CASE REPORT

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Primary Clear Cell Sarcoma of the Lung: a Case Report

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ABSTRACT

Background: Clear Cell Sarcoma of Soft Tissue (CCSST), or melanoma of the soft part, is a rare, aggressive tumor that originates in the aponeurosis and fasciae of the distal parts of the extremities. Reports from other sites of the body are rare. **Objective**: We are reporting an extremely rare tumor that presented as a central left-sided lung mass and found to be clear cell sarcoma of soft tissue. **Methods:** We report a 24-year-old male patient presented with recurrent attacks of left-sided chest pain associated with cough and dyspnea. **Results:** Imaging showed a central left-sided 8*5.5*5 cm lung mass. The age of the patient and the radiological characteristics of the lesion were suggestive of a benign pathology. After histopathological assessment of the lesion, suspicion of the malignant process was raised, mainly melanoma of soft part and PEComa. The patient underwent left-sided pneumonectomy. The postoperative histological examination, immunohistochemical findings including positive staining for S-100, HMB-45, and Melan-A, and positive FISH study for EWSR1 gene rearrangements supported the diagnosis of CCSST originating primarily in the major fissure of left the lung. **Conclusion**: The rarity of CCSST in general and tumors originating in the lung primarily raise the challenges in hypothesizing a differential diagnosis, choosing proper investigations and treatment methods. The histological examination, immunohistochemical, and cytogenetics of the tumor are mandatory to reach the final diagnosis.

Keywords: Clear cell sarcoma, primary pulmonary melanoma, EWSR1 gene rearrangement.

1. BACKGROUND

Clear Cell Sarcoma of Soft Tissue (CCSST), or melanoma of the soft part, is a sporadic tumor originating from neural crest cells. It was first described by Enzinger in 1965 (1). It occurs mainly in the lower extremities, especially around the ankle joint (2). Other sites, including the head and neck, kidneys, gastrointestinal tract, chest wall, mediastinum, trunk, and penis, have been described (2). To our best knowledge, three cases were reported in the lung (3, 4). Herein we describe a case of CCSST, which presented as a central left-sided lung mass.

2. OBJECTIVE

The aim of this case report was to describe an extremely rare tumor that presented as a central left-sided lung mass and found to be clear cell sarcoma of soft tissue.

3. CASE REPORT

A 24-year-old male, a smoker of 10 pack-year, was referred to the thoracic surgery outpatient clinic at the King Abdullah University Hospital. His chest X-Ray showed a central left lung radiopaque lesion measuring around 8*5 cm. He reported recurrent attacks of left side localized chest pain for the last three years. These attacks were associated with occasional dyspnea and dry cough. Other respiratory or constitutional symptoms were denied, and the physical examination revealed no relevant physical sign. The computer tomography CT of the chest showed a well-defined heterogeneous 8*5*5.5 cm enhancing soft tissue mass in the base of the major fissure with extension to both lobes of the lung. The lesion was abutting but not invading branches of the pulmonary artery. It contained peripheral popcorn calcification and fluid attenuation areas consistent with necrosis (Figures 1a, 1b). Although the features are consistent mostly with a benign pathology, the presence of central necrosis was suspicious. Accordingly, fiberoptic bronchoscopy revealed

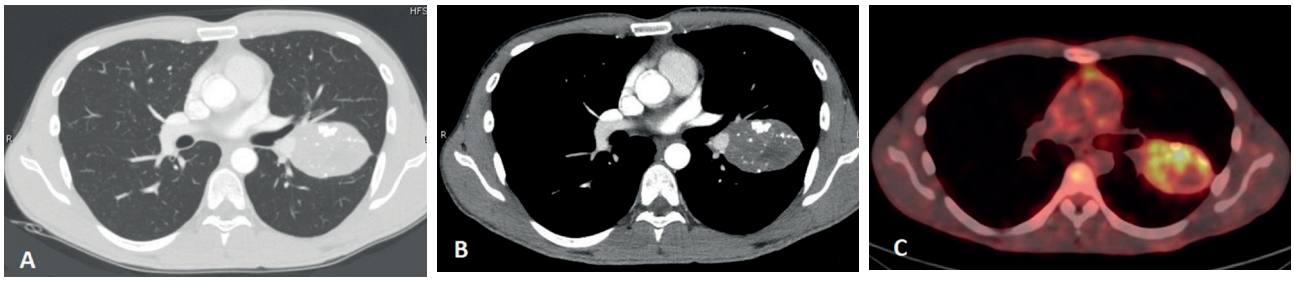

Figure 1. a) CT pulmonary window shows a well-defined heterogeneous 8*5*5.5 cm enhancing soft tissue mass in the base of the major fissure with extension to both lobes of the lung. b) CT mediastinal window shows the lesion abutting but not invading branches of the pulmonary artery, peripheral popcorn calcification, and areas of fluid attenuation consistent with necrosis. c) PET-CT shows mildly hypermetabolic areas at the periphery of the lesion with central photopenia.

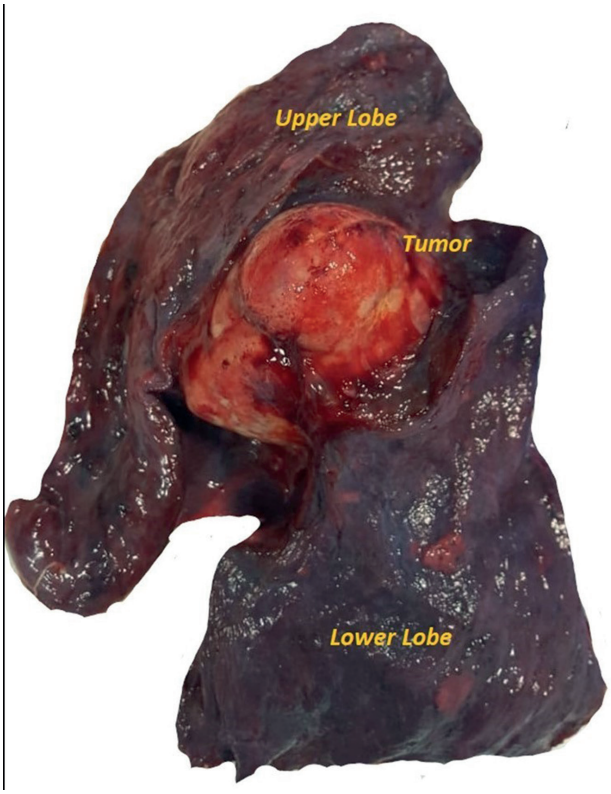

Figure 2. A gray tan soft tissue mass in the fissure invading both lung lobes.

the absence of endobronchial pathology. A transbronchial biopsy was not done due to the anatomical location anterior to the pulmonary artery. A CT guided tru-cut biopsy revealed microscopic features consistent with inflammatory myofibroblastic tumor (IMT), despite some atypical large cells with vesicular nuclei, which raised the possibility of a malignant process.

Further immunohistochemical stains including CD15, ALK-1, STAT-6, CD34, CD117, CD23, and MPO immunostains were performed and were negative. However, the melanocytic markers HBM 45 and Melan-A showed focal positivity. PEComa and, to a lesser degree, melanoma could not be excluded. The integrated positron emission tomography - computer tomography (PET-CT) showed mildly hypermetabolic areas at the lesion's periphery with central photopenia on PET images (Figure 1c). No other hypermetabolic areas could be detected. After assessment of the patient's pulmonary function, the decision was to go for resection. Due to the size of the lesion, we opted for an open approach. After double--lumen intubation, a muscle-sparing anterolateral left thoracotomy was performed and revealed gray tan soft tissue mass in the fissure invading both lung lobes (Figure 2), so left-sided pneumonectomy and lymphadenectomy were performed. The postoperative period was uneventful, and the patient was discharged on the fourth postoperative day. The pathological examination showed a high-grade tumor composed of pleomorphic neoplastic cells with mixed spindle and epithelioid appearance arranged in fascicles, sheets, and nested focal patterns. Of all performed immunohistochemical stains HMB 45, Melan A, CD99, and bcl-2 showed diffuse positivity and focal positivity for S100 (Figures 3a, 3b,3c,3d,3e). Other stains, including SOX10, were negative (Figure 3f). The diagnosis was made based on the fluorescence in situ hybridization (FISH) technique for identification of Ewing Sarcoma breakpoint Region 1 locus (EWSR1) gene rearrangement (22q12) (Figures 4a,4b), which is in association with Melan-A, HMB-45, S-100 and CD99 led to the diagnosis of CCSST primarily originating in the lung.

4. DISCUSSION

Clear Cell Sarcoma of soft tissue is a rare, aggressive malignant tumor, which is also known as melanoma of soft tissue part because it shares immunohistochemical and ultrastructural characteristics of malignant melanoma (2). In around 83% of cases, it arises mainly in the aponeurosis and fasciae of the lower and upper extremities, especially around the ankle joint. It also affects the trunk (5). The literature described sporadic cases affecting different locations of the body like scapula, chest wall, penis, dermis, and tongue (2). Clinically those tumors affect the young age group in the second and third decade of life. Nevertheless, it has been described in age groups' extremes ranging from 2 years to 83 years old with no noticeable gender difference (2).

The tumor is slowly progressing. It is associated with pain and tenderness in up to two-thirds of the cases. The size of the reported tumors varies from 0.5-15 cm (2, 5). CCSST are considered aggressive tumors with a tendency to metastasize, commonly to regional lymph nodes followed by the lungs and the bone (6). The size of more than 5cm is considered the most important and the only

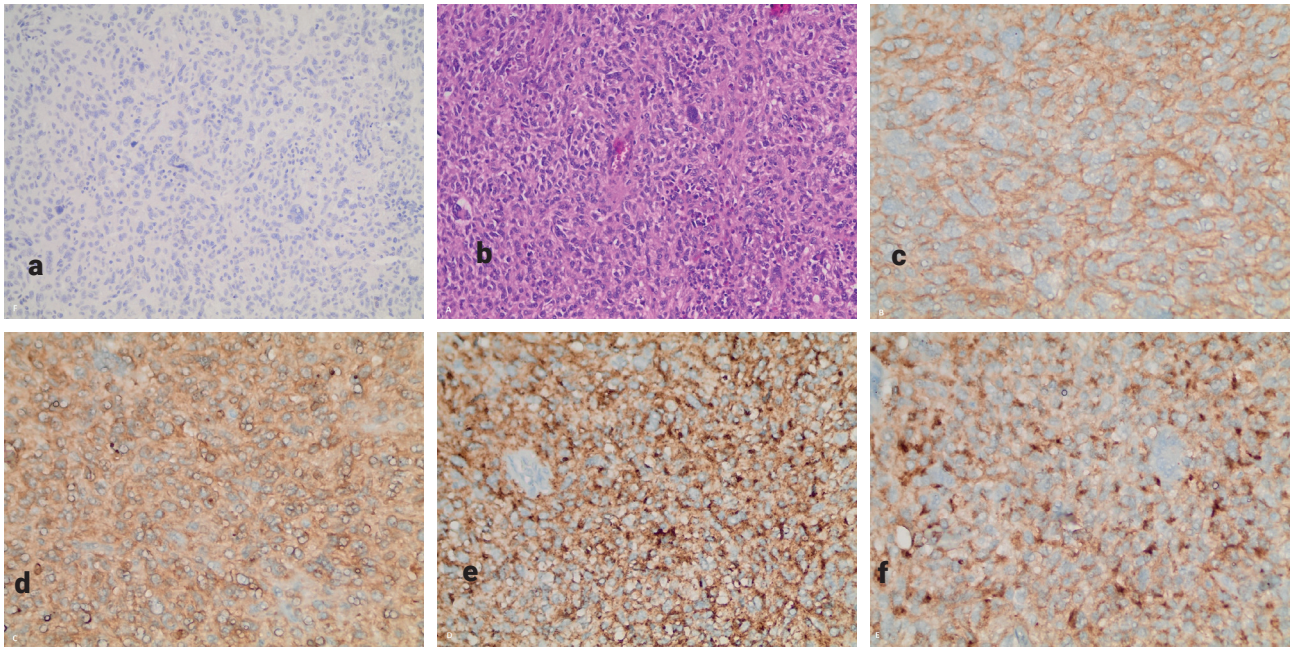

Figure 3. a) H&E demonstrates a high-grade tumor composed of mixed bizarre neoplastic cells with spindle and epithelioid appearance, arranged in fascicles, sheets, and nested focal pattern (X400). b) CD 99 immunostain shows diffuse membranous staining in most of the tumor cells (X400). c) bcl-2 immunostain shows diffuse staining in most of the tumor cells (X400). d) HMB 45 immunostain reveals strong and diffuse staining in most of the tumor cells (X400). e) Melan A immunostains shows diffuse staining in most of the tumor cells (X400). f) a negative SOX 10 immunostain (X400).

prognostic factor after multivariate analysis of other studied prognostic factors like tumor necrosis, TNM staging, DNA content, surgical margin, and depth of invasion (5).

The rarity of occurrence of the CCSST in sites other than the extremities, mainly when it arises in the intraabdominal or intrathoracic cavities, presentation at a young age group, and the slow progression of the lesion result in a real challenge to the treating physicians. The challenge is mainly during the diagnostic phase. The constellation of the three factors mentioned above has created a real challenge in our case's diagnostic process.

The usual investigation of choice for the extremity CCSST is a magnetic resonance imaging MRI that shows T1 hypointensity, T2 hyperintensity, and gadolinium uptake (2, 6). This imaging study usually is followed by histological diagnosis done by different types of biopsy methods. The histological diagnosis is also challenging as it has a broad spectrum of differential diagnoses that include malignant melanoma, paraganglioma-like dermal melanocytic tumor, clear cell myomelanocytic tumor (PEComas), malignant peripheral nerve sheath tumor, cellular blue naevus, alveolar soft part sarcoma, paraganglioma, epithelioid sarcoma, and synovial sarcoma, especially the monophasic type (2, 6). In general, CCSST does not express prominent pleomorphism or high mitotic count unless the tumor is recurrent or has metastasized. The significant pleomorphism encountered in our case is unusual for primary CCSST, which we believe is a peculiar feature and should not exclude this tumor from the differential diagnosis. The diagnosis of

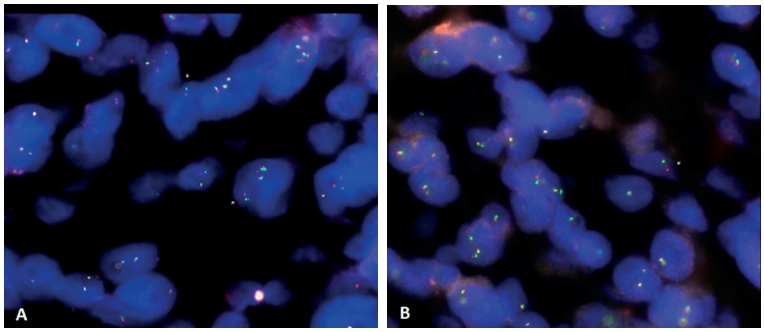

Figure 4. a and b: Fluorescence in situ hybridization FISH was performed using Vsys LSI EWSR1 dual color, break apart rearrangement probe. This probe hyperdizes to chromosome 22 at the band (q12.2). (spectrum green on the centromeric side and spectrum orange on the telometric side of the EWSR1 gene breakpoint. A total of 200 interphases were analyzed. Split signals were observed in 35% of the tumor, indicating EWSR1 gene rearrangement positive cells.

CCSST relies on fluorescence *in situ* hybridization identification of rearrangement of the EWSR1 locus, which in most cases leads to fusion of the EWSR1 gene with the activating transcription factor-1 gene (ATF1) in a recurrent translocation (12;22) (q13; q12). This translocation is not present in other mentioned differential diagnoses, especially melanoma (2-6). Other supportive immunohistochemical studies showed antigens' expression associated with melanin synthesis, including diffuse cytoplasmic immunoreactivity with HMB-45, nuclear and cytoplasmic immunoreactivity to S100 protein, and reactivity with the microphthalmia transcription factor. There may be reactivity with Melan-A, CD99, neuron-specific enolase, and vimentin (2, 5, 6).

In our case, the initial diagnosis was IMT, but other differential diagnoses as PEComa and melanoma were not

excluded. The final diagnosis was confirmed by the identification of *EWSR1* and *AFT1* gene rearrangements.

The three previously described cases of the primary lung CCSST presented differently. The first case was a 55-year-old, and the second was a 50-year-old; both were asymptomatic (3), while the 3rd was a 28-year-old who presented with Pancoast syndrome, spinal cord compression, and paraplegia (4). The lesions' sizes were 4, 2.5, and 8*6 cm locally advanced tumor, respectively (3, 4). All the lesions were in the left upper lobe. While the first and second cases were treated surgically with left upper lobectomy, and patients were still in the follow up until the date they have been reported. The first case showed five interlobar lymph node metastases (3). The 3rd case was treated by T8-T10 laminectomy followed by radiotherapy because it presented with a locally advanced tumor associated with local invasion, hilar, mediastinal, supraclavicular, and cervical lymphadenopathy, as well as spine metastasis. The outcome in the latter case was fatal immediately after discontinuation of therapy (4).

The recommended treatment of CCSST is radical resection with a wide safety margin. This type of resection is advisable to decrease the recurrence rate that is relatively common (5, 7). Regional radical lymph node dissection is of no proven benefit for the late outcome. Some authorities advised sentinel lymph node mapping followed by dissection once indicated (5, 7). Based on the guidelines for treating malignant lung tumors, it is advisable to perform anatomical lung resection lobectomy or pneumonectomy. After complete resection, adjuvant therapy with chemotherapy or radiotherapy is of no proven benefit. Radiotherapy may be indicated in close positive resection margins to have better local control (6). Chemotherapy may be of benefit in patients with metastatic disease (6, 7).

A report that included a 75 patient, the 5- and 10-year survival was 47 and 36%, respectively (7). Mavrogenis et al. reported that 5-year, 10-year, and 20-year-survival of the patients with CCSST, varies from 67% to 10%. The rates of local recurrence can reach up to 84%, late metastases up to 63%, and metastases at presentation up to 30% of patients. Moreover, metastases may occur early or as late as 29 years after diagnosis and surgical treatment (6). All of these indicate the aggressiveness as well as the poor prognosis of the disease. Due to this, it is advisable to have a regular close follow-up for patients who have been treated to look for local, locoregional recurrences and late metastasis using the appropriate investigation tools like CT, MRI, and PET-CT (7). For completely resected pulmonary CCSST, we would advise a lifelong follow-up of 3 months intervals in patients with poor prognostic factors, including size >5cm or locally advanced tumor and 6-12 months intervals for patients with tumors <5cm.

5. CONCLUSION

The rarity of CCSST in general and tumors originating in the lung primarily in particular raise the challenges in hypothesizing a differential diagnosis, choosing a proper imaging tool, and recommending an ideal treatment method. The histological examination, immunohistochemical, and cytogenetics of the tumor by identifying *EWSR1* and *AFT1* gene rearrangements will help reach the final diagnosis.

- **Ethics approval and consent to participate**: Institutional Review Board Committee of Jordan University of Science and Technology approved this case report (Ref number: 885/2020).
- **Patient Consent Form**: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.
- **Author's contribution**: All authors were involved in preparaton this case report. Final proofreading was made by the first author.
- **Conflict of interest**: The authors declare that they have no competing interests.
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