Int J Clin Exp Pathol 2016;9(5):5746-5752
www.ijcep.com /ISSN:1936-2625/IJCEP0024039

Case Report

Epithelioid hemangioendothelioma of the anterior mediastinum: a case report

Yang Liu[1,2], Yue-Feng Jiang[1,2], Ye-Lin Wang[1,2], Hong-Yi Cao[1,2], Liang Wang[1,2], Qing-Chang Li[1,2], Hong-Tao Xu[1,2], Xue-Shan Qiu[1,2], En-Hua Wang[1,2]

[1]Department of Pathology, The First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, Shenyang 110001, China; [2]Institute of Pathology and Pathophysiology, China Medical University, Shenyang 110001, China

Received January 14, 2016; Accepted March 25, 2016; Epub May 1, 2016; Published May 15, 2016

Abstract: Epithelioid hemangioendothelioma (EHE) is a subtype of hemangioendothelioma which is a kind of vascular tumor with the biologic behavior between a hemangioma and a conventional angiosarcoma. Among the 6 subtypes of the hemangioendothelioma, EHE is the most aggressive member of this family and may cause distant metastasis and even death in a minority of cases. We herein present one case of EHE exhibiting prominent eosinophils in the background, which happened in a 29-year-old Chinese male patient. Contrast-enhanced computed tomography (CT) scanning revealed a solitary mass in the anterior mediastinum adherent to pleura and multiple scattered small nodules in the both lung lobes. Histologically, the tumor was predominately composed of vast eosinophils and scattered histiocytoid tumor cells. The unusual histological appearance maybe misdiagnosed as inflammatory pseudotumor or epithelioid hemangioma, especially if the specimen is limited or from fine-needle aspiration.

Keywords: Epithelioid hemangioendothelioma, epithelioid hemangioma, mediastinum

Introduction

Epithelioid hemangioendothelioma (EHE) was first described by Weiss and Enzinger in 1982 [1]. Hemangioendothelioma is cataloged under the vascular tumors with intermediate malignancy [2-4]. Hemangioendothelioma is used to describe a group of vascular tumors included EHE, malignant endovascular papillary angioendothelioma, Kaposiform hemangioendothelioma, hobnail (Dabska-Retiform) hemangioendothelioma, epitheloid sarcoma-like hemangioendothelioma and composite hemangioendothelioma. Compared with the other subtypes, EHE has a more aggressive biologic behavior [2, 3].

The age range for EHE is broad (first to eighth decade), but it seldom occurs during childhood. EHE often presents in patients aged from 20-30 year without sex bias. The common sites of involvement include bone (especially involved the long tubular bones in lower extremity), soft tissue, liver and lung [4]. Occasionally, it can occur in mediastinum. To our knowledge, there are no more than 20 cases which reported the EHE occurred in mediastinum [5-17]. EHE usually presents as a solitary, slightly painful mass in soft tissue. However, it may occur multifocally in a localized region in some cases. Histologically, EHE is composed of a distinctive type of endothelial cells having an epithelioid or histiocytoid appearance. The cytoplasm is abundant and eosinophilic, often vacuolated. The stroma may be scanty or have a prominent myxoid appearance. Although occasional cases contain eosinophils and lymphocytes, this feature is rarely as pronounced as it is in the epithelioid hemangioma [3]. Herein, we report a case of EHE occurred in anterior mediastinum. The tumor was characterized by the vast eosinophils infiltration, and the scattered histiocytoid tumor cells fallen in are hardly to be recognized. The histological appearance mimics inflammatory pseudotumor or epithelioid hemangioma which makes us confused to diagnose.

Case presentation

Clinical history

A 29-year-old male patient was admitted to the First Affiliated Hospital of China Medical University in June of 2015 for complaining of

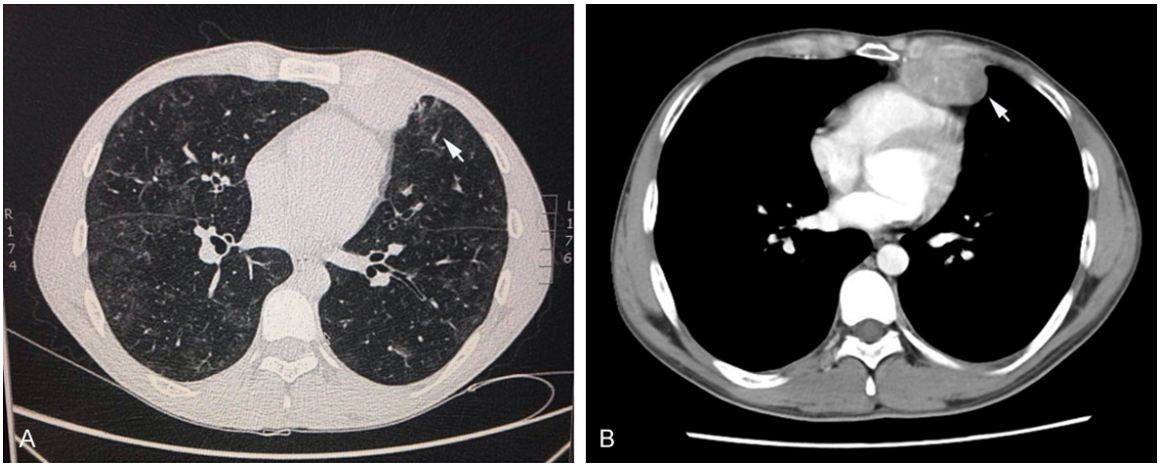

Figure 1. Contrast-enhanced CT scanning of the tumor. CT scanning revealed a solitary mass of 7.2 × 4.8 cm in the anterior mediastinum adherent to pleura and multiple scattered small nodules in the both lung lobes. A. Multiple scattered small nodules in the both lung lobes, the arrow showed the suspicious nodule. B. A solitary mass of 7.2 × 4.8 cm in the anterior mediastinum adherent to pleura, the arrow showed the mass.

chest distress and cough. Hematological and chemical studies showed normal except the elevation of eosinophils level. CT scanning revealed a solitary mass of 7.2 × 4.8 cm in the anterior mediastinum adherent to pleura and multiple scattered small nodules in the both lung lobes (**Figure 1**). The tumor was clinically diagnosed as a thymoma, and underwent a mass excision in thoracic surgery. In the operation, the mass in the anterior mediastinum and the suspicious intra-pulmonary nodule adjacent to the mass were fully resected and subjected to pathology. The postoperative pathology demonstrated the diagnosis of high-risk EHE. The patient refused the adjuvant chemotherapy and was alive with no tumor recurrence or metastasis within 11 months of follow-up.

Materials and methods

The tumor tissues were fixed in 10% formalin and embedded in paraffin. Several 4-μm sections were cut from each paraffin block, and one was stained with H&E, the others were stained with IHC (immunohistochemistry). Immunohistochemical staining was performed using the streptavidin-peroxidase system (Ultrasensitive; Mai Xin Inc., Fuzhou, China) according to the manufacturer's instruction. Commercially available prediluted monoclonal antibodies against the following antigens were employed: Pan-cytokeratin (AE1/AE3), Vimentin, CD31, CD34, Fli-1, factor VIII, p63, INI1, CD68, thyroid transcription factor 1 (TTF-1), CD5, CD3, CD20, TdT, CD15, CD30, Pax-5, CD21, CD1α, CD99, ALK, Calretinin, Actin (SM), CD117, S-100, HMB-45 (melanoma-associated marker), melan-A and Ki67. For the negative controls, the primary antibody was replaced with PBS.

Gross features

Gross examination showed an elastic hard mass (7 cm × 5 cm × 4 cm) with rough surface. The cross-section was grey-red in color. A suspicious mass (4 cm × 3 cm × 1 cm) resected from the lung was also subjected to pathology.

Microscopic features

The neoplasm was demarcated from the surrounding tissues with relative clear boundary, presenting with lobulated pattern within the tumor (**Figure 2A**, **2B**). The tumor was characterized by the infiltration of numerous eosinophils in the background (**Figure 2C**). The proportion of tumor area with eosinophils infiltration was more than 70%. We could observe the scattered epithelioid cells within some lobulated pattern (**Figure 2D**). The tumor cells were spindled and histiocytoid in shape, with slightly eosinophilic cytoplasm and oval to round vesicular nuclei (**Figure 3E** and **3F**). The typical cells with vacuolated cytoplasm could be found, but difficult (**Figure 3E**). Focally, the severe atypical nuclei, pleomorphism and mitotic figures (1/10 HPF) could also be observed (**Figure 3F**). The suspicious intra-pulmonary lesion showed the similar histological features with the prima-

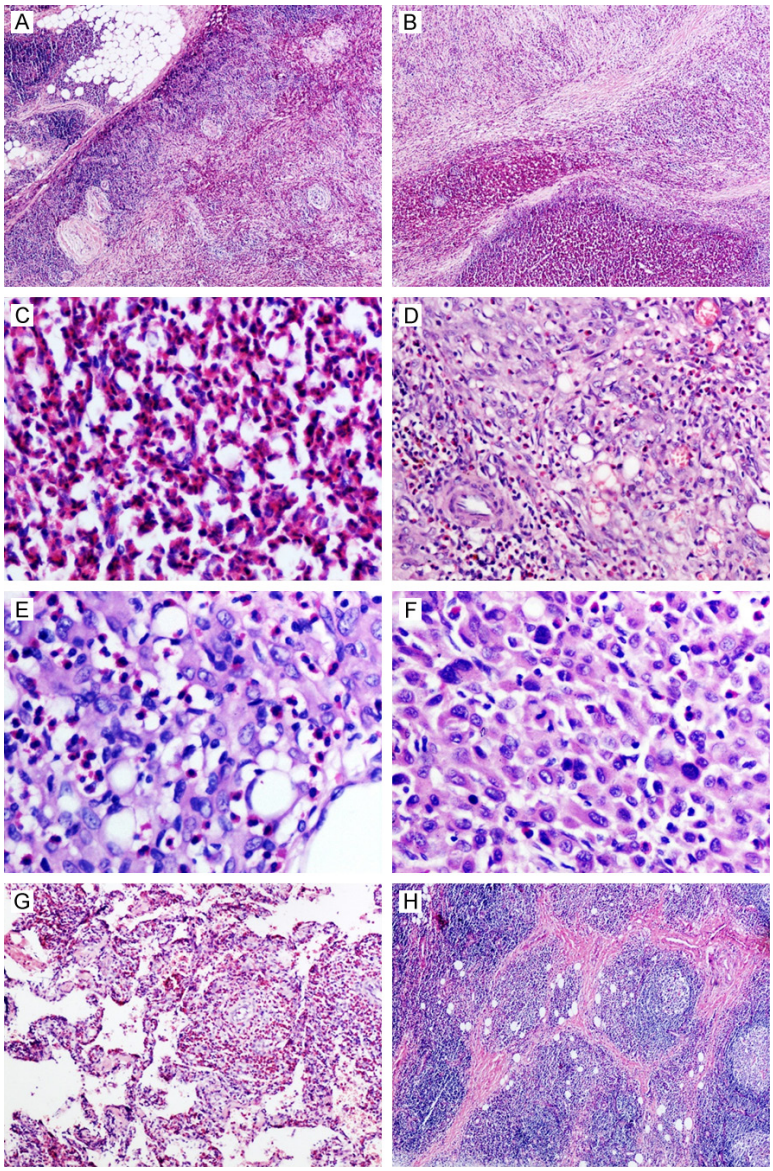

Figure 2. Histological features of this case. A. The neoplasm was demarcated from the surrounding tissues with relative clear boundary. B. The lobulated pattern within the tumor. C. The tumor was characterized by the infiltration of numerous eosinophils in the background. D. The scattered epithelioid cells within some lobulated pattern. E. The tumor cells were spindled and histiocytoid in shape, with slightly eosinophilic cytoplasm and oval to round vesicular nuclei. F. The severe atypical nuclei, pleomorphism and mitotic figures (1/10 HPF). G. The suspicious intra-pulmonary lesion showed the similar histological features with the primary lesion. H. Well-formed germinal centers were observed in the periphery tissue.

ry lesion (**Figure 3G**). In addition, well-formed germinal centers were observed in the periphery tissues (**Figure 3H**).

Immunohistochemistry

The immunohistochemical study showed that the histiocytoid cells were focally positive for AE1/AE3 (**Figure 3A**), strongly diffuse positive for vimentin (**Figure 3B**), p63 (**Figure 3C**), CD31 (**Figure 3D**), Fli-1 (**Figure 3E**) and INI1. They were strictly negative for CD34 (**Figure 3F**), factor VIII, CD68, TTF-1, CD5 (**Figure 3G**), CD15, CD30, Pax-5, TdT, CD21, CD1α, CD99, ALK, Calretinin, Actin (SM), CD117, S-100, HMB-45 and melan-A. The lymphocytes among the epithelioid cells were mainly positive for CD3 and focally positive for CD20. Ki67 index was about 15% **Figure 3H**. The results were listed in **Table 1**.

Discussion

The most common site for EHE is skeleton especially the long tubular bones. The other sites such as lung, liver, soft tissue, were also reported to be involved. However, the primary mediastinal EHE is quite rare, only few cases were reported [5-17]. So far, the largest retrospective study reported 12 cases of primary mediastinal EHE. Five of 12 cases were found with the involvement of adjacent tissues such as pleura, diaphragm and vessels. Two of the 12 patients experienced recurrence or died in the follow-up. The involvement of pleura and lung was also observed in our case. It is interesting that the multiple scattered small nodules in both of the lung lobes were disappeared after surgery, which was demonstrated by CT scanning. Meanwhile, the high level of eosinophils also fell back to normal. We speculate that the multiple scattered small nodules except the one adjacent to the mass in anterior mediastinum, was the secondary change of EHE.

Histologically, EHE is composed of epithelioid or spindle endothelial cells with abundant, eosinophilic, often vacuolated cytoplasm and round, vesicular, occasionally indented nuclei.

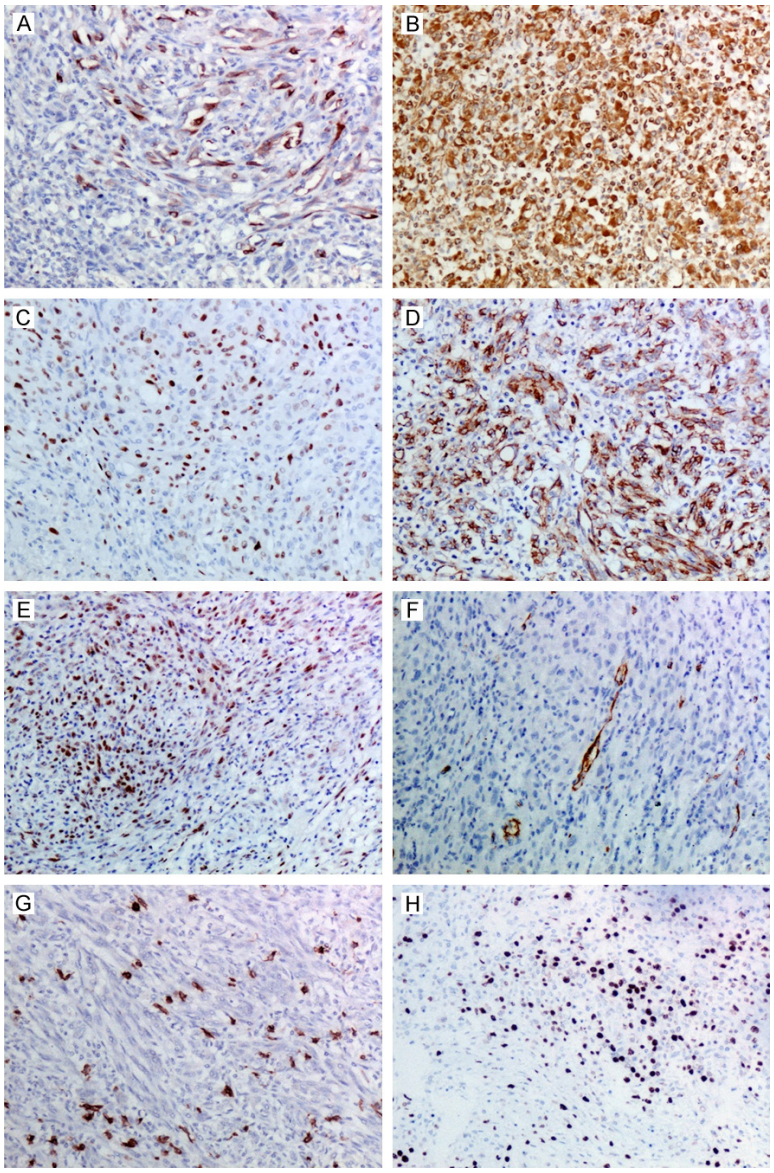

Figure 3. Immunohistochemical staining. A. The histiocytoid cells were focally positive for AE1/AE3. B-E. The histiocytoid cells were strongly diffuse positive staining for vimentin, p63, CD34 and Fli-1. F, G. The histiocytoid cells were negative staining for CD34 and CD5. H. Ki67 index was about 15%.

Intracytoplasmic lumina appear as vacuoles that may contain intact or fragmented erythrocytes. Mitoses, pleomorphism, and necrosis are variable but usually scanty or absent. The stroma may be scanty or have a prominent myxoid to hyalinized appearance. Osteoclast like multinucleated giant cells may be present [3].

In this case, the striking feature was the infiltration of numerous eosinophils with scattered histiocytoid cells among them, so the first diagnosis come to our mind is inflammatory pseudotumor (IPT) and inflammatory myofibroblastic tumor (IMT) instead of EHE. It's also hard to totally rule out classic Hodgkin's lymphoma, Langerhans cell histiocytosis (LH) and other dendritic cell tumor on morphologic grounds, so we perform immunostaining to distinguish among them. To our surprise, the immunophenotype (CD21, CD68-, CD15-, CD30, Pax-5-, S100-, SMA-, ALK-) overthrows the diagnosis of IPT and IMT, Hodgkin's lymphoma, LH, and other dendritic cell tumor, so we reviewed this case carefully and the focal vessel structure caught our attention. We also noticed, in focal area, some cells with vesicular cytoplasm (As shown in **Figure 2E**) which mimics the immature adipocytes or the hemangioendothelial cells. Combined with the eosinophils background, we considered that it may be inflammatory angioleiomyolipoma or vascular tumors. Next, HMB-45, Melan-A, CD31, CD34, FLi-1, factor VIII were added to stain and the result (HMB-45-, Melan-A-, CD31+, CD34-, FLi-1+, factor VIII-) ruled out the diagnosis of inflammatory angioleiomyolipoma. The supplement staining results indicate the vascular tumor, and is likely to be hemangioendothelioma.

Considering the histiocytoid appearance of the tumor cells which was also focally positive for CK and the aggressive biologic behavior, we think it should be better diagnosed as EHE. However, it is an uncommon site for EHE, so we searched the similar case on PubMed (www.ncbi.nlm.nih.gov) and found there are no more than 20 cases of mediastinal EHE. Among these cases, there is no one case share the similar histological structure (vast numerous eosinophils in the background) with this one. Considering this, we think it is necessary to review the features of EHE and also necessary

Table 1. Panel of Immunohistochemical Stains

Immunohistochemical Stain	Result
Pan-cytokeratin (AE1/AE3)	+, focally
vimentin	+
CD31	+
Fli-1	+
p63	+
INI1	+
Thyroid transcription factor 1 (TTF-1)	-
HMB-45 (melanoma-associated marker)	-
CD34	-
Factor VIII	-
melan-A	-
smooth muscle actin (SMA)	-
CD68	-
S100 protein	-
Calretinin	-
ALK	-
CD1a	-
CD21	-
CD5	-
CD3	-
CD15	-
CD30	-
Pax-5	-
CD20	-
CD117	-
TdT	-
CD99	-
Ki67	about 15%

to describe this uncommon histological structure in mediastinal EHE in order to avoid misdiagnosis.

EHE should be distinguished from other vascular tumors especially epithelioid hemangioma and epithelioid sarcoma. EHE is characterized by the epithelioid or histiocytoid morphology, and often accompanied with the immunoreactivity for keratin. All these features make it originally embraced under the generic category of histiocytoid hemangioma. Unlike the epithelioid hemangioma, in which vascular differentiation proceeds through the formation of multicellular, canalized vascular channels, vascular differentiation in EHE is more primitive and is expressed primarily at the cellular level. The endothelial cells in EHE are round to spindle and often form the short strands or solid nests. Intracytoplasmic lumen appears as vacuoles that may contain intact or fragmented erythrocytes. These features also indicate the primitive vascular differentiation compared with those of epithelioid hemangioma. However, the infectious process, which is always observed in epithelioid hemangioma, is seldom occurred in EHE. In this case, we truly doubted whether it is epithelioid hemangioma or Kimura disease because the eosinophils infiltration. Considering the site and the staining results (CD34-, CD31+), epithelioid hemangioma always occurs in superficial site such as subcutis or dermis and seldom involve deep soft tissue, vessels and parenchymal organs, we excluded the possibility of epithelioid hemangioma. Kimura disease presents as lymphadenopathy with or without an associated soft tissue mass. The well-formed germinal centers in the peripheral tissue (As shown in **Figure 2A** and **2H**) and a large number of eosinophils in this case also indicate the possibility of secondary reaction of Kimura disease. We carefully reviewed the whole sections and found no suspicious lymph node structure and the physical examination and ultrasound result are also normal, so we gave up this idea. In addition, Rosai indicated this uncommon feature of EHE, that is, an inflammatory infiltrate is often present at the periphery and this may contain well-formed germinal centers and/or a large number of eosinophils [2]. He also pointed out this infectious processes can also occur in epithelioid hemangioma and malignant epithelioid angiosarcoma [2].

In the focal area of this case, we found the significant nuclear hyperchromasia and pleomorphism, and also the pathological mitosis (As shown in **Figure 2F**). All these histological features should be distinguished with epithelioid angiosarcoma. However, these areas which indicated malignant are limited in the whole section, and the immunohistochemical staining results (CD34-, CD31+) also supported the diagnosis of EHE.

To date, no predisposing factors have been identified, and the prognosis of mediastinal EHE is unknown because of the limited cases. The majority of EHEs have a relatively better clinical course than highly aggressive angiosarcoma [2-4]. However, the tumor with marked cellular atypia, mitotic activity (> 1 mitosis per

10 HPF), necrosis and extensive spindling, may have a more aggressive course [19]. Deyrup et al. also used the tumor size (over 3 cm) as a factor for poor prognosis [20]. Considering all about these factors, our case should be diagnosed as "high-risk" mediastinal EHE. The lesion in lung maybe the invasion of mediastinal EHE, but we still cannot exclude the possibility for coincidence. In the current case, the mass has been fully removed by surgical resection. Although the patient refused adjuvant chemotherapy, there is no tumor recurrence or metastasis within 11 months of follow-up.

Conclusion

In this case, the uncommon site and histological appearance which make us confused to diagnose. Therefore, EHE must be included in the differential diagnosis of mediastinal tumors with histiocytoid appearance and eosinophils background to not underestimate this tumor in this location and so to better evaluate its real frequency. Using combination of immunohistochemistry may be helpful to some rare mediastinal tumors.

Acknowledgements

We wish to thank the patient, who requested anonymity, for agreeing our report and provided a detailed history. This study was supported by grants from the National Natural Science Foundation of China (No. 81302312 to Yang Liu) and Natural Science Foundation of Liaoning Province (No. L2013292 to Yang Liu) and Scientific Research Foundation for the Returned Overseas Chinese Scholars (No. 2013277 to Yang Liu). Ethical approval for this study was obtained from the local trials committee of the China Medical University. The informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yang Liu, Department of Pathology, The First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, Shenyang 110001, China. Tel: +86 24 23261638; Fax: +86 24 23261638; E-mail: cmuliuyang@qq.com

References

[1] Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. Cancer 1982; 50: 970-81.
[2] Rosai J, Ackerman LV. Rosai and Ackerman's surgical pathology. 9th edition. Edinburgh, New York: Mosby; 2004.
[3] Goldblum JR, Folpe AL, Weiss SW, Enzinger FM, Weiss SW. Enzinger and Weiss's soft tissue tumors. 6th edition. Philadelphia, PA: Saunders/Elsevier; 2014.
[4] Fletcher CDM, World Health Organization. International Agency for Research on Cancer. WHO classification of tumours of soft tissue and bone. World Health Organization classification of tumours. 4th edition. Lyon: IARC Press; 2013.
[5] Wethasinghe J, Sood J, Walmsley R, Milne D, Jafer A, Gordon-Glassford N. Primary pleural epithelioid hemangioendothelioma mimicking as a posterior mediastinal tumor. Respirol Case Rep 2015; 3: 75-7.
[6] Li XM, Lin XY, Xu HT, Yu JH, Wang L, Fan CF, Liu Y, Wang EH. Mediastinal epithelioid hemangioendothelioma with abundant spindle cells and osteoclast-like giant cells mimicking malignant fibrous histiocytoma. Diagn Pathol 2013; 8: 103.
[7] Konstantinova AM, Klimashevskii VF, Shelekhova KV. [Epithelioid hemangioendothelioma of the mediastinum]. Arkh Patol 2013; 75: 30-3.
[8] Mansour Z, Neuville A, Massard G. Mediastinal epithelioid haemangioendothelioma: a rare mediastinal tumour. Interact Cardiovasc Thorac Surg 2010; 10: 122-4.
[9] Carassai P, Caput M. Report of a case of epithelioid hemangioendothelioma of the anterior mediastinum metastatic to pleura. Pathologica 2010; 102: 112-4.
[10] Maamouri F, Ennaifer Jerbi E, Tounsi Guettiti H, Boussen H, Dellagi K, Boubaker S. [Multicentric epithelioid hemangioendothelioma involving lung, mediastinum and liver]. Tunis Med 2008; 86: 616-7.
[11] Campos J, Otero E, Dominguez MJ, Gonzalez-Quintela A. Epithelioid hemangioendothelioma in the posterior mediastinum. Eur J Intern Med 2007; 18: 331-2.
[12] Isowa N, Hasegawa S, Mino M, Morimoto K, Wada H. Mediastinal epithelioid hemangioendothelioma resected by hemi-plastron window technique. Ann Thorac Surg 2002; 74: 567-9.
[13] Begbie SD, Bell DR, Nevell DF. Mediastinal epithelioid hemangioendothelioma in a patient

with type IV Ehlers-Danlos syndrome: a case report and review of the literature. Am J Clin Oncol 1997; 20: 412-5.
[14] Suster S, Moran CA, Koss MN. Epithelioid hemangioendothelioma of the anterior mediastinum. Clinicopathologic, immunohistochemical, and ultrastructural analysis of 12 cases. Am J Surg Pathol 1994; 18: 871-81.
[15] Weidner N. Atypical tumor of the mediastinum: epithelioid hemangioendothelioma containing metaplastic bone and osteoclastlike giant cells. Ultrastruct Pathol 1991; 15: 481-8.
[16] Toursarkissian B, O'Connor WN, Dillon ML. Mediastinal epithelioid hemangioendothelioma. Ann Thorac Surg 1990; 49: 680-5.
[17] Lamovec J, Sobel HJ, Zidar A, Jerman J. Epithelioid hemangioendothelioma of the anterior mediastinum with osteoclast-like giant cells. Light microscopic, immunohistochemical, and electron microscopic study. Am J Clin Pathol 1990; 93: 813-7.
[18] Mineo TC, Biancari F, Cristino B, D'Andrea V. Benign vascular tumours of the Mediastinum: presentation of three cases and review of the literature. Thorac Cardiovasc Surg 1995; 43: 361-4.
[19] Mentzel T, Beham A, Calonje E, Katenkamp D, Fletcher CD. Epithelioid hemangioendothelioma of skin and soft tissues: clinicopathologic and immunohistochemical study of 30 cases. Am J Surg Pathol 1997; 21: 363-74.
[20] Lokich J, Anderson N, Bern M, Coco F, Zipoli T, Moore C, Gonsalves L. Dual modulation of 5-fluorouracil using leucovorin and hydroxyurea. A phase I trial. Cancer 1991; 68: 744-6.