Primary Ewing sarcoma of the lung: a challenging case

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Abstract

Ewing sarcoma usually develops in the second decade of life as a primary osseous malignancy. An extraskeletal primary source of this condition from the lung parenchyma is extremely uncommon. We report the case of a 33-year old man with primary Ewing sarcoma of the lung diagnosed upon postsurgical histological examination. Initially presenting with unilateral pleural effusion, our patient underwent various investigations before final diagnosis. This case report reviews the available literature of similarly reported cases and discusses the current developments on managing this rare and aggressive disease. As a supplementary learning point, this case reminds us always to consider unusual possibilities and seek further sub-specialist opinion when presented with unresolved clinical and radiological abnormalities that require further exploring beyond the primary line of investigations and treatment.

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Introduction

We present a case that highlights the need for broad differential diagnoses in all patients presenting with a unilateral pleural effusion. Pleural malignancy needs to be considered even in young patients and performing early diagnostic aspiration is paramount. Thoracic ultrasound assessment and discussion with experienced radiology colleagues can help ensure safe chest drain placement and early evaluation for underlying masses.

Case presentation

A 33-year-old non-smoker Caucasian male was admitted to hospital with a six-month history of progressive dyspnoea. The patient had past medical history of HLA-B27 associated arthropathy and had recently stopped methotrexate as he planned to start a family. Other than shortness of breath, he described the presence of a persistent mild pleuritic chest pain which radiated to the posterior chest wall upon upper body movement. He denied any history of fever, productive cough or recent chest trauma. He was not anticoagulated and had no history of bleeding tendencies. On examination, the patient appeared pale and clammy but apyrexial. There was no clubbing and he appeared euvolaemic. No cutaneous lesions were observed. There was reduced air entry throughout the right lung and tachypnoea (respiratory rate 24 breaths/min). No abdominal masses were found. He was alert and orientated throughout history taking and examination.

Initial investigations of note were markedly raised inflammatory markers (white blood cell count 20.2 x 109 cells/l, C-reactive protein 219.5mg/l) and normocytic anaemia (haemoglobin 104g/l). Erythrocyte sedimentation rate was 38mm/hr. Electrocardiography showed sinus tachycardia at a rate of 135 beats/min and the initial chest X-Ray displayed general right-lung shadowing suggestive of pleural effusion. Blood culture and atypical infection screening were negative. Arterial blood gas was unremarkable apart from a marginally raised lactate. The patient was admitted with a differential diagnosis of right-sided parapneumonic effusion or empyema. Intravenous antibiotics, fluids and analgesia were started.

Thoracic ultrasound revealed a small to moderate right posterior echogenic pleural effusion with lung collapse. The left lung appeared normal. Pleural aspiration revealed dark haemorrhagic fluid. In the context of the patient appearing unwell and the fluid not being simple in nature,

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Figure 1: CT thorax-abdomen-pelvis showing high density collection in the right upper lung lobe

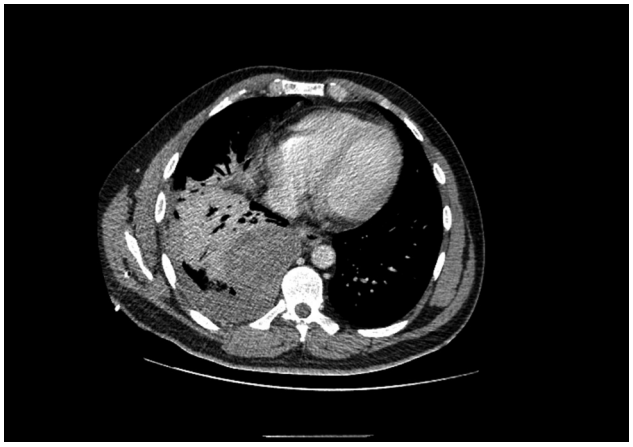
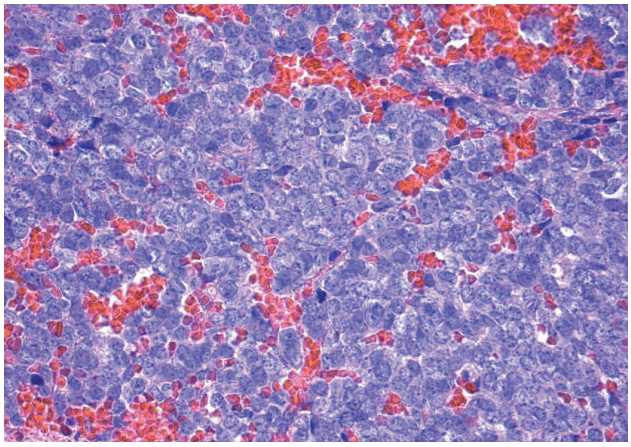


Figure 2: Post-VATS biopsy displaying small round blue cell tumour after haematoxylin andeosin staining (at x400 magnification)



a 12F Seldinger chest drain was inserted. In light of the haemorrhagic fluid, a wider differential diagnosis was formulated following aspiration which included iatrogenic haemothorax, previous trauma, malignant effusion or pulmonary embolism. Further investigations were organised including a CT pulmonary angiogram, CT thorax-abdomen-pelvis and a repeat full blood count.

CT thorax-abdomen-pelvis (Figure 1) described a small hydropneumothorax and 8.4 x 7.2cm high-density collection in the right upper lung lobe. The reporting radiologist felt this was most likely secondary to an iatrogenic haematoma. Approximately two litres of haemorrhagic fluid was drained in the next 24 hours. Pleural fluid cytology and microbiology showed normal findings, protein level was 67g/l and lactate dehydrogenase level was 1996 IU/l. Excessive red blood cells, neutrophilia and monocytosis were reported. In the context of a pleural collection and uncertain diagnosis, we referred the patient to the cardiothoracic ward for video-assisted thoracoscopic surgery (VATS). CT pulmonary angiogram did not suggest the presence of pulmonary embolism.

Biopsy of the right upper lung lobe that was performed during VATS identified a poorly differentiated tumour in the area surrounding the hematoma, likely to be an angiosarcoma. The malignancy was not deemed fully resectable. Postsurgical histology (Figure 2) revealed a small round blue cell tumour after haematoxylin and eosin staining, diagnostic of the Ewing family of tumours. Diagnosis was confirmed by molecular profiling.

The consensus of the multi-disciplinary team (MDT) was that this was a lung angiosarcoma associated with Ewing sarcoma. The patient was subsequently referred to the tertiary sarcoma unit to receive further care. The patient was managed with intensive chemotherapy including a regime of vincristine, ilfosfamide, doxorubicin and etoposide (VIDE). He was able to tolerate six cycles of chemotherapy and radiology in November 2018 revealed much decreased tumour size. However, further risks of metastatic dissemination are present; spinal metastases are considered to be most likely due to the tumour's posterior anatomy within the base of the lung. In November 2018, the patient was enlisted on the EURO EWING 2012 (EE2012) pathway as part of the international randomised controlled trial for the treatment of newly-diagnosed Ewing Sarcoma. EE2012 is an international randomised controlled trial comparing the event-free survival rates when participants are treated with two different chemotherapy regimens (VIDE strategy and the vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide (VDC/IE) strategy). The secondary aim of the trial is to compare the relative toxicity that participants experience prior and after using either of these two regimens to control the primary tumour.[1] The clinical effects of adding zoledronic acid to the treatment regime is also being investigated.[2] Another key component of this trial is to determine informative biomarkers which could be applied for assessing disease progression and prognosis as well as response to the treatment administered[1]

The patient underwent radiotherapy to the primary tumour and the right hemithorax at the local tertiary cancer centre. Further surgical intervention was considered. Decision to operate or not hinged on factors such as tumour size and spread, previous success of radiotherapy, preoperative fitness and patient choice.[3,4] After extensive MDT discussion, the patient was eventually deemed unsuitable for surgical treatment and continued management under the EURO EWING 2012 pathway.

Discussion

Ewing sarcoma was first described and named after the American pathologist Dr James Ewing in 1921. It is an uncommon malignancy which usually first presents as an undifferentiated primary bone tumour. Ewing sarcomas are neuroectodermal tumours which are histologically identified as monotonous small round cells arranged in sheets. Incidence in the USA population is one per million and it most commonly affects teenage age group.[5] Diagnosis after the age of 30 is unusual. The disease is more common in males and in white Caucasian populations than other ethnic groups.[5] The Ewing family of tumours (EFT) has now been extended to include primitive neuroectodermal tumours as

they share similar histological and immunohistochemical characteristics.[6] This group includes malignant small cell tumours of the chest wall (also known as Askin tumour) and atypical Ewing tumours.[7] Although the aetiology of this group of tumours is not fully understood, there is an established correlation with chromosomal translocations: the EWS gene on chromosome 22 and the FLI1 gene on chromosome 11 in 85% of cases.[8]

For Ewing tumours, the most common anatomical sites involved at first presentation are the pelvis and long bones. Primary tumours arising from soft tissues are less common and are separately classified as extraosseous Ewing sarcomas.[8] Although only a quarter of patients present with distant metastatic disease, up to 90% will have relapses later in life, suggesting subclinical metastatic spread early in the clinical course. Unlike osteosarcoma, however, Ewing sarcoma is sensitive to both radiotherapy and chemotherapy.[9] Survival rates reported are variable and depend hugely on the extent of disease spread at presentation.[8,10] Patients with metastatic disease at first presentation have a 5-year survival rate of 20 to 30%.[9] Though younger age at first presentation may improve survival rate, other factors such as size of primary tumour are not considered to affect prognosis.[11]

Primary EFT of the lung is extremely rare and our literature review identified only 17 reported cases.[2,9,12] These were treated with various combinations of surgical resection and chemotherapy with or without radiotherapy. Due to the lack of data available, current evidence is insufficient to form a conclusion on the optimal treatment modalities of primary EFT of the lung, though patients with primary extraosseous Ewing sarcoma are shown to have better outcomes with surgical resection.[11] Out of 11 patients whose outcomes were available, six survived after a two-year follow-up period. Amongst the five patients who died within two years of resectional surgery, two of them received only surgical treatment.[12]

Conclusion

Though extraosseous Ewing sarcoma is a rare diagnosis, this case emphasises the importance of considering unusual differentials when the conventional line of investigations does not reveal a diagnosis and standard treatment does not result in resolution of unilateral pleural effusions. Because of the risk of invasive investigations, similar cases of unclear diagnoses after primary investigations and treatment should be discussed with an experienced MDT prior to further intervention.

Pulmonary malignancies can present with pleural effusions which may obscure the underlying primary tumour. Early histological sampling and CT staging is advisable. In extraosseous Ewing sarcoma, the extent of tumour development and the patient's fitness and preferences should guide decision-making on management: surgical resection, systemic therapy or a combination of both. The uncertainty regarding optimal management due to the lack of a clear evidence base for treatment needs to be explained to patients. It is hoped that increased participation in randomised clinical treatment trials of extraosseous Ewing sarcoma will provide more conclusive evidence to guide clinicians in this decision-making process.

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