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Endothelial Neoplasms of the Lungs

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In the period of 20 years, the author had an opportunity to observe 14 cases of endothelial neoplasms of the lungs. The group consisted of eight women and six men, differing in age from 18 to 75 years. These cases presented as two subsets: low grade malignancy epithelioid hemangioendothelioma (PEH) (12 cases - eight women and four men, aged between 18 and 75 years) and highly malignant endotheliosarcoma seen in two men, 28 and 47 years old.

The patients with epithelioid hemangioendothelioma reported to hospitals mainly because routine chest X-ray examinations accidentally revealed nodular lesions involving both lungs. Histological examination of the material collected from the bronchi and sputum was negative for neoplasm. The patients were suspected of suffering from tuberculosis or sarcoidosis and in some cases therapy was even initiated. Correct diagnoses were established based on histological examinations of material from the lesions taken during thoracotomy or thoracoscopy. In these cases, the course of the disease was slow and the patients were in a good condition for many years. In one case (a 27-year old woman), the diagnosis was possible after autopsy.

The morphological appearance of these tumors is very characteristic. In case of any doubts, we can perform immunohistochemical examinations using endothelial markers, mainly CD34, possibly CD31 or factor VIII.

Highly malignant endothelial sarcomas were seen in two men with a poor clinical status; one of them died shortly after histological diagnosis had been established based on material taken during a thoracotomy. In the second case, the diagnosis was possible on autopsy

The prognosis for patients with these highly malignant tumors is highly unfavorable.

Introduction

Mesenchymal neoplasms of the lungs are very rare as compared to lung carcinomas, while neoplasms arising from the pulmonary vascular endothelium, both primary and metastatic, are highly infrequent [3, 39, 63]. Such neoplasms encompass two types: epithelioid hemangioendotheliomas with a low malignant potential and highly malignant hemangiosarcomas. At the time of diagnosis, epithelioid hemangioendotheliomas most often present as a multifocal diffuse lesion involving the lungs. The neoplasm was first described by Liebow and Dail in 1975; the authors termed it IVBAT (intravascular bronchioloalveolar tumor) [19]. At that time, the investigators supposed that the tumor, which behaved similarly as bronchioloalveolar carcinoma, most likely originated in the epithelium [18, 19]. Their view found no confirmation in further immunohistochemical and ultrastructural investigations. In 1979 Corrin focused attention on the vascular endothelial origin of the neoplasm [14]. In ultrastructural examinations, tumor cells demonstrate the presence of the Weibel-Pallade bodies, which are characteristic of endothelium, while immunohistochemistry shows positivity to factor VIII and CD34 and CD31 antigens, or at least one of the above reactions is positive [27, 60, 61].

The literature on the subject has referred to the neoplasm using various terms: intravascular bronchioloalveolar tumor (IVBAT)[17, 18, 20, 21, 41], sclerosing angiogenic tumor, sclerosing interstitial vascular sarcoma [3], sclerosing epithelial angiosarcoma [6] and low-grade sclerosing angiosarcoma [14]. The term “pulmonary epithelioid hemangioendothelioma” was introduced by Weiss and Enzinger in 1982 [57] and this name has been

finally widely accepted. In the Polish literature, the first description of the neoplasm was provided in a case report presented by Papla et al. in 1986 [41]; there is also other, isolated description published at 2004 year [12].

In view of the observed multifocal character of the pulmonary lesion seen upon diagnosis, it is often difficult to establish its primary origin. In many cases, the tumor may arise from various organs, such as the liver, peripheral soft tissues or bones [56]. Alternatively, the patient may have a primary multifocal neoplasm of the lungs. In some cases, the pulmonary tumor lesion presents as a single tumor (10% cases according to Weiss, 19% as reported by Kitaichi et al.) [29].

Highly malignant endothelial sarcomas of the lungs are as a rule metastatic, multifocal tumors originating from variously situated primary peripheral vascular endothelia.

Materials and Methods

Within the period spanning twenty years, the author have observed 14 cases of endothelial neoplasms of the lungs. Some of these patients were presented at the Pathomorphology Congress in Wrocław [42]. The group included eight females and six males aged between 18 and 75 years.

These cases include two types of tumors: pulmonary epithelioid hemangioendothelioma with a low malignancy - 12 patients (eight females and four males aged 18 to 75 years, with the mean age of 45.7 years) (Table 1) and two cases of metastatic highly malignant endothelial sarcomas (two males aged 28 and 47 years) (Table 2).

In the group of pulmonary epithelioid hemangioendotheliomas (PEH), in eight cases clinical symptoms were barely perceptible or the patients were asymptomatic; they usually reported for further diagnostic management following detection of nodular pulmonary lesions on chest X-ray, either on routine check-up or while undergoing medical assessment before commencing work. In two cases, the first symptom was pulmonary hemorrhage, which necessitated a surgical procedure (Case 9 and 10). Radiologically, the lesions were manifested as disseminated, moderately large nodules involving both lungs. In two cases (5 and 10), 75 and 57 years old men, single tumors were observed.

Cytology and histology of bronchial sections did not demonstrate the presence of neoplastic cells. Some patients were suspected of suffering from tuberculosis or sarcoidosis and often subjected to preliminary, unsuccessful treatment. Only when a lung material was taken during thoracotomy or thoracoscopy, could a firm diagnosis be established.

The further course of the disease was generally slow, spanning many – often more than 10 - years, with a slow nodule growth and a good general state of the patient. Only one case, which escaped intravital diagnosis, was represented by a 27-year old female in a very poor condition, who died soon after admission and the diagnosis was established based on postmortem materials (Case 2).

The two highly malignant endothelial sarcomas were characterized by a very poor condition of the patients, who died of the disease within a short time. Also in these cases the diagnosis required histological examination lung specimens in the course of thoracotomy or autopsy. Radiologically, the patients demonstrated nodular or diffuse lesions of the lungs.

Histopathologic examinations were performed in lung specimens collected in the course of thoracotomy or thoracoscopy and fixed in formalin, or else collected on autopsy (Case 2 presented in Table 1 and Case 1 listed in Table 2), which were embedded in paraffin and slides were stained routine HE and were additionally used in immunohistochemical examination employing sera manufactured by DAKO to detect the presence of such antigens as EMA, cytokeratin, factor VIII, CD34, CD31, CD68, and to perform control tests.

Results

The morphological picture of both tumors was different and characteristic for each neoplasm.

In pulmonary epithelioid hemangioendothelioma (PEH), the lungs usually manifested grey-whitish nodules, 1-2 cm in diameter, with a sharp border (Fig. 1) or a single, larger tumor. The central portion of the tumor usually showed a few cells, was myxoid, often demonstrated foci of necrosis and hyalinization, and sometimes was calcified or ossified, while the peripheral part of the lesion was rich in cells (Fig. 2). In the center of the tumor, the primary structure of the lung might be seen; the walls of alveoli and bronchioli was not destroyed, what might be particularly well demonstrated using the Gomori silver stain. The pulmonary stroma was not congested and did not contain inflammatory infiltrate. Scarce lymphocyte infiltrations were seen at some sites at the periphery of the tumors (Fig. 3). Although it arises from the endothelium, the entire tumor is devoid of vessels in its peripheral portion, and is nourished by osmosis from the surrounding tissues. Degenerative changes were seen in the central part of the lesions, but the single tumor demonstrated sinusoid blood vessels with thin walls, which resembled cavernous hemangioma (Case 12) (Fig. 4).

TABLE 1

Hemangioendothelioma epithelioides of the lung

	Nr. Initials	Sex	Age	Localization	Year of diagnosis	Follow –up
1	927128-9 A.R.	F	18	Disseminated small tumors of the lungs.	1985	Alive more than 10 years after diagnosis
2	116758 S.A.	F	27	Disseminated tumors of the lungs. Bilateral pleural and diaphragmatic infiltrations.	1988	Autopsy case
3	2460	F	19	Disseminated small tumors of the lungs.	1990	Alive 10 years after diagnosis
4	105302 D.E.	F	19	Disseminated small tumors of the lungs.	2000	Chemotherapy Alive 3 years after diagnosis
5	1457626 3409/01 Ch.J.	M	75	Single tumor, left upper lobe (4 x 4 x 2.5 cm).	2001	Obliterative arteritis in legs. Alive 3 years after diagnosis. 2004 - carcinoma tonsillae
6	1456071 K.B.	F	50	Disseminated small tumors involving both lungs. Mesenchymoma femoris sin resected 1996 .	2001	Alive 3 years after diagnosis
7	1515641 P.S.	F	44	Disseminated small tumors of the lungs.	2003	Alive 1 year after diagnosis
8	122735 B.B.	F	65	Disseminated small tumors of the lungs.	2003	Alive 1 year after diagnosis
9	123962 P.Z.	M	41	Massive pulmonary hemorrhage. Disseminated tumors	2003	Alive 1 year after diagnosis
10	1535886 133271 K.E.	M	57	Single tumor of the left upper lobe.	2004	Alive
11	1554959	M	67	Disseminated small and larger tumors of the lungs. Plasmocytoma.	2005	Alive
12	4126/071 622710	F	67	Disseminated round tumors of the right lung.	2007	Alive

TABLE 2

Angiosarcoma

	Nr Initials	Sex	Age	Localization	Year of diagnosis	Follow- up
1	1275787 K.E.	M	47	Tumor of the liver. Disseminated tumor of the lungs.	1994	Autopsy case
2	1402606 F.J.	M	28	Scrotal tumor. Disseminated tumors and hemorrhages from the lungs.	1999	Died shortly after surgery

The tumor cells varied in shape, usually being epithelioid and of moderate size, or spindle-shaped. The nuclei of tumor cells were oval, slightly irregular or convoluted. Some nuclei demonstrated pink, eosinophilic inclusions. The nucleoli were blurred or absent. The cytoplasm was diversified, from hyalinized, granular and fibrous to mucoid. The margins of polygonal cells were varied: from distinct to blurred. In more myxoid regions, the cell borders were more distinct and their margins were more irregular. The cytoplasm of fairly numerous cells demonstrated structures that resembled vacuoles, which are a highly characteristic property of vessel formation, a significant diagnostic indicator of the tumor (Fig. 5). The cells situated on the periphery showed signs of proliferation, spreading from one pulmonary alveolus to another via the respiratory connections or through the Kohn's pores (Fig. 6), initially forming

crowd-like structures and then growing towards the center of the alveolus; when the alveolus was completely filled, the cells stopped growing. They were not pneumocyte-coated, what differentiated them from the so-called haemangioma sclerosans (pneumocytoma benignum).

Mitotic figures were seen in the peripheral portions of the tumor and their number might be varied. Usually the number of proliferating cells was low, what was confirmed by a poor Ki67 reaction, and they were situated chiefly on the periphery of the tumor adjacent to the intact lung tissue (Fig. 7). In Case 10, a portion of the tumor resembled a typical picture, while a large peripheral fragment was abundant in cells and contained mainly spindle-shaped cells with numerous mitotic figures (a very strong Ki67 reaction – Fig. 8). The peripheral cells were also characterized by higher atypia (Fig. 9).

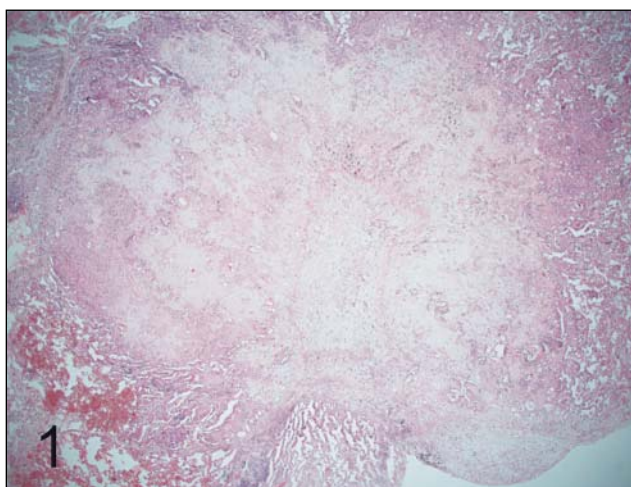


Fig. 1. One of numerous disseminated tumors in the vicinity of the pleura, showing a distinct outline and degenerative lesions in the central portion.

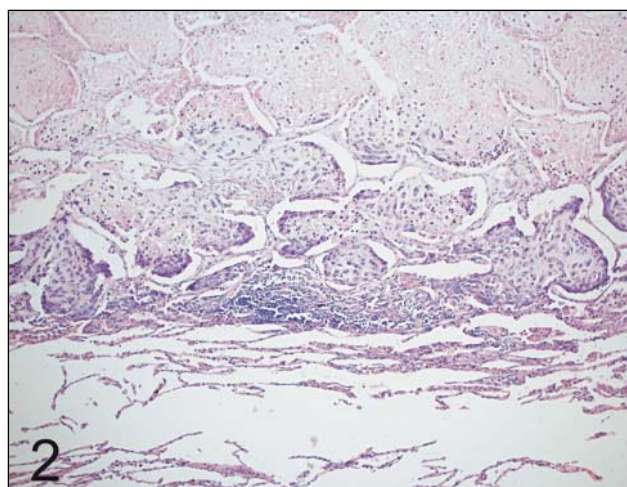


Fig. 2. The fairly rich in cells peripheral part of pulmonary epithelioid hemangioendothelioma (PEH).

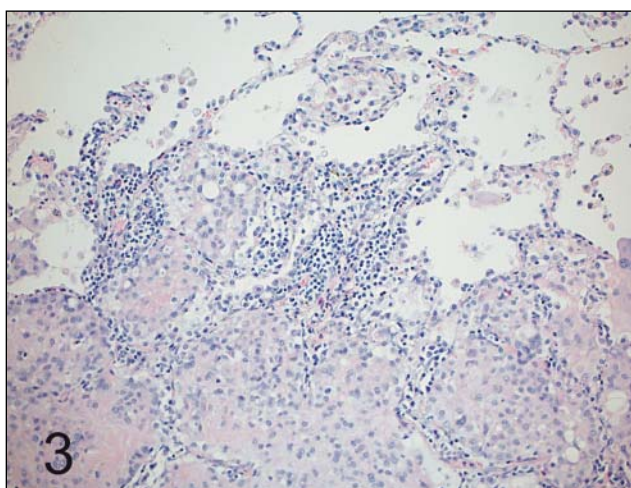


Fig. 3. Lymphocyte infiltrations at the periphery of PEH.

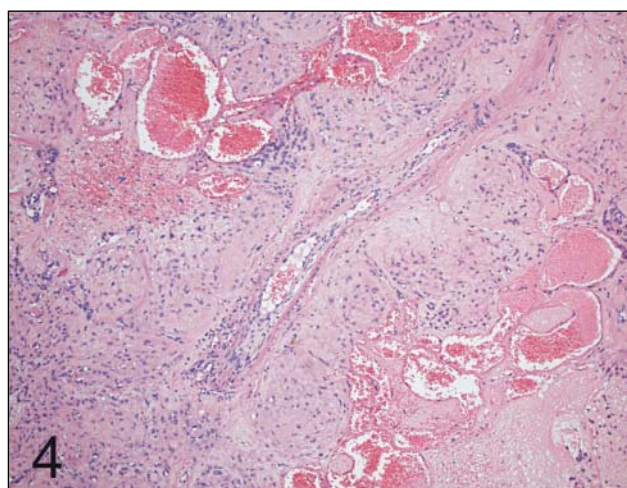


Fig. 4. Central part of the tumor (Case 12) with numerous sinusoid blood-containing vascular structures (Case 12).

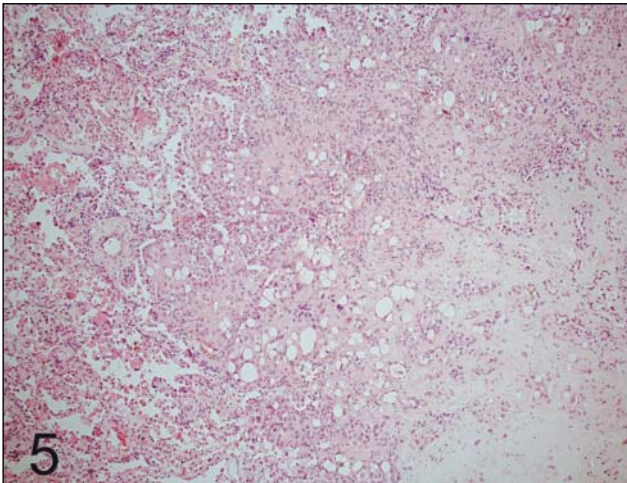


Fig. 5. Numerous cytoplasmic vacuoles in PEH cells representing an attempt at forming capillary vessels by the cells of neoplastic endothelium.

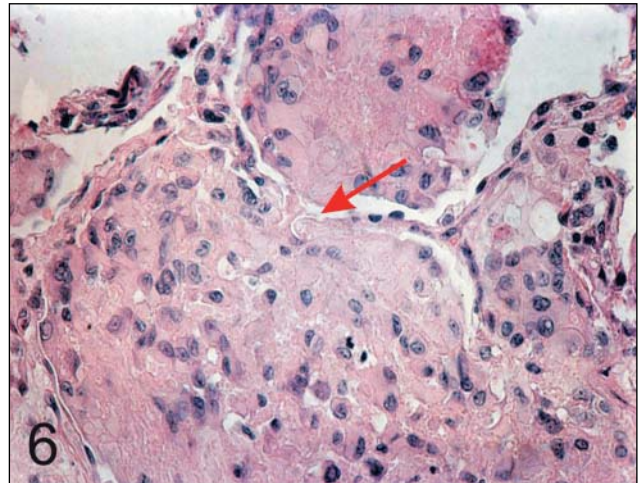


Fig. 6. Spread of the tumor through the Kohn's pores among the pulmonary alveoli (marked by an arrow), with an intact structure of the lung.

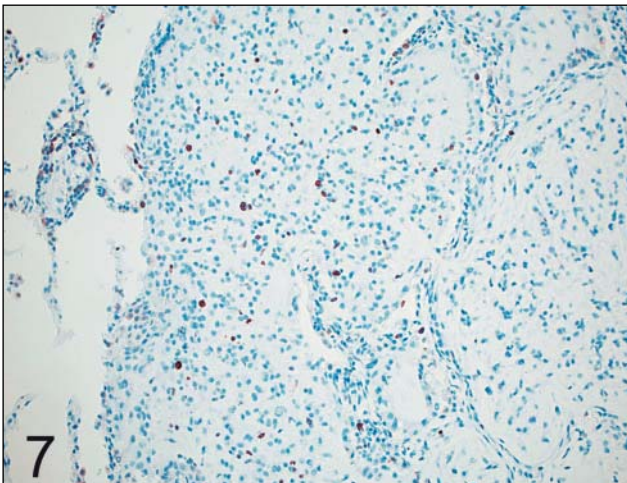


Fig. 7. A scarce number of cells on the periphery of the tumor demonstrate positive Ki67 reaction, what confirms the low proliferation activity of the lesion.

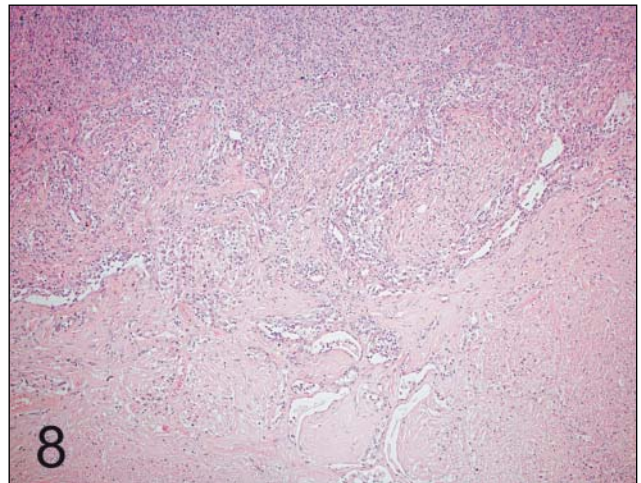


Fig. 8. Case 10, PEH, a portion of the tumor was typical, while the remaining fragment was abundant in cells and contained mainly spindle-shaped cells with features of atypia and numerous mitotic figures.

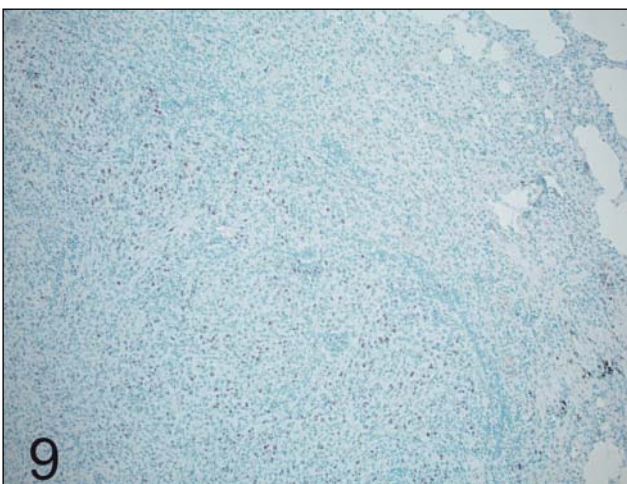


Fig. 9. The same case as that illustrated in Fig. 8 – numerous tumor cells show positive nuclear Ki67 reaction.

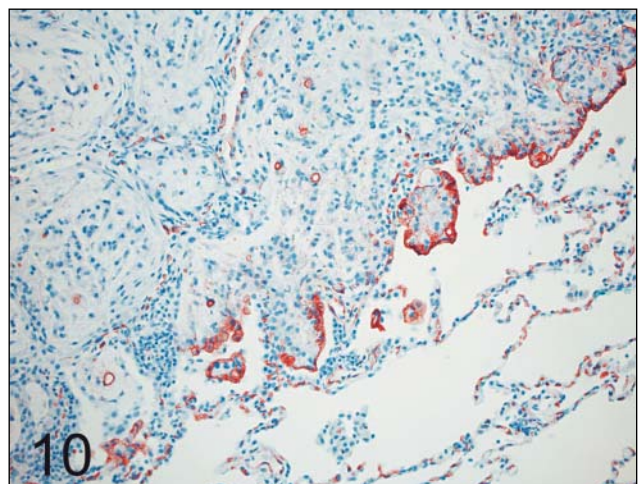


Fig. 10. A distinctly positive CD34 reaction in the peripheral cells of PEH.

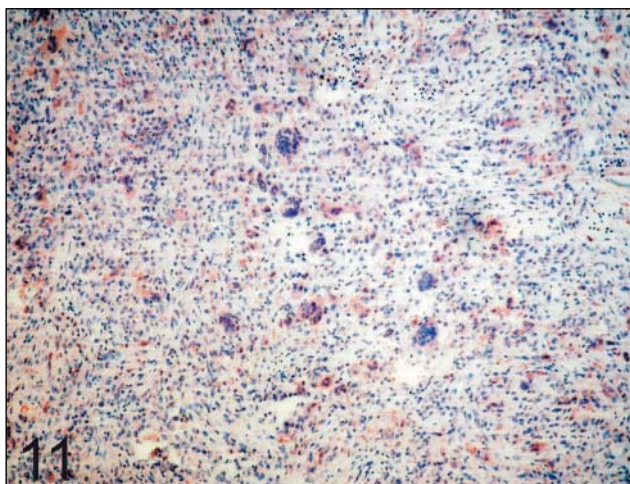


Fig. 11. Giant multinucleate cells in the central portion of PEH.

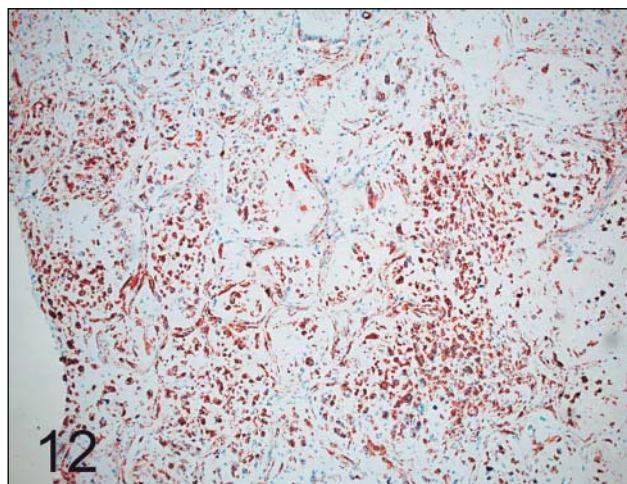


Fig. 12. Abundant, highly positive CD34 reaction in numerous PEH cells.

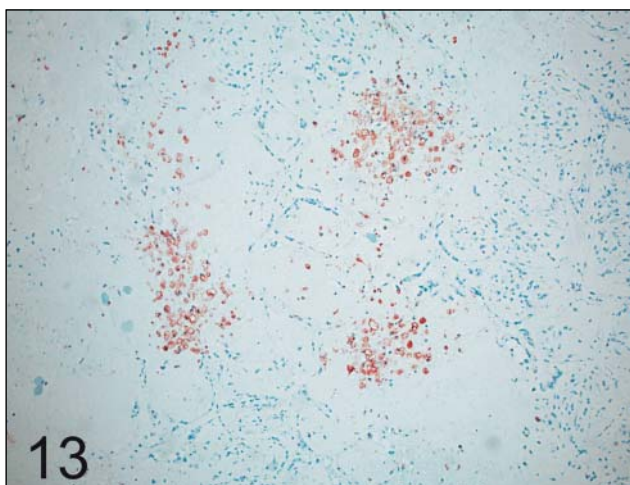


Fig. 13. Clusters of CD68+ histiocytes seen in the central fragment of the tumor.

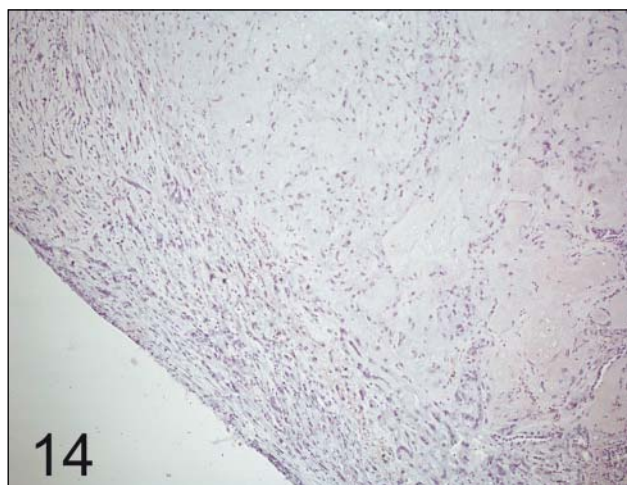


Fig. 14. PEH infiltrating the pleura – the cells within the infiltrate are spindle-shaped.

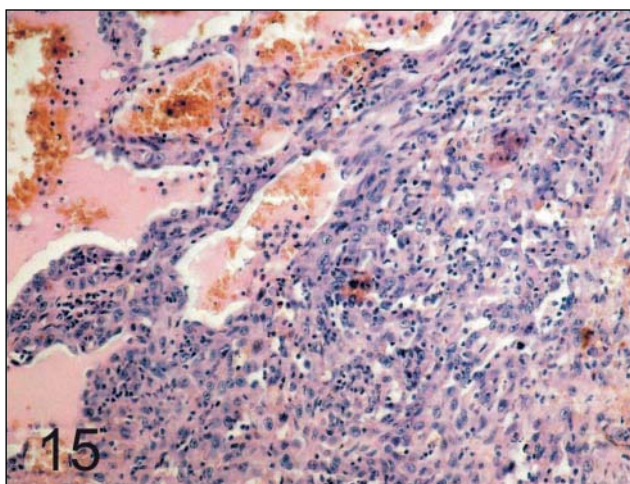


Fig. 15. Metastatic angiosarcoma does not form nodular structures, but rather extensive intraparenchymal infiltrations.

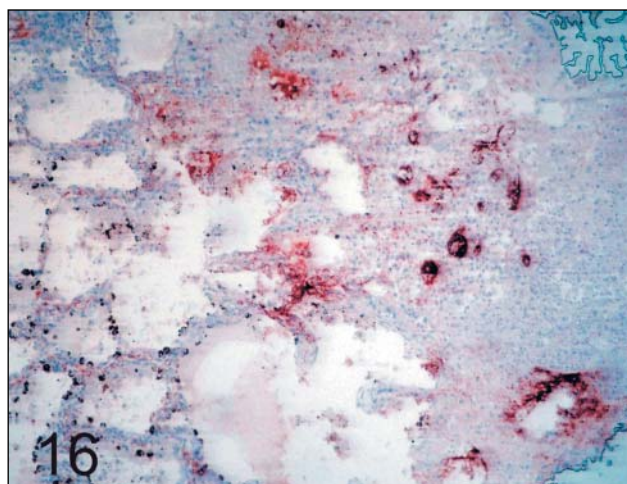


Fig. 16. A positive reaction to CD34 in the cells of the angiosarcoma (Case 2).

Any doubts as to the type of the proliferating cell were solved by immunohistochemical reactions characteristic for vascular endothelium - CD34, CD31 and factor VIII, where positivity to at least one antigen was observed (Fig. 10). In two cases, osteoclast-type giant cells were noted within the tumors; these cells might have been CD68+ histiocytic cells (Fig. 11). Relatively numerous CD68 phagocytes were frequently encountered in the central part of the tumor (Fig. 13).

In some cases, pleural infiltration was noted, macroscopically manifested as irregularly shaped areas of maculate thickening. Histologically, these areas almost solely showed the presence of spindle-shaped cells; no hyalinization or necrosis features were observed (Fig. 14). In the presented cases, pleural involvement was not associated with pleural transudate.

The two cases of endotheliosarcoma were morphologically much different from epithelioid hemangioendotheliomas. Lung sections did not show any solid tumors, but rather extensive, massive thickening of the pulmonary stroma, packed with spindle-shaped and very atypical cells with mitotic figures (Fig. 15). These cells demonstrated immunohistochemical reactions that were similar to endothelial cell reactions. Study materials of one of the tumors that metastasized from the liver originated from autopsy; the other patient with the tumor originating in the scrotum died within a short time.

Discussion

At present, pulmonary epithelioid endotheliomas (PEH) are treated separately from the remaining endothelial neoplasms and included in the group of malignant tumors. Epithelioid hemangioendotheliomas are situated between benign hemangiomas, which practically never affect the lungs, and very clearly malignant angiosarcomas [65, 66].

Before 1983, these tumors were described under various names [17, 18, 19], what resulted from their difficult to interpret morphology and slow course, spanning many years. While evaluating such lesions, non-neoplastic processes were taken into consideration, especially granulomatous processes, hamartomas, incipient infarction, incipient primary pulmonary alveolar proteinosis, amyloid lesions or decidualis. The latter view was a result of the fact that the lesion was more commonly observed in young females and of some similarity to the deciduas undergoing hyalinization. With respect to possible neoplastic processes, the following entities were considered: fibrohistiocytomas, chemodectomas, mesotheliomas, chondromyxosarcomas, leiomyosarcomas, angiosarcomas or else bronchioalveolar

carcinomas. In multifocal lesions, attention was focused mainly on metastatic carcinomas arising from the salivary gland, thyroid, mammary gland, ovary or on carcinomas of an unknown origin [13, 19]. In the majority of cases, PEH was mistaken for decidualis [25] or for chondrosarcomas.

Clinically, these pulmonary neoplasms are often asymptomatic ((76% of cases in (29) or 50% in (13)). Sometimes, the patients present with moderate coughing and shortness of breath. Radiology usually demonstrates the presence of disseminated nodules, less than 2 cm in diameter [17, 58]. The patients are oftentimes without a primary diagnosis and treated for tuberculosis or sarcoidosis or else suspected of suffering from multiple neoplastic metastatic disease. A correct diagnosis may be established only following a histopathologic examination of a section collected in the course of thoracotomy or thoracoscopy. The literature on the subject presents scarce reports on cytological diagnoses based on biopsy material evaluation [10, 30]. In some cases, the presenting symptom is pulmonary hemorrhage [8, 11, 47, 50], similarly as in Case 9 and 10 from the present series. A patient has been described, who clinically presented with thromboembolic lesions of the lungs and pulmonary hypertension [64].

Multiple lesions involving both lungs raise a question whether they represent primary pulmonary tumors [56]. It may be also surmised that they represent a primary pulmonary tumor disseminating within the same lung or involving both lungs. Such lesions are often considered to represent multiple pulmonary metastases of tumors with unidentified sites of primary origin. Various authors emphasize a high probability that the primary neoplasm may be located in the liver, hence multiple metastases in the lungs. Two cases (5 and 10) of a single tumor in the left lung should undoubtedly be considered primary. Case 5, with the patient followed-up for three years, has not demonstrated any signs of relapse or disseminated disease. The case is the more interesting in that morphologically, the tumor showed distinct signs of cellular atypia and proliferation in the peripheral portions (numerous mitoses).

The investigations of Nerlich et al. [38], which have not been confirmed by any other publications, demonstrate that the basement membrane of multiple pulmonary tumors differs in its structure from the membrane of tumors situated in the liver. According to the above-mentioned authors, in the liver, the basement membrane is composed mostly of collagen IV with a minimal and focal amount of laminin and basement-associated heparan sulphate proteoglycan, while in the lungs, all these elements are present in the basement membranes of the tumor. In the opinion of Nerlich et al, this fact would support the primary multifocal character of pulmonary tumors.

Epithelioid hemangioendothelioma of the lungs is much more common in females (approximately 80% of cases) and in young women at that, it is sometimes seen in children [44], more than one half of cases are noted in individuals below 40 years of life [4, 13, 17, 34, 45, 54]. It should be borne in mind, however, that epithelioid hemangioendotheliomas involving other sites than the lung and liver are equally frequently noted in both sexes and they do not demonstrate similar age-associated preferences.

The higher incidence of the tumor involving the lungs in female patients indicates the possibility of estrogen or progesterone receptors being present in tumor cells. Studies carried out in formalin-fixed materials have not been unequivocal, however. Nakatani et al. [37] demonstrated a single positive case in a male, while Ohori et al. [40] noted one tumor in a man per five studied patients. A possible association between epithelioid hemangioendothelioma with hormonal contraceptives has been also proposed. Yet, the thesis is doubtful when we consider the incidence of the tumor in less recent series of patients and in males [20]. In case when the above-mentioned receptors are indeed present, one may consider anti-estrogen treatment. The higher incidence of such tumors in recent years, especially in women, may – in the opinion of the present author – favor considering whether such processes may not be associated with environmental factors, e.g. with the use of cosmetics.

According to some investigators, there are two forms of the neoplasm, characterized by a lower and higher degree of differentiation; this view is also supported by the studies carried out by the present author. One may also note the tumors undergoing transformation into hemangioma (Case 12), as well as malignant transformation of a portion of the lesion (Case 10). Tumors with low malignant potential demonstrate no mitoses or only single mitoses in the peripheral fragments of the lesion and are associated with long-term survival. More malignant tumors are characterized by larger and varied in shape nuclei and more numerous mitotic figures, larger number positive staining nuclei with Ki67; they are generally associated with a less favorable prognosis. Here, intraparenchymal infiltrations, pleural infiltrations and involvement of lymph nodes and other organs are more frequently observed. According to Dail [17], factors associated with a poorer prognosis include patients presenting with clinical pulmonary signs upon the preliminary diagnosis, lymphatic vessels infiltrations, pleural infiltrations, extensive vascular and bronchial infiltrations, also involving the pulmonary stroma, as well as metastases to the liver and peripheral lymphadenopathy.

Kitachi et al. [29] believe that fluid accumulated in the pleural space, and especially inflammatory lesions and

infiltrations involving the pleura, are also associated with an unfavorable prognosis, similarly as the presence of spindle-shaped cells. Nevertheless, in their series, two patients with pleural involvement but without pleural exudate spontaneously regressed. Also in the my present cases, pleural involvement mostly by spindle cells has not been associated with a poor prognosis.

The tumor situated in the lung spreads through the pores of Kohn, but it is also capable of retrograde spreading into the bronchioles, small arteries, veins and lymphatic vessels [23, 62], and infiltrating the pleura. Infiltration of interalveolar septa is not detected in paraffin-embedded sections, but it was detected by Azumi and Churg [3] in plastic-embedded and sections (1 micron). Lymphogenous spread of the neoplasm [62] is often manifested by the presence of spindle-shaped cells. When this type of cells is more abundant, such an observation may indicate a less favorable prognosis [29, 56]. Involvement of lymph vessels, especially in the case of multiple tumors, may be associated with distension of peripheral lymph vessels in the lung (Case 3).

In some forms of the tumor, giant, osteoclast-type cells were detected [51]. Similar cells have been observed in two cases from the present series (Case 4 and 10).

Pleural infiltration is macroscopically manifested as irregular areas of maculate thickening, within which histology reveals predominantly spindle-shaped cells without necrosis and hyalinization, since the lesions are rather thin. They may be easily mistaken for diffuse mesenchymal-type mesothelioma. However, in these cases from our series where the pleura was involved, no transudate has been noted in the pleural cavity.

According to Corrin et al. [16], electron microscopy of PEH shows the tumor cell cytoplasm abounding in intermediate fibers and with a reduced number of other organelles. The cell membrane are connected with surrounding cells through small desmosomes or zonula adherens. Small pinocytic vesicles are noted along the cell membrane. There are no dense bodies and dense plaques that are visible in smooth muscle cells. Ultrastructural studies confirm the presence of nuclear invaginations in cytoplasmic intermediate fibers. The Weibel-Palade bodies are encountered [9, 59], but they are not seen in all tumors of this type.

Immunohistochemical reactions are in many cases positive to factor VIII and CD34, as well as CD31 and vimentin [54, 55, 59]. Reactions to EMA are always negative, while some tumors demonstrate positivity to cytokeratin [7, 26]. However, a problem much discussed in the literature focuses on the question whether all tumors originating from the endothelium are characterized by a positive reaction to CD34. Suster et al. [51] failed to demonstrate the presence

of the antigen in similar mediastinal tumors, while factor VIII was always present. Sirgi et al. [49] obtained positive reactions in four of seven tumors of this type. In another report, Suster and Wong [52] demonstrated that neoplastic processes of the angiosarcoma and PEH type did not produce positive reactions to CD34 (HPCA-1) in neoplastic endothelium. Only in hemangiomas, some papillary intravascular proliferations, as well as in vessels of Kaposi's sarcomas and at times in some spindle-shaped cells was the reaction positive. The presence of the CD34 antigen, apart from stem cells, has been also detected in mature endothelium of small vessels and embryonal fibroblasts. In addition, the group of cells reacting positively to this antigen has been recently extended, to include for example dermatofibrosarcoma cells. Therefore, Suster and Wong are of the opinion that the antigen may not be considered typical and characteristic for vascular endothelium and for neoplasms arising from such endothelium. In unequivocal cases, it is advisable to perform other reactions verifying the presence of the FVIII and CD31 antigens. A more extensive report on immunohistochemical reactions in the endothelium of vascular tumors was presented by Miettinen et al. [35]. In the present case of a single pulmonary tumor (Case 5), reaction to the CD34 antigen was negative.

Chromosomal studies in epithelioid hemangioendothelioma provide a wealth of interesting information. In two tumors of this type situated in the liver and soft tissues, Mendlick et al. [33] detected translocations in chromosomes 1 and 3; the authors believed the translocations to be characteristic of tumors of this type, what, however, requires confirmation in further investigations. Translocations between chromosome 1 and 3 have been previously described in angiosarcomas and hemangiopericytomas. The search for translocations characteristic of sarcomas also finds confirmation in investigations of Ewing's sarcomas, PNET, synovial sarcoma or liposarcomas.

In differential diagnosis we should take into consideration metastatic lesions of other sarcomas, such as chondrosarcoma, leiomyosarcoma or osteosarcoma. Although sometimes developing as small polyps, such tumors nevertheless do destroy the stroma, a phenomenon which is not observed in the pulmonary form of epithelioid hemangioendothelioma. They also demonstrate the presence of fairly numerous mitotic figures. In such cases, careful clinical examinations may also reveal primary foci of such neoplasms.

Sclerosing hemangioma (benign pneumocytoma) of the lungs, contrary to epithelioid hemangioendothelioma, usually appears as a single tumor, although cases of multiple tumors have been also described. The former is similarly common in females. Yet the tumors show no reaction

to CD34, CD31 and factor VIII, and demonstrate no endothelial features in electron microscopy. Also micropolyps in PEH are not coated by type II pneumocytes, what is characteristic of hemangioma sclerosans. Sometimes, the neoplastic process needs to be differentiated from tumors belonging to the so-called pseudoangiosarcomatous carcinomas [5, 36]. Clinically, PEH may be also mistaken for Langerhans cell histiocytosis [28].

In patients with pleural involvement, a problem arises in establishing differential type diagnosis of the lesions and discern them from mesenchymal type mesotheliomas [24, 32, 48]. In such cases, a helpful diagnostic tool may be provided by reactions to calretinin, which is present in mesotheliomas, as well as reactions to epithelial cells, cytokeratin and EMA, which usually are not observed in tumors of endothelial origin. A single case of concomitant PEH and bronchioloalveolar carcinoma of the lungs was also described [17, 19].

Surgical treatment may be taken into consideration in case of single tumors [4] usually, tumors are multiple and their number is higher than visualized by radiology. In such instances surgical treatment is not recommended. The course of the disease allows for differentiating between two distinct types of the condition. Some patients die within a year after the diagnosis, present with a symptomatic disease with a higher degree of aggressiveness, while in others, the course is slow, spanning many years, but it leads to pulmonary insufficiency and right heart hypertrophy, what in consequence results in death. Cases that are considered to be related with a poor prognosis are associated with weight loss, anemia, pulmonary symptoms, and especially bleeding into the pleural cavity and hemoptysis. Such patients do not survive beyond one year [1, 4]. The literature on the subject presents reports on long-term survival of such patients [31], up to 30 years in individuals with multiple tumors of the lungs [29, 53], or 24 years [34]. The fact is also supported by long-term follow-up of the present patients.

Some patients were treated with interferon, what resulted in slight tumor regression [46], or with chemotherapy [43] with carboplatin and etoposide, sometimes with positive results. In all cases of PEH, radiotherapy is ineffective. Partial, spontaneous regression of tumors was also noted in some patients [29]. According to Kitachi, individuals without subjective symptoms definitely have a more favorable prognosis. Case 11 with concomitant multiple myeloma will be treated with Thalidomide, which inhibits angiogenesis; it will be of interest to observe the effect of the medication on the preexisting tumors of the lungs. In recent years, attempts have been made at treating PEH employing agents blocking vascular endothelial growth factor (VEGF) or its receptors (VEGFR).

The prognosis in highly malignant endotheliosarcomas (angiosarcomas) of the lungs is very poor and there is no effective chemotherapy or radiotherapy, especially in view of the fact that these patients demonstrate high-stage neoplastic processes with pulmonary dissemination.

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