Case Report

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Epithelioid haemangioendothelioma—a rare cause of right pleural effusion and multiple primary nodules: Case report & review of the literature

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Summary

Pulmonary epithelioid haemangioendothelioma (PEH) is a rare vascular neoplasm. The thoracic manifestation of this disorder is identified via three major imaging patterns, namely multiple primary nodules, diffuse infiltrative pleural thickening, and multiple pulmonary reticulonodular opacities. The commonest pattern of presentation is bilateral multiple nodules. Diagnosis is based on histopathological findings and verified by positive immunochemistry staining. Patients with PEH are usually asymptomatic. We report the case of a 51-year-old female who presented to our facility with a five-month history of cough, pleural nodularity, and pleural effusion. She underwent surgical washout with right pleural biopsies that showed a malignant epithelioid tumor with features of epithelioid haemangioendothelioma (EH). A CXR after treatment did not demonstrate a residual pleural effusion.

Keywords

Epithelioid haemangioendothelioma, case report, literature review

Introduction

Epithelioid haemangioendothelioma (EH) was first described as a vascular tumor of soft tissue with borderline malignancy.[1] EH acts in a locally aggressive fashion, with very rare occurrence of metastases. Patients with primary pulmonary EH (PEH) are usually asymptomatic, though sometimes they present with nonspecific symptoms. Chest Xray or CT usually reveals the presence of bilateral pulmonary lesions. A lung biopsy is usually required, and surgery is recommended in the presence of more than one unilateral nodule.[2] In this paper, we discuss the case of a 51-year-old female who presented to our facility with a five-month history of cough, pleural nodularity, and pleural effusion.

Case presentation

A 51-year-old female patient known case of Asthma and Gastro-oesophageal reflux disease (GORD) presented with a five-month history of persistent dry cough was referred to our facility.

On examination, vitals were within normal range. On auscultation, the base of the right lung was dull on percussion, and the sound of breathing was reduced on the right lung region. On the X-ray, a pleural effusion could be detected on the right side of the chest. The remainder of the examination was unremarkable.

Her lung function tests (LFTs) showed a restrictive pattern with FEV1 of 0.99 L (42% predicted), an FVC of 1.38 L (47% predicted) and an FEV1/FVC ratio of 0.72. Vital capacity was 48% of predicted, residual volume was 43% of predicted.

Thus, the decision was made to proceed with Video-assisted thoracoscopic surgery (VATS) for evaluation and treatment. Intra-operatively, a loculated effusion with overall impression of stage III empyema was noted. Extensive biopsies taken from multiple pleural sites and a right lower lobe wedge biopsies were sent for histopathological analysis. Histopathology showed pleura and underlying lung parenchyma infiltrated by mildly atypical ovoid and epithelioid cells forming small nests and cords in a myxohyaline stroma, and focally showing irregular vasoformative structures. Some tumour cells had cytoplasmic vacuoles containing red blood cells, and some had cytoplasmic vacuoles with septation. On immunohistochemistry the tumour cells were positive for vascular markers CD31, CD34 and ERG. Next Generation Sequencing found a CAMTA1-WWTR1 fusion which confirmed the histological diagnosis of epithelioid haemangioendothelioma.[3] The patient's surgical drain was removed on day three post operatively where her chest x-ray and blood tests were satisfactory.

Discussion

Epidemiology and number of cases in literature

PEH is an uncommon malignant vascular neoplasm, of low-to-intermediate grade malignancy which can present

in the lung or pleura as either solitary or multifocal disease.[4] Originally thought to be an epithelial tumour, it was originally called intravascular sclerosing bronchioloalveolar tumour (IVBAT), but was subsequently recognised to derive from endothelial cells[5] and reclassified as a primary vascular tumour. More than 120 cases have been reported so far in the literature,[6] with patients having a mean (SD) age of 40.1 (17.5) years, and 73% of them being females.[7] Our patient, a 51-year-old female, fits this demography. Patients may present with cough, chest pain or haemoptysis but 20% are asymptomatic. It presents in adults over a wide age range. In many cases, physical examination presents a normal result, but there have been several reports of pleural effusions and digital clubbing.

Imaging

The size of the nodules may reach 2cm, but in most cases, they remain within the ≤1cm range. Nodules usually occur near the bronchi and medium-sized vessels. Some authorities suggest running a diagnostic test using 18F-fluorodeoxyglucose positron emission tomography[1] as this is a promising method by which to assess EHE patients. However, since PEH may be overlooked by PET, it is best utilised in conjunction with CT or MRI to provide the most accurate results.[1]

Pathological findings

Histologically EHE is characterised by epithelioid cells with solid and cord like architecture in a myoxohyaline stroma. Tumour cells have moderate amounts of eosinophilic cytoplasm with intracytoplasmic vacuoles which may contain red blood cells.[8] The tumour is often grows around arterioles, venules or lymphatics and can show cystic degeneration and haemorrhage. Morpholically these tumour can mimic adenocarcinoma, epithelioid sarcoma and other epithelioid neoplasms, and diagnosis requires confirmation by immunohistochemistry and molecular testing. On immunohistochemistry tumour cells express endothelial markers including CD31 and CD34, as well as showing focal cytokeratin expression.[3] EHE has a recurrent t(1;3)(p36;q23-q25) translocation resulting in fusion of WWTR1 (3q23-q24) to CAMTA1 (1p36) in 90% of cases.[3] Around 5% of cases have a YAP1-TFE3 fusion gene, show distinctive morphological features including solid morphology and formation of vascular spaces and tend to arise in a younger age group [Antonescu]. Clonality studies show that in patients with multifocal tumours, these are clonally related and arise from local or metastatic spread from a single primary tumour.

Treatment

PEH treatment is non-standardised. Surgery applies when there is a single pulmonary nodule or unilateral multiple nodules.[1] Transplant of the lung should be applied in patients experiencing vascular infiltration. Some authorities have reported various chemotherapies for metastatic or unresectable PEH, though effectiveness varies.[1] Hormonal therapy (progesterone and antiestrogens) is believed to play a strong role in cases of diffuse disease where the progesterone and estrogen receptors are expressed by neoplastic cells.[4]

Prognosis

Although the prognosis of primary pulmonary angiosarcoma is worse than that of pulmonary EHE, it is difficult to predict due to the tumours' varied aggressiveness. A worse prognosis has been linked to respiratory symptoms, weight loss, anaemia, extensive lymphangitic, interstitial, intravascular, or endobronchial tumour dissemination, pleural effusion, hilar metastases, liver metastases, peripheral lymphadenopathy, and spindle cell histology. Hemorrhagic symptoms, such as hemoptysis and hemorrhagic pleural effusion, have been recognised by Bagan et al. as important prognostic indicators.[1] Less than one year to more than 20 years of survival have been documented. A few instances of spontaneous regression have been documented. Removing a single or a small number of nodules, radiation therapy, interferon, and chemotherapy drugs like mitomycin C, 5 fluorouracil, cyclophosphamide, vincristine, Adriamycin, and cisplatin are some of the different treatments available.

Radiotherapy and chemotherapy are frequently used to treat distant metastases as well as intrathoracic tumour spread. Due to the tumor's general slow development, radiation therapy is ineffective, and chemotherapy appears to have no added advantages. "Watchful waiting" has been suggested in asymptomatic patients with bilateral tumour nodules to prevent therapeutic adverse effects. Long-term survival in patients who received no therapy has been documented.

There is a 60% five-year survival rate (ranging from 47–71%). As a matter of fact, two groups of PEH appear at the clinical presentation: an asymptomatic group and either a unilateral multiple nodule or a solitary pulmonary nodule. In many cases, this can be managed with surgery, and patients are extremely unlikely to suffer lymphatic invasion. Prognosis is favourable, with a 10-year median survival range. The symptomatic group presents with several bilateral pulmonary nodules and pleural effusion with very minimal response to chemotherapy. This group has poor prognosis, with mortality being attributed to pulmonary insufficiency due to increasing number of nodules.[9] The prognosis of PEH, on the other

hand, is determined by the presence of pleural effusion, hemorrhagic signs (alveolar hemorrhage and/or hemoptysis), and anaemia. Individuals presenting with pleural effusion have a 2% five-year survival rate, while patients without effusion have a 73% five-year survival rate.[10]

Conclusion

The case study illustrates unusual PEH in a 51-year-old female patient. PEH was a fortuitous discovery, and diagnosis was confirmed via histological, immunohistochemical and molecular analysis of a lung biopsy. There has been no validation of any standardized treatment and treatment is not necessary in asymptomatic conditions. In cases where a single nodule is present, surgery suffices as the treatment of choice. Prognosis is variable, though the condition tends to evolve slowly except when complicated by pleural effusion, hemoptysis, hemothorax, hepatic spread, or mediastinal lymphadenopathy. It is important to establish an international clinical registry for this rare neoplasm, and further investigations are essential to elucidate disease progression and therapeutic options for PEH patients.

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