CASE REPORT

Soft tissue epithelioid angiosarcoma

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Abstract

We present a case of 48-year-old male with a nine months history of right inferior thoracic (T_{10}–T_{12}) paravertebral mass, which became painful after a back trauma; dyspnea and hemoptysis were associated. The preoperative native and with contrast substance CT revealed a tumor mass extended from the right paravertebral muscles to the diaphragmatic right pillar muscle, invading the postero-basal pleura and the posterior arches of the right XIth and 12th ribs with osteolysis. Fragments of 10 cm large tumor resection specimen (striated muscle, dense connective tissue, adipose tissue, lymph nodes and intercostals nerves) were routinely processed, further immunohistochemical investigations were needed, using Dako antibodies pan-CK clone MNF116, CD34, CD20, vimentin, synaptophysin, melanoma HMB45 clone, with LSAB 2Kits system and further CK AE1/AE3, CK7, CK20, CEA, S-100 protein, CD31, von Willebrand factor, D2-40/podoplanin, Ki-67 antigen, with EnVision system and DAB visualization in both systems. The histological and immunohistochemical aspects were indicative for soft tissue epithelioid angiosarcoma, which was misdiagnosed on frozen and HE sections as a carcinoma, because of the cohesiveness and nesting properties of the malignant cells, together with the presence of lymph node metastases. The proliferative activity of the malignant cells, highlighted by Ki-67 antibody, clone MIB 1 was high (30% of malignant cells were positive at HPF). The patient was discharged with adjuvant therapy indication: radiotherapy and chemotherapy. The tumor locally recurred 12 months afterwards, but the patient is still alive 22 months after surgery.

***Keywords*:** soft tissue tumors, epithelioid angiosarcoma, immunohistochemistry, prognosis.

Introduction

Angiosarcoma of soft tissue is a rare lesion; hence, relatively little is known regarding its clinicopathologic features and prognosis. By definition is a malignant tumor of cells that recapitulate the morphological and functional features of normal endothelium [1], lymphatic or blood vessel or with mixed phenotype. It is presumed to be a high-grade sarcoma, although little data has been published in support of this contention. Even scattered case reports describe the epithelioid variant of soft tissue angiosarcoma [2–4]. Moreover, the frequency of epithelioid areas that may be confused with other entities is unknown. The latter feature is particularly important, accordingly to Meis-Kindblom JM and Kindblom LG [5], in view of several reports describing cytokeratins in epithelioid angiosarcoma of parenchymatous organs, skin, and soft tissues. On the other hand they may vary from highly differentiated tumors that resemble hemangiomas to those in which anaplasia makes them difficult to distinguish from carcinomas or melanomas, so is needed a complex algorithm putting together all data from imagistic department, intraoperative, gross and classical light microscopy, immunohistochemistry and ultrastructural examination. The immunophenotype and the ultrastructural characteristics of various types of angiosarcoma have been reported previously, but their diagnostic utility in morphologically diverse angiosarcomas of soft tissue is not applied routinely. In addition, some prognostic markers must be underline in order to determine their biologic behavior.

Material and Methods

We present a case of 48-year-old male with a nine months history of right inferior thoracic (T_{10}–T_{12}) paravertebral mass, which became painful after a back trauma; dyspnea and hemoptysis were associated. The connection between the onset of pain and tumor growing with a traumatic event was inevitable for the patient due to a "personal history" of 38-year-old right flank parietal hematoma persistent from childhood. The thoracic CT revealed an 8/5.5 cm tumor mass involving the right paravertebral muscles, the posterior arches of the XIth and XIIth right ribs with osteolysis of these structures and invasion of the diaphragmatic (right pillar muscle, as well as the right postero-basal pleura (Figure 1). The presence of some pulmonary fibro-calcified nodules in the right superior lobe and left inferior one were considered arrest tubercle lesions and, finally, no pathological mediastinal adenopathy was observed. The imagistic diagnosis of the right paravertebral mass was in the favor of a primary malignant tumor (rhabdomyosarcoma) that had to be confirmed by biopsy, hence indication for admittance to Thoracic Surgery. The analyses showed an elevated speed blood clotting (50 mm/h) and relative granulocytosis (74.2%), with resilient thoracic back pain to opioid analgesics (Tramadolum). On physical examination was evident

the right, T_{10}–T_{12} paravertebral tumor with rounded, renitent, large (up to 10/8 cm), painful, imprecisely delineated, and fixed with deeper structures features. Surgery (P.O. 31–32/16.01.2008) consisted of removal right flank hematoma and the evacuation of the black clotted blood (300 mL) from the paravertebral tumor, together with the inspection of the inner surface of the resulting cavity, multiple muscle biopsies together with fragments of rib with osteolysis, and 3 cm long right XIth intercostal nerve resection; hemostasis, posterior right chest wall stitches, and drainage. The histopathological result described a carcinomatous invasion of the striated muscle and rib with unknown (possible kidney, lung and others) primary for the right paravertebral mass, along with an encapsulated old hematoma – the right flank pseudotumor. The post-surgery thoracic and abdominal CT (native and with contrast substance) was unable to find a presumed primary site of a carcinoma, only the fast recurrence of the right paravertebral blood collection (Figure 2).

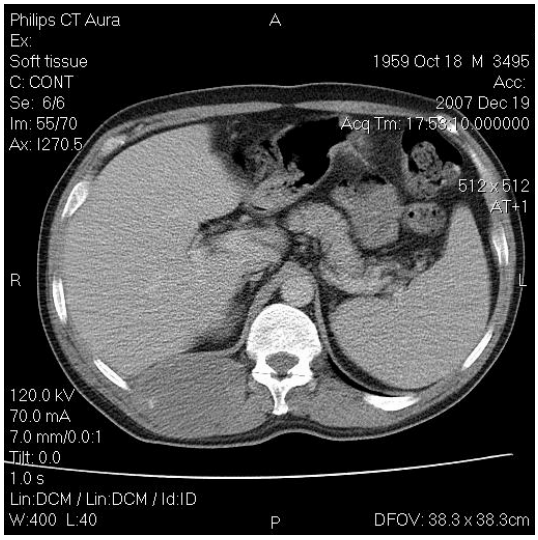

Figure 1 – ***Thoracic contrast-substance CT with a large paravertebral mass, allegedly a rhabdomyosarcoma.***

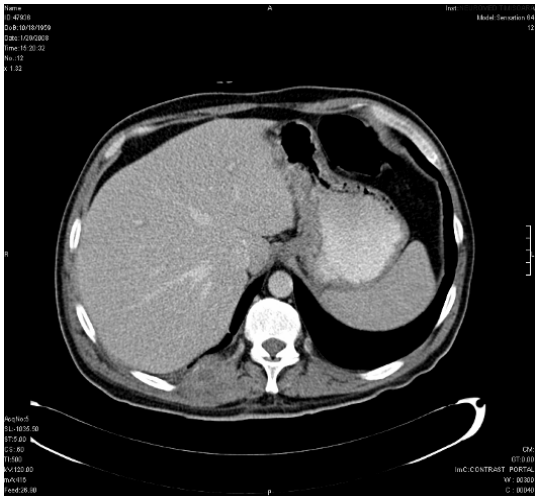

Figure 2 – ***Thoracic contrast-substance CT with recurrence of right paravertebral blood collection.***

The patient continued to feel tremendous pain despite major analgesics therapy, so re-intervention (P.O. 128/22.02.2008) was decided with tumorectomy (Figure 3) together with lateral ends of XIth and XIIth ribs and resection of all striated muscle tissue that seemed infiltrated from intervertebral Xth and XIth, postero-inferior serratus, erector spinae, external and internal oblique and transversus thoracic muscles, throughout fascia transversalis. Frozen sections of submitted pathological muscles appeared again as epithelial malignant tumor (carcinoma). In the same time with the removal of the hematoma-like paravertebral tumor, the right pleural cavity was explored through posterior costophrenic sinus – without any pathological feature (Figure 4), and through fascia renalis, the right kidney, which also grossly looked normal: so, the possible primaries from previous histopathological report were infirmed. The major thoracic wall defect was followed by stabilization with a substitution network (reconstructive surgery).

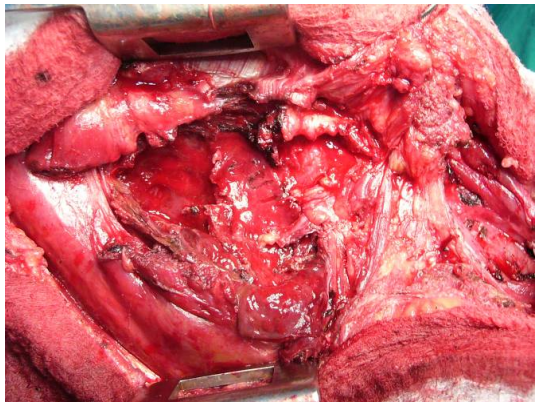

Figure 3 – ***Intraoperative appearance of the overbleeding deep situated right paravertebral tumor (hematoma-like).***

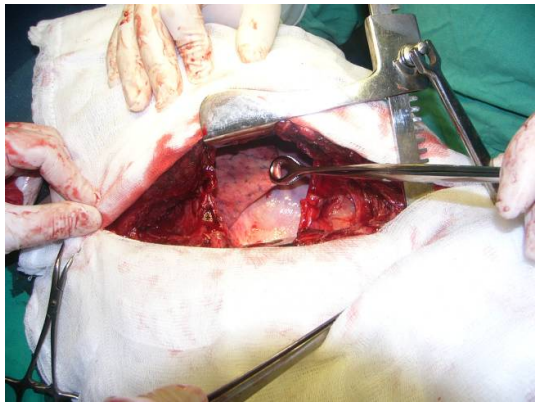

Figure 4 – ***Right pleural cavity checking: no pathological gross findings.***

Fragments of the large tumor resection specimen (striated muscle, dense connective tissue, adipose tissue, lymph nodes and intercostal nerves) were routinely processed. Immunohistochemical investigations were added, using Dako antibodies pan-CK clone MNF116, CD34, CD20, vimentin, synaptophysin, melanoma HMB45 clone, with LSAB 2Kits system and further CK AE1/AE3, CK7, CK20, CEA, S-100 protein, CD31, von Willebrand factor, D2-40/podoplanin, Ki-67 antigen, with EnVision system and DAB visualization in both systems.

After a conclusive pathological result, the patient was submitted to the Oncology Department of City

Hospital, Timişoara, with adjuvant therapy: radiation, followed by chemotherapy cures. Despite all therapeutic measures, the tumor locally recurred 12 months afterwards, but the patient is still alive 22 months after surgery (and correct diagnosis).

Results

On *routine stain* some tissue fragments consisting of proper dense connective tissue, adipose tissue and striated muscles presented a tumoral proliferation arranged in islands and nests with a vaguely lobular architecture at low magnification. The cellular type was that of epithelioid cells, with abundant eosinophilic cytoplasm, pleomorphic, but large vesicular nuclei and prominent nucleoli (Figure 5). They were arranged in a variety of patterns, including large gaping vascular channels, small nests of cells grouped around a lumen, single or cord-like arrangements of vacuolated cells ("signet-ring" morphology), slit-like branching vascular channels lined by atypical endothelial cells, and sheets of cells. Few cells presented intracytoplasmic lumina with RBCs or remnants within. Besides predominantly solid areas, papillary foci simulating papillary endothelial hyperplasia with prominent fibrinous to hyalinized cores were observed. However, the lining endothelial cells in these papillary areas were distinctly malignant. Where cellular density was prominent, the extracellular matrix was scant, but with recent and older (hemosiderin pigment present) hemorrhages, as well as with limited tumor necrosis and myxomatous degeneration. No spindled tumor cells or hemangioma-like structures were identified.

Peripheral nerves (Figure 6) and lymph nodes (Figure 7) from the intercostal space, together with rib bones and hyaline cartilage showed large areas of tumor invasion.

Immunohistochemical profile

Pan-cytokeratin and cytokeratins of various molecular weights were not detected (pan-CK MNF116, CK AE1/AE3, CK7, CK20 negative). Endothelial markers were positive in a large range of intensity, extent and antigenic substrates. The plasmalemma and cytoplasm of epithelioid cells was weak to strong positive for anti-CD34 antibodies (Figure 8).

CD31 was relatively positive in the cytoplasm of malignant cells, with weak, but diffuse pattern. The cytoplasm of epithelioid cells was focally but intense positive for factor VIII-related antigen/von Willebrand factor. The last was the most sensitive of the endothelial markers (Figure 9). Finally, D2-40/podoplanin revealed a weak, but diffuse nuclear and cytoplasmic immunostaining of atypical cells (Figure 10).

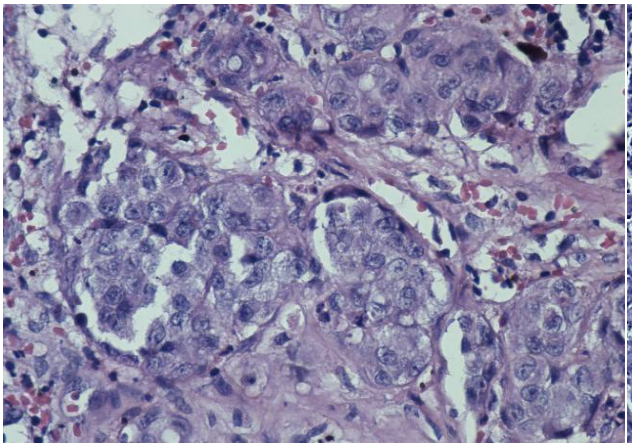

Figure 5 – ***Nested epithelioid malignant cells, some with rudimentary vascular lumina, some with signet-ring appearance; well-developed vascular channels (HE stain, ×400).***

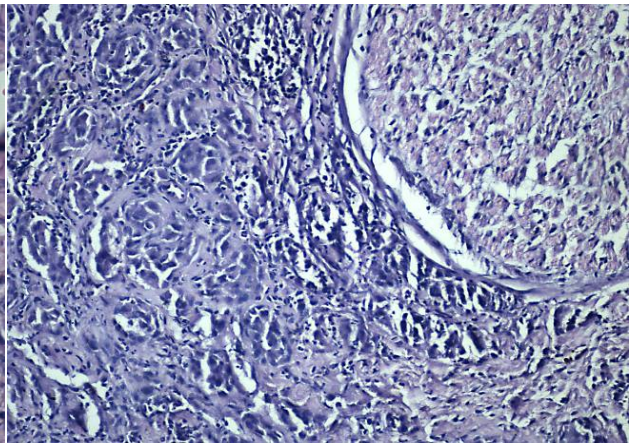

Figure 6 – ***Perineural invasion by nested epithelioid malignant cells (HE stain, ×200).***

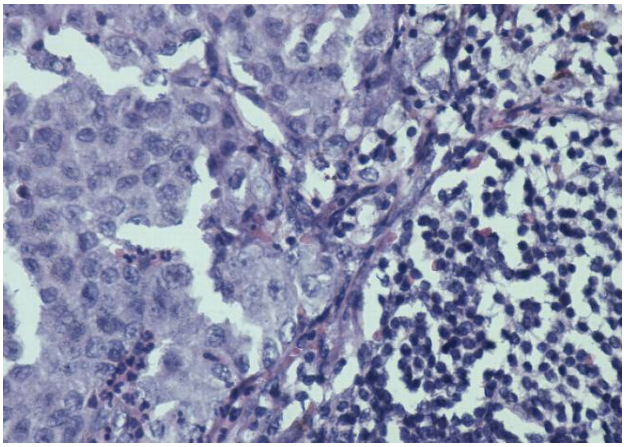

Figure 7 – ***Lymph node (from intercostal space) metastasis (HE stain, ×400).***

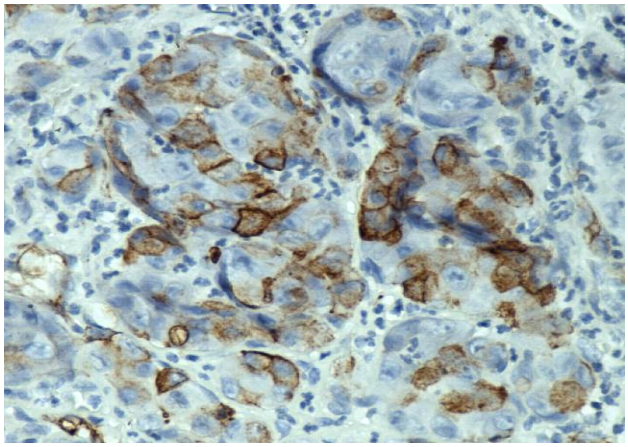

Figure 8 – ***Epithelioid cells positive with CD34, LSAB method (DAB visualization, ×400).***

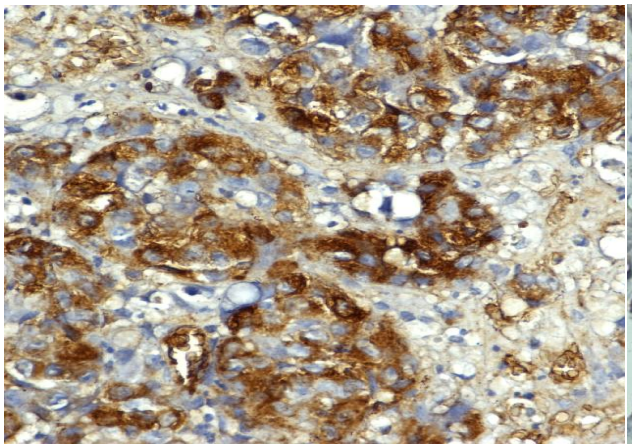

Figure 9 – ***Focally intense reaction of epithelioid cells for factor VIII-related antigen, EnVision method (DAB visualization, ×400).***

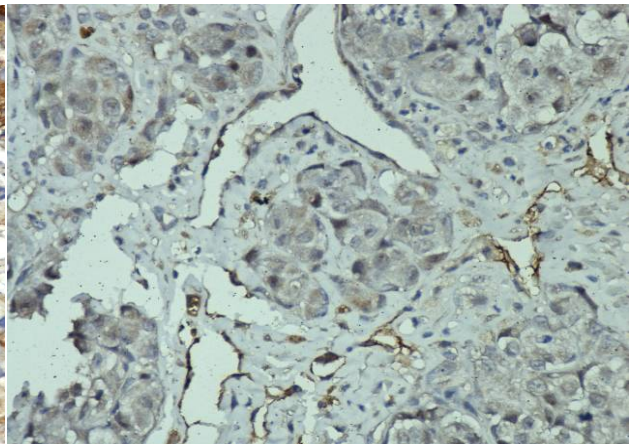

Figure 10 – ***Weak nuclear and cytoplasm positive stain of epithelioid cells with D2-40/podoplanin, EnVision method (DAB visualization, ×400).***

Vimentin immunostaining of the neoplastic cells was strikingly positive and served to accentuate vascular lumen formation by the tumor cells, particularly those with epithelioid features (Figure 11). The epithelioid tumor cells were negative for: synaptophysin, CEA, S-100 protein, CD20 and HMB45. Immuno-reaction for MIB1 was performed and had shown a relatively high mitotic activity (30% of tumor cells on HPFs were had labeled nuclei – Figure 12).

With the respect of all routine and immuno-histochemical aspects, in conjunction with clinical, imagistic, and intraoperative data a final and conclusive diagnosis was made: epithelioid angiosarcoma of soft tissue, and further treatment was established accordingly.

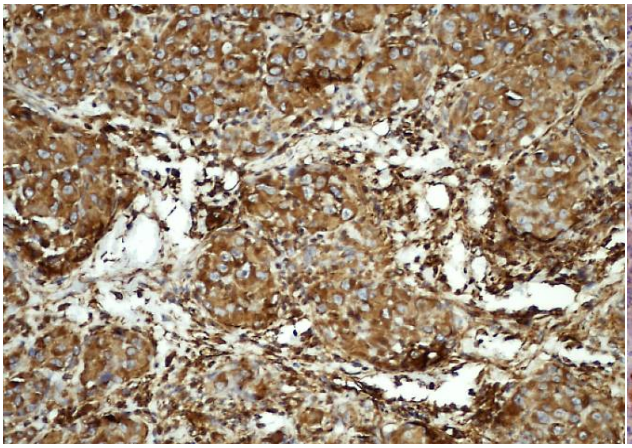

Figure 11 – ***Intense and diffuse cytoplasm immuno-reaction of epithelioid nested cells for vimentin, EnVision method (DAB visualization, ×200).***

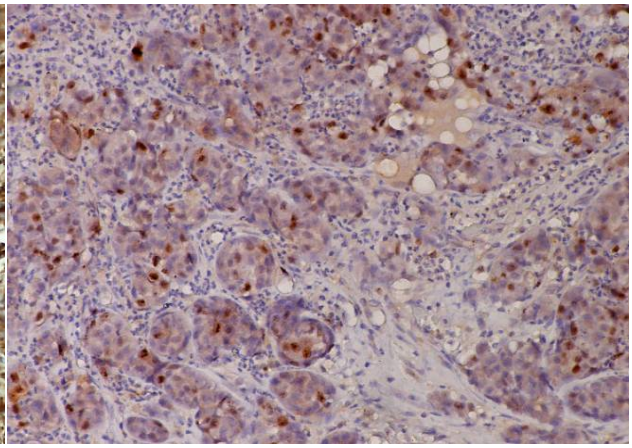

Figure 12 – ***High mitotic activity of neoplastic cells underlined with Ki-67 antigen, MIB 1 clone, EnVision method (DAB visualization, ×200).***

Discussion

Despite some well-documented studies and series about angiosarcoma in general [5], and particular its deep soft tissue epithelioid variant [3], still little is known about the clinical presentation, extended immuno-profile, and prognostic factors, because it is a relatively rare neoplasm with a false clinical appearance as a hematoma and microscopically (on routine stain) confusion with a carcinoma (primary or metastatic). Added to above mentioned diagnostic entrapments, a lot of case reports have focused on the detection of cytokeratins in this epithelioid variants of soft tissue angiosarcoma [3, 4, 6–9]. Even the authors of the *WHO Classification* of soft tissue tumors mentioned that about 1/3 of soft tissue angiosarcomas, particularly in the epithelioid forms, cytokeratin is present, reflecting the fact that cytokeratin cannot be used as an absolute discriminant between angiosarcoma and carcinoma [10]. The theory sustaining the above allegations considers that epithelial features occurred in neoplastic endothelial cells are based on the presence of an unusually large amount of intermediate filaments in the cytoplasm, hence the co-expression of cytokeratin with vimentin, an epiphenomenon of epithelial metaplasia.

Regarding our case some features mirrored clinical, pathological and prognostic data from the literature, in other aspects being disregardful. The original site of involvement was located in the deep striated muscle (the intramuscular soft tissue), as in the lot of Fletcher CDM *et al.* [3], not in a limb or limb girdle, but somewhat axial – the right paravertebral thoracic region, it was associated with trauma history as in conditions enumerated by Meis-Kindblom JM and Kindblom LG [5],

clinically it was designated as a persistent hematoma-like mass, but on CT images the presumed diagnosis was of rhabdomyosarcoma. What was puzzling even from the first surgery was the involvement of bone matrix of the XIth and XIIth right ribs posterior arches, intercostal XIth right nerve and the right postero-basal right pleura without hemothorax. Because literature mentioned the possibility of epithelioid angiosarcoma to arise in all those histological structures: bone [11–14], peripheral nerve sheath [15–17] and pleura [18]). But, what misled us to a first (and wrong) diagnosis (and we have to admit, this was the easy way out of the puzzle) was the involvement of the regional lymph nodes by cohesive sheets of epithelioid cells, so we have formulated a carcinomatous spread in all above mentioned structures (muscle, bone, nerve, pleura, lymph node) with a primary unknown, but most likely a renal cell carcinoma. Approximately a month later, due to the exacerbating pain felt by the patient together with the renewal of paravertebral blood collection and the absence of imagistic detection of a primary tumor nearby, pieces of the tumorectomy specimen underwent immunohistochemical investigation of first line. Luckily for us and for the patient, pan-cytokeratin was negative and the most important breakthrough was the positive reaction for CD34, then other endothelial markers followed; factor VIII-related antigen immunostaining was generally focal, but intense – being the most sensitive of the endothelial markers, D2-40/podoplanin was diffuse but weak, and CD31 was relatively insensitive with weak immunostaining. The nonspecific but ubiquitous mesenchymal/endothelial cell intermediate filament vimentin was strongly expressed, so the immunoprofile of the epithelioid malignant cells was: endothelial markers (CD31, CD34, von Willebrand related antigen, D2-40) positive, mesenchymal marker (vimentin) positive, epithelial markers (panCK MNF116, AE1/AE3, CK7, CK20, CEA) negative, melanocytic markers (HMB45, S-100) negative, neuroendocrine (synaptophysin) and lymphoid respectively (CD20) marker negative.

It is our believe that the co-expression of podoplanin (a marker of lymphatic endothelium) with markers of blood vessel endothelium (especially von Willebrand related antigen) proved the mixed malignant endothelial cells phenotype (lymphatic and blood vessel malignant endothelial cells) and explained the lymph node metastasis, not secondarily extension from the primary soft tissue tumor as Meis-Kindblom JM and Kindblom LG observed in their cornerstone study about soft tissue angiosarcomas [5].

The proliferative rate, measured by the median percentage of labeled malignant nuclei with Ki-67 antigen, in 10 HPFs was 30% in the range of Meis-Kindblom's study (≥10% up to 80% [5]), but higher than the values found by Rossi S and Fletcher CDM (median 5%; from 1% to 25% [19]).

Deep-seated epithelioid angiosarcomas are clinically aggressive neoplasm that rapidly develops metastases, with high rate of tumor deaths and short survival (53% of patients died of their tumors at a median interval of 11 months, accordingly to Meis-Kindblom JM and Kindblom LG [5]) and a significant incidence of local recurrences. However, 31% of patients were alive with no evidence of disease from nine months to nearly 16.5 years after diagnosis (median 46 months), indicating that some patients can survive for a long time [5]. In our case, one year after surgery followed by radiotherapy and chemotherapy, the patient had 1 cm large tumor recurrence in the same place (local recurrence), but he is still alive, with the disease 22 months after the diagnosis of soft tissue epithelioid angiosarcoma.

Conclusions

A correct diagnosis of the epithelioid variant of an angiosarcoma of the thoracic wall is very difficult due to its rarity, multiple possible origins (pleura, bone, striated muscle as primary or it can be a metastatic tumor) and to its epithelial features on routine stain, which are readily misjudged. The poor outcome (local recurrence) correlates with tumor large size and a high Ki-67 value.

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Received: September 5th, 2010

Accepted: November 20th, 2010