochvil FJ III (1986) Epithelioid hemangioendothelioma of the head and neck: A clinicopathologic and follow-up study of twelve cases. Oral Surg 61:61–68 and Dorfman HD, Tsuneyoshi M, Bauer TW (1986) Epithelioid hemangioendothelioma of bone. Lab Invest 54:17A.

References

Angervall L, Kindblom L-G, Karlsson K, Stener B (1985) Atypical haemangioendothelioma of venous origin. Am J Surg Pathol 9:504–516

Arnold G, Klein PJ, Fischer R (1986) Epithelioid haemangioendothelioma. Virchows Arch [Pathol Anat] 408:435–443

Azumi N, Churg A (1981) Intravascular and sclerosing bronchioloalveolar tumor. Am J Surg Pathol 5:587–596

Bhagavan BS, Dorfman HD, Murthy MSN, Eggleston JC (1982) Intravascular bronchioloalveolar tumor (IVBAT). Am J Surg Pathol 6:41–52

Corrin B, Harrison WJ, Wright DH (1983) The so-called intravascular bronchioloalveolar tumour of lung (Low grade sclerosing angiosarcoma): Presentation with extrapulmonary deposits. Diagn Histopathol 6:229–237

Corrin B, Manners B, Millard M, Weaver L (1979) Histogenesis of so-called intravascular bronchioloalveolar tumour. J Pathol 128:163–167

Dail DH, Liebow AA (1975) Intravascular bronchioloalveolar tumor. Am J Pathol 78:6a–7a

Dail DH, Liebow AA, Gmelich JT, Friedman MD, Miyai K, Myer W, Petterson SD, Hammar SP (1983) Intravascular, bronchiolar, and alveolar tumor of the lung (IVBAT). Cancer 51:452–464

Dean PJ, Haggitt RC, O'Hara CJ (1985) Malignant epithelioid hemangioendothelioma of the liver in young women. Am J Surg Pathol 9:695–704

Echevarria RA (1981) Angiogenic nature of "intravascular bronchioloalveolar tumor". Arch Pathol Lab Med 105:627–628

Echevarria RA, Arean VM, Galindo L (1978) Hepatic tumors of long duration with eventual metastases. Am J Clin Pathol 69:624–631

Farinacci CJ, Blauw AS, Jennings EM (1973) Multifocal pulmonary lesions of possible decidual origin (so-called pulmonary deciduosis): Report of a case. Am J Clin Pathol 59:508–514

Ferrer-Roca O (1980) Intravascular and sclerosing bronchioalveolar tumor. Am J Surg Pathol 4:375–381

Haimoto H, Tsutsumi Y, Nagura H, Nakashima N, Watanabe K (1985) Immunohistochemical study of so-called sclerosing hemangioma of the lung. Virchows Arch [Pathol Anat] 407:419–430

Hartmann WH, Stewart FW (1962) Haemangioendothelioma of bone. Cancer 15:846–854

Ishak KG, Sesterhenn IA, Goodman MZD, Rabin L, Stromeyer FW (1984) Epithelioid haemangioendothelioma of the liver: A clinicopathologic and follow-up study of 32 cases. Hum Pathol 15:839–852

Liebow AA, Hubbell DS (1956) Sclerosing hemangioma (histiocytoma, xanthoma) of the lung. Cancer 9:53–75

Ludwig J, Grier MW, Hoffman II HN, McGill DB (1975) Calcified mixed malignant tumor of the liver. Arch Pathol 99:162–166

Meister P, Hoede N, Rumpelt H-J (1985) Epitheloid hemangioendothelioma of the scalp. Pathol Res Pract 180:220–226

Mirra JM, Kameda N (1985) Myxoid angioblastomatosis of bones. Am J Surg Pathol 9:450–458

Monroe PS, Riddel RH, Siegler M, Baker AL (1981) Hepatic angiosarcoma: possible relationship to long-term oral contraceptive ingestion. JAMA 246:64–65

Morgan AG, Walker WC, Mason MK, Herlinger H, Losowsky MS (1972) A new syndrome associated with hepatocellular carcinoma. Gastroenterol 63:340–345

Reed RJ (1982) Consultation case. Am J Surg Pathol 6:159–163

Rosai J, Gold J, Landy R (1979) The histiocytoid hemangiomas. Hum Pathol 10:707–730

Sherman JL, Rykwalder PJ, Tashkin DP (1981) Intravascular bronchioloalveolar tumor. Am Rev Resp Dis 123:468–470

Spencer H (1985) Pathology of the lung. Fourth edition. Pergamon Press, London

Tang TT, Zuege RC, Bappitt DP, Blount WP, McCreadie SR (1976) Angioglomoid tumor of bone. A case report. J Bone Joint Surg (Am) 58:873–876

Volpe R, Carbone A, Manconi R (1985) Haemangioendothelioma of bone. A report of an unusual case with lymph node metastasis. Pathol Res Pract 180:521–525

Weiss SW, Enzinger FM (1982) Epithelioid haemangioendothelioma. A vascular tumor often mistaken for a carcinoma. Cancer 50:970–981

Weldon-Linne CM, Victor TA, Christ ML, Fry WA (1981a) Angiogenic nature of the intravascular bronchioloalveolar tumor of the lung. Arch Pathol Lab Med 105:174–179

Weldon-Linne CM, Victor TA, Christ ML (1981b) Immunohistochemical identification of factor VIII-related antigen in the intravascular bronchioloalveolar tumor of the lung. Arch Pathol Lab Med 105:628–629

Wenisch HCJ, Lulay M (1980) Lymphogenous spread of an intravascular bronchioloalveolar tumour. Virchows Arch [Pathol Anat] 387:117–123

Yousem SA (1986) Angiosarcoma presenting in the lung. Arch Pathol Lab Med 110:112–115

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