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CASE REPORT

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Epithelioid hemangioendothelioma – an unexpected diagnosis of a mediastinal tumor with extensive local thrombosis

MIRCEA LIŢESCU[1,2], TAMER ABDURAIM[1], LAURA PAVERMAN[3], CAMELIA DOINA VRABIE[4,5], ION DINA[3,6], IANCU EMIL PLEŞEA[4,7,8], VALENTIN TITUS GRIGOREAN[1,9]

[1]*Department of Surgery, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

[2]*Department of Surgery, Sf. Ioan Emergency Clinical Hospital, Bucharest, Romania*

[3]*Department of Internal Medicine, Sf. Ioan Emergency Clinical Hospital, Bucharest, Romania*

[4]*Department of Pathology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

[5]*Department of Pathology, Sf. Ioan Emergency Clinical Hospital, Bucharest, Romania*

[6]*Department 1 – Medical Semiology, Faculty of Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

[7]*Department of Pathology, Fundeni Clinical Institute, Bucharest, Romania*

[8]*Victor Babeş National Institute for Research and Development in Pathology and Biomedical Sciences, Bucharest, Romania*

[9]*Department of Surgery, Bagdasar–Arseni Emergency Clinical Hospital, Bucharest, Romania*

Abstract

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor and the mediastinal localization is amongst the most infrequent. We present the case of a 37-year-old woman with a history of resected left thyroid tumor that presented to our department for evaluation of a left supraclavicular palpable mass in close contact with local vascular structures, and with heterogeneous contrast enhancement as described by computed tomography (CT) and magnetic resonance imaging (MRI). Considering the history of the patient, the presumptive diagnosis of thyroid tumor recurrence was established, and the patient was referred to surgical department. During procedure, we encountered important bleeding from a ruptured jugular vein branch, which we assumed to be a newly formed tumor blood vessel. After surgery (48 hours postoperatively), the patient developed important local thrombosis that encompassed the left internal jugular vein, left subclavian vein and the left brachiocephalic trunk that partially subsided after anticoagulant therapy. The histological examination revealed the presence of a vascular tumor proliferation of epithelioid endothelial cells that was characteristic of an EHE confirmed later on the immunohistochemical studies as Yes-associated protein 1–transcription factor E3 (YAP1–TFE3) subtype. In addition to the case report, some relevant information from the scarce literature data about mediastinal EHE were reviewed here.

Keywords: epithelioid hemangioendothelioma, vascular tumor, mediastinum.

Introduction

Epithelioid hemangioendothelioma (EHE) is a vascular tumor that was described for the first time in 1975 by Dail & Liebow who identified it as a tumor in the lung; at that point they recognized it as an aggressive form of bronchoalveolar carcinoma. Only in 1982, Weiss & Enzinger named it "epithelioid hemangioendothelioma" after finding a bone and soft tissue tumor that resembled both hemangioma and angiosarcoma [1, 2]. In 2002, the *World Health Organization* (WHO) included the EHE in the composite hemangioendothelioma category, as being a locally aggressive tumor with metastatic potential [3].

EHE is very rare, representing less than 1% of vascular tumors. It affects both sexes with a small predominance in females for the pulmonary localization, and has a very large age distribution, ranging from seven to 83 years, with a predominance in the middle age [1, 2]. It is most frequently located in the lung (30%), liver (21%) and bones (14%) but can arise in any other region of the body (head, neck, breast, mediastinum, abdomen, etc.) [2]. Usually, the tumor is found incidentally, only a small group of patients are symptomatic at the time of diagnosis. Due to a metastatic rate comprised between 15% and 30%, the 2002 *WHO* Classification reclassified the EHE as a malignant lesion [4]. The symptoms described in literature are nonspecific and vary according to the localization of the tumor, ranging from chest pain, dyspnea, persistent cough, hemoptysis to bone pain, anemia, neurological symptoms and edema [2].

Because of its rarity and non-specific presentation, it is very often misleading, resulting in many misdiagnosed patients or cases that are only diagnosed in advanced stages.

Aim

In this paper, we report the case of a 37-year-old female presenting with a completely asymptomatic retroclavicular mass that later on proved to be a mediastinal EHE.

Case presentation

We report the case of a 37-year-old female with a history of left thyroid lobectomy performed six years ago who was referred to our Department of Surgery for an asymptomatic swelling located in the left supraclavicular fossa.

The clinical examination revealed a painless supraclavicular tumor whose dimensions were 3/4/3 cm and without any other symptomatology. This was the only abnormality detected during the physical examination of a low body mass index (BMI) patient. Laboratory tests revealed values within normal ranges for all parameters, even thyroid hormones and thyroid stimulating hormone (TSH).

The cervicothoracic magnetic resonance imaging (MRI) examination identified the status of the previous left thyroid lobectomy and a left anterior mediastinal nodular tumor of about 3/3.7/2.4 cm in diameter with the upper pole as high as the lower pole of the right thyroid lobe (Figure 1, a and b).

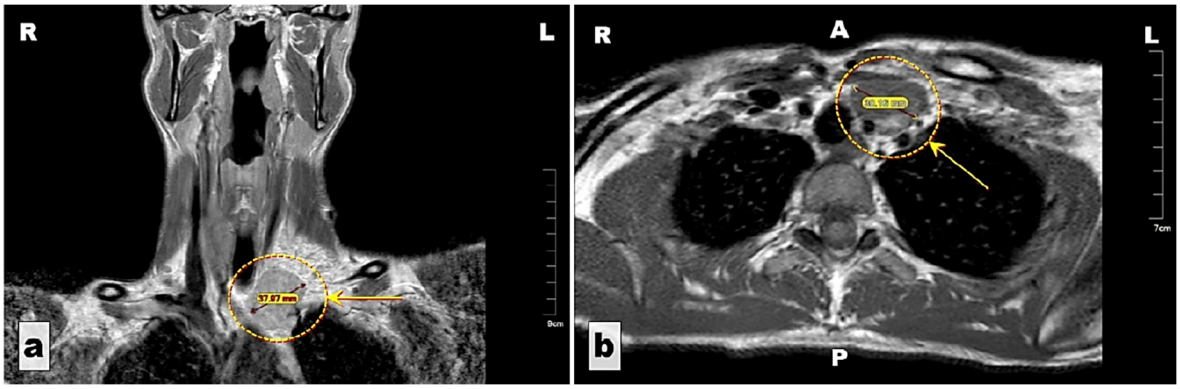

Figure 1 – ***Left anterior mediastinal mass (yellow circles and arrows): (a) MRI – coronal view; (b) MRI – axial view. A: Anterior; L: Left side; MRI: Magnetic resonance imaging; P: Posterior; R: Right side.***

The lower limit of the tumor was delimited by a plane passing through the lower edge of the sternal end of the left clavicle and had contact with the left common carotid artery, left subclavian artery, and left brachiocephalic venous trunk, without any evidence of their infiltration. The tumor was inhomogeneous and had a clear external contour.

The patient could not provide any information about the histopathological aspect of the resected thyroid lobe from the past surgery, so a malignancy with a local recurrence could not be ruled out. The information obtained by clinical, biochemical, and paraclinical examinations were evaluated by a Tumor Board, which included a radiologist, an endocrinologist, a general surgeon, a pathologist, and an oncologist. Due to the uncertainty of diagnosis and possible malignant etiology of the nodule, the Tumor Board established the indication for the surgical excision of the tumor under general anesthesia.

After presenting the potential risks and obtaining the patient's informed consent, surgery was performed by an iterative anterior cervicotomy. Following the dissection of the superficial planes, the upper pole of a firm tumor was identified by palpation, posterior to the clavicular insertion of the sternocleidomastoid muscle. Cervicotomy did not allow the circumferential approach of the tumor due to the fibrotic scarring induced by the previous intervention and also to the fact that the lower pole of the tumor descended retroclavicular. For these reasons, we have decided to enlarge the operating field by a partial longitudinal sternotomy (5 cm) for an easier approach and better visibility. During the dissection of the tumor, in the attempt to release its lower pole, abundant bleeding started from the proximal segment of the left inferior thyroid vein, which was controlled by suturing the affected venous element. The dissection of the tumor was continued, in an apparently intracapsular avascular cleavage plane which was identified, and the tumor was completely excised. In the remaining posterior-inferior lodge of the lesion, the left subclavian artery, subclavian vein, left common carotid artery, and the anteriorly ligated venous branch with the origin at the shedding of the left internal jugular in the left brachiocephalic venous trunk was identified. To complete the hemostasis in the remnant cavity after tumor excision, three pieces of hemostatic sponge were applied at the end of the intervention.

At 48 hours postoperatively, the patient developed important left upper limb edema. The Doppler ultrasound and computed tomography (CT) scan showed incomplete thrombosis of the left internal jugular vein extended to the left brachiocephalic trunk, so that antithrombotic therapy was immediately started. Afterwards, postoperative evolution was satisfactory with remission of edema and Doppler confirmation of partial venous recanalization. Two months after discharge, the CT scan suggested left brachiocephalic trunk thrombosis; despite of the lack of clinical manifestation and complete resolution of upper limb edema, together with the vascular surgeon, we recommended the continuation of antithrombotic therapy for at least another six months.

The firm tumor mass, with white tan appearance on section surface, proved to be, on histological examination, a proliferation of endothelial cells, with round to ovoid nuclei, with variable size and abundant, densely eosinophilic cytoplasm.

Tumor cells had a pseudoalveolar arrangement or in solid nests, forming also vascular spaces (Figure 2a), embedded in a fibrous stromal network with areas of hyaline degeneration (Figure 2b). Few mitoses were identified and no areas of necrosis.

The tumor morphology suggested the diagnosis of EHE that was further enhanced by immunohistochemical (IHC) staining with a panel of long time known and still useful markers indicators of endothelial differentiation, *i.e.*, cluster of differentiation (CD)34, CD31, Friend leukemia integration 1 transcription factor (FLI1) and early growth response 1 (ERG1) [4–7], which all proved to be positive

(Figure 2, c–f). The further immunostaining with transcription factor E3 (TFE3), which was also positive, helped us to define more precisely our tumor as a Yes-associated protein 1 (YAP1)–TFE3 t(X;11)(p11;q22) subtype of EHE (Figure 2g). Finally, we tested also the tumor aggressiveness by immunolabeling with Ki67. The calculated index was 5%, indicating a low degree of aggressiveness (Figure 2h).

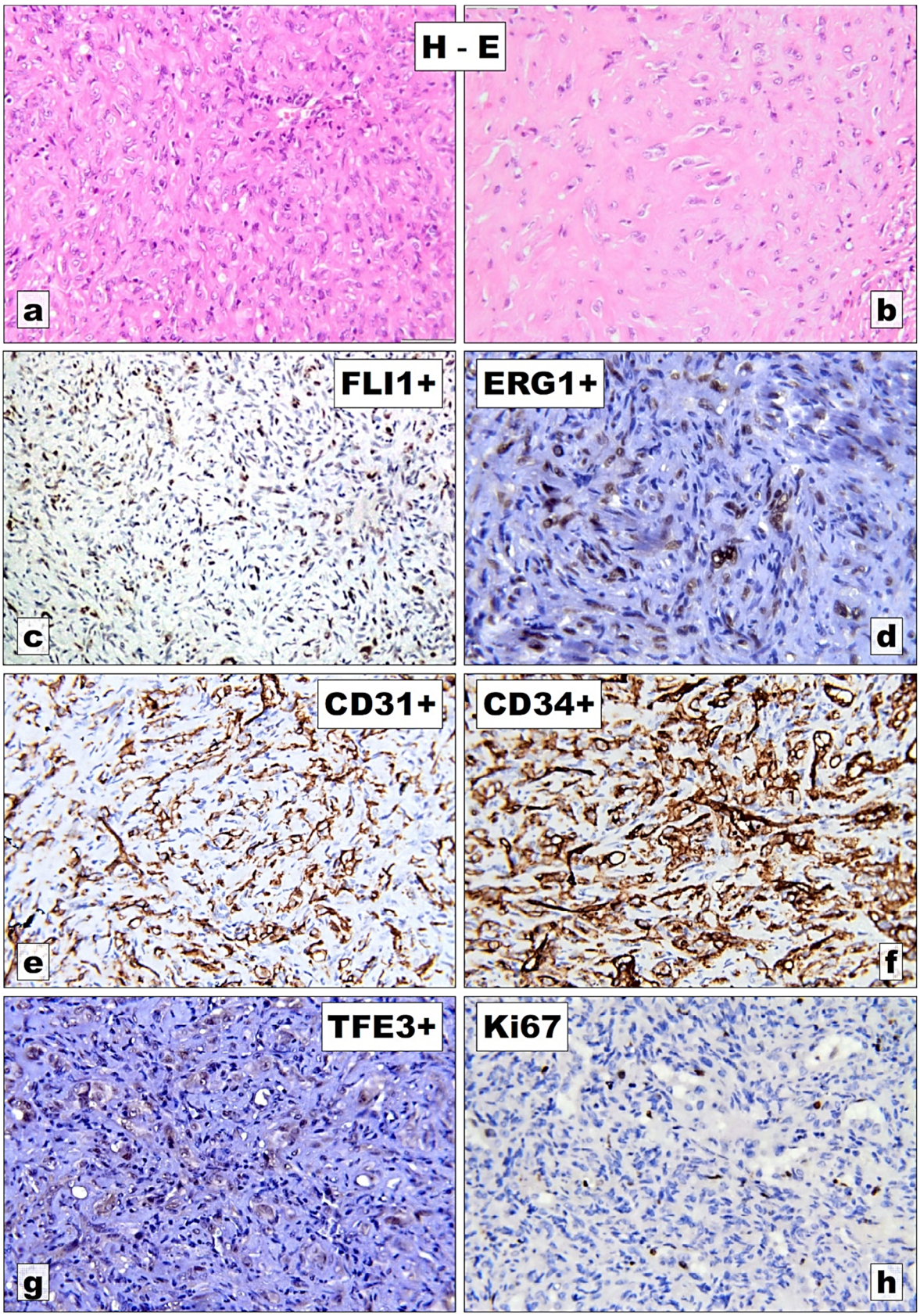

Figure 2 – ***Epithelioid hemangioendothelioma: (a and b) Morphological aspects, HE staining, ×400; (c–h) Immunohistochemical profile of studied tumor (×400). CD: Cluster of differentiation; ERG1: Early growth response 1; FLI1: Friend leukemia integration 1 transcription factor; HE: Hematoxylin–Eosin; TFE3: Transcription factor E3.***

According to *Fédération Nationale des Centres de Lutte Contre le Cancer* (FNCLCC) grading system, the tumor was framed as a G2 EHE (tumor differentiation score – 2 points; mitotic count score – 1 point; <50% tumor necrosis score – 1 point; total score – 4 points → G2).

With the histology report of malignant disease, the patient was addressed to the Department of Oncology for evaluation and specific treatment.

To rule out the possibility of residual tumoral tissue due to the intracapsular dissection of the tumor and to evaluate the necessity of radiotherapy the oncologist recommended a positron emission tomography (PET)–CT. This showed the presence of a small amount of residual metabolically active tissue in the anterior mediastinum (Figure 3).

The patient underwent local radiotherapy adopting the intensity modulated radiotherapy (IMRT)–volumetric-modulated Arc therapy (VMAT)/Rapid Arc technique which delivers the prescribed radiation dose during one single 360º rotation, usually in a 2-minute interval associated with daily imaging guidance using cone beam CT. The total dose, following the oncologist`s recommendation, was 60 Gy/30 fractions/six weeks. At the six months follow-up, the CT scan showed regression of tumoral mass.

Next follow-up CT scans at one year and the next four years after the surgical excision were also without signs of local recurrence (Figure 4, a and b).

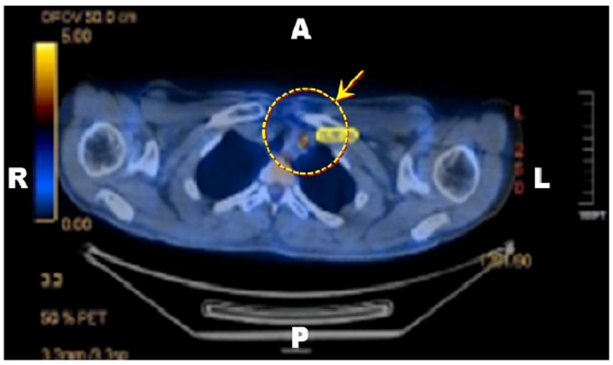

Figure 3 – ***PET–CT scan: residual metabolically active tissue (yellow circle and arrow). A: Anterior; L: Left side; P: Posterior; PET–CT: Positron emission tomography–computed tomography; R: Right side.***

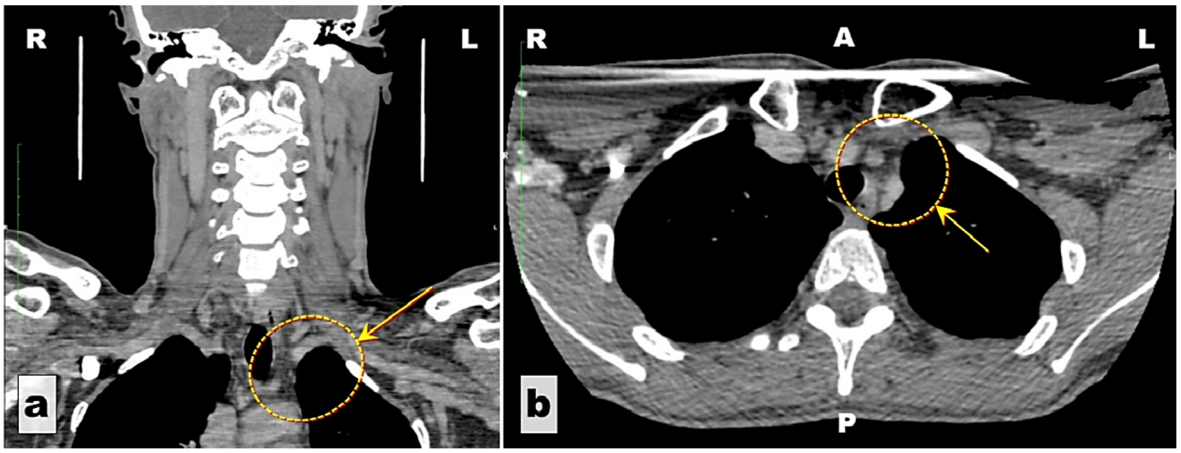

Figure 4 – ***CT five years after surgery: (a) Coronal view – normal aspect (yellow circle and arrow); (b) Axial view – normal aspect (yellow circle and arrow). A: Anterior; CT: Computed tomography; L: Left side; P: Posterior; R: Right side.***

Discussions

Back in 1975, Dail & Liebow were describing a vascular tumor found in the lung as a new aggressive form of bronchoalveolar carcinoma. Seven years later, in 1982, the same tumor, more aggressive than hemangioma but less aggressive than angiosarcoma would be found in bone and soft tissue by Weiss & Enzinger and named EHE [1].

The first large statistical paper dedicated to this tumor dates back 40 years ago, in 1981, when Sharon Weiss and Franz M. Enzinger published an evaluation of 41 cases whose specimens represented an experience starting from 1950 to 1980 retrospectively analyzed in the Armed Forces Institute of Pathology (AFIP) [8]. The authors considered that the tumor is rather evenly found during adult life with only three cases occurring before 21 years of age. Regarding gender ratio, there was a slightly more frequent presence in male patients than in females (23 *vs* 17 cases and one with sex unknown). In this first series of patients, most of the lesions were located at the level of the extremities, less usually in the rest of the body and only one tumor was located in the mediastinum [8].

Another large series published in 2014 found only one tumor with mediastinal location from 39 cases investigated [9]. Later studies confirmed the lack of gender propensity except for the pulmonary form (P-EHE), which is characterized by female predominance of 4:1 of this very rare vascular tumor, having a prevalence of less than one in a million cases [1]. Also, the age of the patient varies greatly, from seven to 83 years, with a median of 36 years [1, 2].

EHE arises from the proliferation of epithelioid endothelial cells and most frequently originates from a blood vessel [3]. The pathogenesis is still unclear but the knowledge in this area greatly improved throughout the last few years. The most important emerging theory regarding oncogenesis in EHE is based on the presence of genetic abnormalities in the tumor cells. One of the mutations observed consistently in most cases of EHE is the translocation between chromosomes 1 and 3 – t(1;3)(p36;q25). This leads to the formation of a fusion gene, known as WW domain-containing transcription regulator 1–calmodulin-binding transcription activator 1 (*WWTR1–CAMTA1*) with important role in oncogenesis [5]. In a smaller group of EHE, about 10% of cases, another mutation was found, t(11;X)(q13;p11)

leading to the occurrence of *YAP1–TFE3* fusion gene with likewise oncogenic effect [6]. This mutation was associated with a different tumor morphology – more obvious vessel formation, eosinophilic cytoplasm and TFE3 positivity on immunohistochemistry [7]. Also, it was characteristic to a younger group of patients and a much favorable outcome than the classically described WWTR1–CAMTA1 form [9, 10].

Regarding etiopathogenesis of EHE, there is also mentioned in literature another theory that implies a causal relation between chronic infection with *Bartonella* spp. and oncogenesis. This is described in immunocompromised patients and rests on the known erythrocytic invasion of this microorganism that inflicts intra-endothelial inflammation. Also, some species of *Bartonella* are capable of upregulating vascular endothelial growth factor (VEGF) having a possible role in vascular tumor formation [1, 11].

More recently, a few cases of EHE with rapid progression or recurrence in pregnant patients have been described. This raises the suspicion of a possible link between either female hormones or pregnancy related factors as placental growth factor (PlGF), and the pathogenicity of the disease [12–14].

The tumor is usually an incidental finding. Most patients are asymptomatic at the time of diagnosis and the few that exhibit symptoms have heterogeneous manifestations. These vary according to the tumor localization or the presence of metastatic disease: dyspnea, cough, chest pain, hemoptysis (for P-EHE), skin lesions, neurological symptoms, back pain, abdominal pain and others or more general symptoms like anemia, fatigue and weight loss [1]. EHE can present in any vascularized tissue, most often in the lung, liver and bone, less frequent localizations being lymph nodes, ovary, retroperitoneum, subcutaneous fat, eyelid or mediastinum like the case of our patient [2]. To our knowledge, there are only around 20 to 25 cases of anterior mediastinal EHE described in literature until 2020 [15, 16].

Diagnosis of EHE is difficult and is based on the histological, IHC and molecular findings. Radiological investigations can guide the diagnosis to a limited extent, but there are no pathognomonic characteristics described in literature [16]. Even if a tumor is discovered during imaging exams, the extreme polymorphism of clinical course and localization make it almost impossible to evoke such a rare diagnostic entity. More frequently, doctors are thinking about other malignancies, metastatic dissemination, or benign teratomas. In our case, the most probable diagnosis was a local recurrence after surgery for an unspecified thyroid nodule. During microscopic examinations, there can typically be found eosinophilic endothelial cells that are either rounded or slightly spindled (a more pronounced spindling of the cells is suggestive of an aggressive course) organized in short strands, cords or solid nests. Cytologically, these cells have an abundant cytoplasm, pleomorphic nuclei and intracytoplasmic lumina. Cells are set in a matrix that appears either light blue if it is chondroid-like, or deep pink if it's hyaline. Sometimes metaplastic bones can also be found. Marked nuclear atypia, mitotic activity of >1 mitoses/10 high-power fields (HPFs), pronounced spindling of the cells and necrosis are all characteristic of a more aggressive form [2, 3]. Immunohistochemistry is also a powerful tool when it comes to diagnosis. The most reliable and sensitive antigens described are CD34, CD31 and FLI1, the last two being the more specific ones when it comes to differentiating EHE from metastatic carcinoma or other vascular tumors [2, 3, 17].

Being such a rare tumor there is limited clinical data regarding the optimal treatment. There are multiple approaches described in literature, ranging from surgical resection, chemotherapy with different agents, radiotherapy and targeted therapies like Apatinib, Sorafenib, Pazopanib and Sirolimus, and different combinations, all with varying results [2]. As a general rule, whenever feasible, surgical resection is the recommended treatment with the possibility of adjuvant radiation therapy in localized disease. In metastatic cases, chemotherapy is preferred [1, 2]. A Medline database interrogation showed only few cases of cases of mediastinal EHE reported in the last 15 years and for most of them the chosen treatment was like in our case, surgical resection, sometimes followed by radiotherapy [18–22].

Conclusions

EHE is a very rare vascular tumor that represents a challenge for the clinician, whether regarding diagnosis or treatment. Like in our case, it is most frequently silent, patients presenting with very non-specific symptoms or no symptoms at all. Diagnostic is also difficult, almost entirely relied upon histological and IHC characteristics, and when the diagnosis is finally made the clinician finds himself in front of another problem – choosing the adequate therapy. There are only a handful of anterior mediastinal EHE reported at this time in literature, so with this case we hope to add value to the general knowledge of this disease and also to raise awareness of the possibility of EHE in the differential diagnosis of a mediastinal mass.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Mircea Liţescu and Laura Paverman contributed to the writing of the manuscript. Iancu Emil Pleşea guided us throughout all the process of preparing this paper. Ion Dina and Valentin Titus Grigorean verified and approved the final form of the document.

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Corresponding author
Iancu Emil Pleşea, Professor, MD, PhD, Departments of Pathology, Carol Davila University of Medicine and Pharmacy, and Fundeni Clinical Institute, 258 Fundeni Road, Sector 2, 022328 Bucharest, Romania; Phone +40722–992 511, e-mail: emil.plesea@umfcd.ro

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