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Original Research Paper

Oncology

EPITHELIOID HEMANGIOENDOTHELIOMA OF THE PLEURA

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KEYWORDS :

INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is a rare neoplasm of vascular endothelial origin. EHE was first described in 1975 by Dail and Leibow, termed ``Intravascular bronchioalveolar tumor`` [1] due to its morphology and propensity for vascular invasion. In 1982, Weiss and Enzinger termed the tumor as `Epithelioid hemangioend othelio ma`. [2] Epidemiology is little known, because of its low incidence. It can arise in any organ, commonly arises in liver, lung, bone and soft tissue. Clinical behavior of EHE is intermediate between hemangioma and angiosarcoma. The natural history of EHE is highly variable. [2]

EHE can present in thorax as various manifestations. In typical pulmonary forms, it presents as either a solitary nodule, or more often as multiple small nodules. Pulmonary EHE involving pleura occurs in patients with disseminated disease. [3, 4] Primary pleural EHE is a very rare neoplasm of vascular origin. Pulmonary EHE has a chronic clinical course, but primary pleural EHE has potentially aggressive behavior. [2, 3] Pleural EHE mimics mesothelioma or adenocarcinoma. Distinguishing Pleural EHE from epithelioid angiosarcoma is also an issue of concern. Although there are no clearly identified risk factors, prior radiation therapy, exposure to asbestos and smoking are unproven risk factors. [2]

CASE REPORT:

Case 1; 27 years male, non-smoker presented with left sided chest pain and left pleural effusion in January 2010. He was treated with anti-tubercular therapy for two months for exudative pleural effusion. He underwent pleural biopsy for non-resolving effusion, showed chronic nonspecific granulomatous inflammation. Metastatic work up was negative. Further he was subjected to decortication and parietal pleurectomy. Pleurectomy specimen confirmed pleural EHE by immunohistochemistry (IHC). As he opted for supportive therapy, no chemotherapy was given. He died because of respiratory failure due to progressive disease in November 2010.

Case 2; 60 year male smoker, type 2 diabetic from 13 years, on oral hypoglycemic agents, presented in April 2010, with cough and breathlessness. On chest x ray, he had multiple nodules in the right pleura. Biopsy of the nodule reported as spindle cell neoplasm, low grade sarcoma. Further evaluation by whole body PET CT scan, had multiple right pleural nodules with minimal pleural effusion. He underwent decortications, pluerectemy specimen confirmed malignant EHE of pleura by IHC. Patient was treated with ifosfamide and Adriamycin 3 weekly for four cycles. Patient tolerated chemotherapy well. Follow-up whole body PET- CT scan after four cycle chemotherapy revealed hypermetabolic multiple right pleural nodules, erosion of right 7 rib, subcarinal node, right adrenal nodule and left parietal and cerebellar lesions. Further patient discontinued systemic chemotherapy and was given palliative radiotherapy to brain. Patient opted for supportive care, died of progressive disease in January 2011.

Case 3; 29 years female non-smoker presented with left sided chest pain and left pleural effusion in June 2010. She was treated empirically with anti-tubercular therapy elsewhere for three months for exudative pleural effusion. On re-evaluation for not responding to therapy, pleural biopsy revealed malignant neoplasm of pleura. PET-CT scan of whole body showed hypermetabolic lesion arising from the entire pleura of left hemithorax and no evidence of distant metastasis. Further patient underwent decortication, IHC confirmed the primary pleural EHE. Patient was treated with one cycle of cisplatin and etoposide chemotherapy. Further patient not willing to continue chemotherapy, she opted for supportive care. She died of respiratory failure due to progressive disease in April 2011.

DISCUSSION;

Pulmonary EHE is more common in young females, while most of the primary pleural EHE are in male. In our series we had two male and a female, age ranging from 27 to 60 years, indicating wide age range at the time of diagnosis. Etiology of pleural EHE is not very clear, possible risk factors which are reported are asbestos exposure, smoking and radiation exposure. [2] These risk factors were not associated in our cases except for smoking in elderly male. Most patients are symptomatic at diagnosis. They present with nonspecific pulmonary complaints, chest pain, cough and dyspnea that is often due to pleural effusion. [2] Hemoptysis reported occasionally in case series none of our patients had at presentation. The sign of Lesser Trelat is a paraneoplastic syndrome of unknown etiology that is marked by the sudden eruption of seborrhoeic keratosis in young patients, is noted in one patient. Multiple tumor types are associated with the sign of Lesser Trelat. [5] Two of our patients were treated with antitubercular therapy because of exudative pleural effusion, which is a usual early finding.

Common clinical and radiological features of lung tumors listed in table 1 & 2. Pleural cytology is inconclusive, thus pleural EHE is usually confirmed by thoracoscopy. [2, 5] Macroscopically, pleural EHE presents as plaques that constrain the lung and extend through fissure and interlobar septum. Microscopically, it is an angiocentric tumor with epithelioid like cells rounded or speculated polygonal with abundant eosinophilic cytoplasm and intracellular vacuoles. These cells form short cords or nests in a myxoid and hyaline stroma with neoformed blood vessels. Electronmicroscopy shows the characteristic Weible and Palade cytoplasmic bodies. [3] While the clinical and gross features of Pleural EHE may mimic mesothelioma, IHC stains for vascular cells such as CD31, CD34 and factor VIII clearly differentiate two diagnosis.[2] (Table 3) Differential diagnosis includes metastases, mesothelioma, sarcomas such as angiosarcoma

or Kaposi sarcoma, angiolypoid hyperplasia, Kimura`s disease, tuberculosis and pseudo pyogenic granuloma. [5]

Clinical course of pleural EHE is unpredictable. Advanced cases present with metastatic involvement of heart, lung and retroperitonium. Hilar and Mediastinal lymphnode involvement is associated with worse outcomes. The main cause of death is respiratory failure. [1, 2] Surgical resection is the treatment of choice for localized disease. Surgical therapies most frequently used ranges from invasive procedures, including aspiration of hemorrhagic effusion. Pleurectomy, decortication, pleurectomy plus resection of lung and diaphragm, visceral and parietal pleurectomy plus partial resection of diaphragm and metastatectomy. Radiation therapy also tried for primary and palliation of metastatic lesions. [2, 3, 4] Pleural EHE are radio and chemo resistant tumors.

There is no consensus regarding therapeutic regimen because of rarity of tumor. Chemotherapy regimens do not obtain homogeneous response. Single agent chemotherapy that are tried include mitomycin C, 5-flurouracil, tegafur, cyclophosphamide, ifosfamide, vincristine, vinorelbine, cisplatin, carboplatin, adriamycin, dacarbazine and paclitaxol, and multiple combinations of these agents. [2, 3, 5, 6] Pinet et al described one case of complete remission of pleural EHE following six courses of carboplatin and etoposide. Reports with interferon are encouraging. Roudier – Pujol et al reported pleural EHE metastatic to skin, liver, lung and bone, demonstrating partial remission with interferon α 2A, the presence of estrogen and progesterone receptors has been reported in pleural EHE, indicating the potential role of hormonal therapy. Retinoids and interleukin 2, inhibit endothelial cell proliferation and migration, shown a low rate of response. High dose chemotherapy with hematopoietic rescue has been reported. Lung transplant has been proposed. [2, 5, 6] Anti angiogenic drugs have been tested in pleural EHE due to its vascular origin. Bevacizumab, monoclonal antibody against vascular endothelial growth factor, did not show benefit with chemotherapeutic agents. Prolonged stable cases have been reported with 100 mg daily thalidomide therapy. [5]

The mean survival in pleural EHE is over 10 – 12 months. The presence of symptoms or pleural effusion, liver metastases and lymphatic, intravascular or intrabronhial spread predicts survival. Thus at present management should emphasize on maintenance of quality of life and performance status. This may include palliative pleurodesis in inoperable cases and systemic treatment in patients with better general condition and organ function in order to prolong the survival. [2, 3, 5]

Till date only 27 cases of primary pleural EHE are reported in English and 3 cases in other literature. (Table; 4) We are reporting three cases, two male and one female. Chest pain, pleural effusion and pleural thickening are the most common clinical presentations, were also present in our cases. Two of them were treated as tubercular pleural effusion elsewhere, before presenting to our center. All cases were diagnosed by clinical, radiological, histopathological studies and confirmed by immunohistochemistry. Two young patents survived for 11 months and one elderly man for 10 months from the onset of symptoms. As reported, our cases also showed the aggressive behaviour. This is the first case series from India and third largest case series reported in literature.

Table:1	**Common Clinical features of lung tumors;[2,3,4]**				
	Pleural EHE	Pulmonary EHE	Adenocarcinoma	Angiosarcoma	Mesothelioma
Age	Older	Young	Middle/older	Middle/older	Older
Sex	M	F	M	M	M
Asbestos exposure	+/-	infrequent	_	Rare	+++
Cough	+	Non productive	+	+	Persistent
Dyspnea	+	+	+	+	Rapid onset
Chest pain	+	+	+	+	+
Weight loss	_	_	+	+	+

Table: 2	**Common Radiological Features of lung tumors;[2,3,4]**				
	Pleural EHE	Pulmonary EHE	Adenocarcinoma	Angiosarcoma	Mesothelioma
Pleural effusion	Loculated	+	+	+ Hemorrhagic	+
Pleural thickening (CT scan)	Nodular, smooth	+	Nodular, smooth	Circumferential, nodular, parietal pleural	Circumferential, nodular, parietal pleural
Associated adenopathies	Infrequent	rare	++	+	++
Volume loss of hemithorax	+	_	_	_	+
Other features (on chest x ray/CT scan)	_	Poorly defined interstitial, nodular lesions with soft tissue thickening	Multiple peripheral density	_	Mediastinal pleural involvement, invasion of chest wall
Metastasis	Rare	Rare	Yes	Rare	Yes

Table:3	**Differential diagnosis of EHE by Immunohistochemistry [3,4]**								
	CD31	CD34	CD99	CK	Ki67	Factor VIII	Calretinin	Vimentin	Others
EHE	+	+	_	+/-	+	+	_	_	_
Epithelioid angiosarcoma	+	+	_	+/-	+++	_	_	_	_
Mesothelioma	_	_	_	_	+++	_	+	+	Wt1+ CK5/6+
Adeno carcinoma	_	_	_	+	+++	_	_	_	TTF1+ CEA + Mucins+
Primary fibrous tumor of pleura	_	+	+	_	+/-	_	_	+	Bcl2+ EMA+

Desmoid tumor of pleura	_	_	_	_	-	_	_	+	Desmin + SMA+ S100-

Table; 4	Case reports of pleural EHE in Literature (1 to 6, English; 7 & 8 Portuguese; 9 Japanese)						
Sl No.	Reference No.	No. of cases	Age (years)	Male	Female	Treatment	Survival (months)
1	2	22	22-77 average	18	4	Surgery, radiation, chemotherapy	Median8 (range 1-24)
2	3	1	80	1	_	Surgery + BSC	6
3	4	1	58	_	1	Surgery + BSC	3
4	5*	1	42	1	_	Surgery + chemotherapy (carboplatin+etoposide+bevacizumab)	6
5	6	1	46	_	1	Surgery + Chemotherapy (carboplatin+etoposide)	23
6	5	1	85	1	_	BSC(biopsy only)	8
7	7	1	52	_	1	NR	29
8	8	1	65	_	1	Surgery + Chemotherapy (carboplatin+etoposide)	13
9	9	1	77	_	1	NR	NR

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