Case report
Multicentric epithelioid hemangioendothelioma involving the lungs, trachea, liver and skeletal muscles
Muna M. Dahabreh, Nisreen I. Hmeideen, Abdelhamid S. Najada*

Department of Pediatric Pulmonology, Queen Rania Alabdallah Hospital, Jordan

Abstract
Epithelioid hemangioendothelioma (EH) is a rare benign vascular tumor, which typically present as multinodular lesions that can involve one organ or more. We report a 12 years old female who presented with one-year history of progressive intolerance to physical activity and 3 months history of dry cough and weight loss. Physical examination was positive for diminished breath sounds and crackles of right hemithorax, and small mass in abdominal wall. CT of chest and abdomen revealed multiple nodular lesions in both lungs, liver, and right abdominal rectal muscle. Bronchoscopy showed multiple small tracheal lesions. Immunohistochecmical staining of biopsy specimens obtained from the trachea, liver and muscle was consistent with EH.

1. Introduction
Epithelioid hemangioendothelioma (EH) is a rare vascular tumor with female predominance that is rarely reported in children. HE involves many organs with predisposition to skin, bone, liver and lungs. It usually manifests as multifocal nodules affecting a single organ with very low risk for metastasis to other organs. However, HE has been reported in few cases with simultaneous involvement of more than one organ. We report a 12-year-old female with HE involving lungs, trachea, liver, and abdominal muscles who presented with nonspecific complains of weight loss, exercise intolerance and dry cough.

2. Case
Patient is a 12-year-old female patient who was referred to the respiratory department at Queen Rania Hospital in Jordan complaining of progressive exercise intolerance for the last one-year and troublesome dry cough for the last 3 months. She lost 8 kg during her illness. Chest X-ray before referral showed multiple nodules in both lungs. Based on X-ray findings, she was initially diagnosed with pulmonary tuberculosis and was treated as such with triple oral anti mycobacterial antibiotics (isoniazid, rifampicin and pyrazinamide) for two months, even though PPD test was negative. She was referred because of lack of improvement on such treatment.

Patient denied any history of skin rash, joint pain, abdominal pain, abdominal distention or constipation. Rest of system review was normal. Upon examination she was frequently coughing but with no sputum production. She was in moderate respiratory distress with use of accessory muscles. Oxygen saturation was 84% on room air. Chest auscultation revealed decrease air movement on the right side with crackles heard best laterally and posteriorly. Cardiac exam revealed loud S2 sound. Abdominal examination revealed a single small nodule in the lower abdominal wall close to midline. The nodule was firm but non-tender on palpation. Liver was not enlarged and there was no splenomegaly. Skeletal muscles were wasted. Early finger clubbing was also appreciated.

CBC showed moderate eosinophilia. Liver function and kidney function were normal. Serum ferritin was 164 ng/ml (5-148), ESR was 12. Hb was 13.7 g/dl. Nitroblue tetrazolium was normal. Sweat chloride test was 44 Meq/L. Urine analysis was normal. Carcinoempryogenic antigen, alpha fetoprotein, and Beta-HCG were normal. Antineutrophil cytoplasmic antibody NKA, antinuclear antibodies and rheumatoid factor were negative. Immunoglobulins and tissue transglutaminase were normal. 2D echocardiography showed pulmonary hypertension with mean pulmonary arterial pressure of 70 mmHg. Skeletal survey, bone isotope scan and bone marrow biopsy were all normal.

Chest X-ray and chest CT scan showed multifocal nodules with ill-defined margins that were randomly distributed in both lungs with no predilection to any lobe and without cavitation (Fig. 1). Most of these lung nodules showed evidence of calcification. No mediastinal lymph node enlargement was noted. Abdominal CT scan with contrast showed multiple soft tissue attenuations in both
lobes of the liver. These lesions were variable in size and with ill-defined shaggy margins and diffuse non-homogenous enhancement during the venous phase (Fig. 2). No regional or para-aortic lymph node enlargement was noted. A small mass 1.5 cm in diameter was noted in the lower third of the right abdominal rectus muscle, which was strongly enhanced with contrast (Fig. 3).

Flexible bronchoscopy was performed and showed multiple small nodular lesions 1 cm below subglotic area on the right tracheal wall. Circular narrowing of the lateral segment of the middle lobe was also noted. Biopsy of the tracheal lesions showed fragments of moderately cellular proliferation of epithelioid to spindle shaped cells having large nuclei, prominent nucleoli and intracytoplasmic bubbly lumina. The cells were present in individual forms and in very small clusters embedded in a dense hyalinized stroma. Cells were tested positive for CD31 and CD34 markers but negative for CD1a and CK (Fig. 4). Liver biopsy showed a needle core of liver tissue replaced by a dense hyalinized stroma within which were embedded scattered large spindle to epithelioid cells, both in individual as well as in very small clusters and very short trabeculae. Cells also contained large nuclei, prominent nucleoli and intracytoplasmic lumina, some containing hemosiderin. No mitotic figures were seen. Immunohistochemistry of the cells revealed the same positivity for CD31 and CD34.

3. Discussion

This case of 12-year-old with Epithelioid hemangioendothelioma presented with simultaneously found multiple lesions in the lungs, trachea, liver and abdominal rectal muscle.

Most of reported cases of EH in the literature have single organ involvement. However EH can arise from many organs, including lungs, liver, bone, and soft tissue, simultaneously or sequentially. When this occurs, it may be difficult to determine if the tumor is multicentric from the beginning or if there is a primary lesion with metastases to the other organ tissue. Kalra et al. reported a 70-year-old female with simultaneous hepatic and pulmonary EH. Kas-teren et al. reported a single case of EH which was misdiagnosed initially as lung histiocytosis but was later found to have multiorgan involvement at autopsy. Adler et al. reported a case of a child with syncopal episodes who was found to have generalized multifocal EH lesions in bones, lung, kidney and liver. Recently Madhusudhan et al. reported an 11-year-old boy with hemoptysis who was diagnosed with EH simultaneously involving lung and liver. Jinghong et al. reported a 20-year-female patient with
indolent course of solitary pulmonary HE with bilateral multiple calcified lung nodules but without any mentioning of other organ involvement.6

Our case presented with respiratory symptoms, mainly cough and shortness of breath on exertion but with no symptoms related to her liver and abdominal wall involvement. Based on the likelihood of several organ involvements in patients with EH, some of which can be asymptomatic, careful and thorough search for lesions is strongly recommended in patients suspected or confirmed to have EH. Our patient was not aware of the lump in her abdominal wall. It was felt accidentally during superficial palpation of the abdomen. It may be useful, therefore, to palpate all the soft tissue in cases of visceral EH.

EH has never been reported before to affect abdominal wall muscles. Most soft tissue EH has been reported to occur in the lower limbs, head, neck and very rarely chest wall.9 EH has also been reported in association with congenital anomalies of the musculoskeletal system such as hemihypertrophy and scoliosis.14

Pulmonary hypertension has also never been reported in association with EH. Pulmonary hypertension in this case could be contributing or aggravating factor of the patient’s symptom of exertional dyspnea. Pulmonary hypertension in this case could be due to the chronic hypoxia, which developed secondary to the disseminated lung lesions or secondary to hypoxia-induced release of cytokines such as vascular endothelial growth factor VEGF. VEGF is strongly expressed in all angioproliferative plexiform lesions and in the lungs of patients with severe primary and secondary forms of pulmonary hypertension.15,16 Several recent reports have suggested an association between VEGF and EH. VEGF and its receptors were found to be elevated in a child with malignant EH as reported by Taege et al.17 Also, VEGF blood levels were decreased after treatment of a similar case of EH with Interferon-alpha.18 Moreover, Kim et al. demonstrated the presence of VEGF in tumor tissue that was taken from the lung metastasis of hepatic HE in a 42-year-old male with hypertrophic osteodystrophy.19

Our patient is also the first case reported with tracheal involvement in the form of localized intraluminal multiple nodules. All cases with pulmonary EH reported thus far had normal flexible bronchoscopy and no report of intraluminal airway involvement. Even in the 11-year-old male patient reported by Madhusudhan et al. with lung mass encasing the right intermediate bronchus, bronchoscopy did not show any abnormalities.8 Leleu et al. in one of three cases reported with pulmonary EH found that tracheal biopsy in one case was contributory to the diagnosis but didn’t mention whether they biopsied normally or abnormally appearing tracheal mucosa.7 In our case we found multiple small nodular lesions in localized area of the trachea where tissue biopsy was obtained and were confirmed to be EH lesions.

It is rare to have extreme weight loss with EH as in our case without significant severe liver involvement. Our patient had normal liver function and denied any abdominal complains. In most of cases reported, there is great degree of discrepancy between symptoms and the extent of organ involvement; and lesions could remain asymptomatic for several years.

We conclude that patients with EH can present with multinodular lesions involving more than one organ. This mandates a careful and thorough search for nodules in all visceral organs, bone and soft tissues. Symptoms are nonspecific and depend on the organ most aggressively involved.

Conflict of interest

None of the authors has any conflict of interest.

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