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Case Report Open Access

An Atypical Etiology of Mediastinal Lymphadenopathy: Extraskeletal Ewing Sarcoma

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Abstract

Background: Ewing's sarcomas and peripheral primitive neuroectodermal tumors are high grade malignant neoplasms, arising from bone and soft tissues and are grouped in the Ewing family of tumors. Primary localization in the mediastinum is extremely rare and was treated in only a few case reports. Lymphatic localization has never been reported. We present a case of an extraskeletal Ewing sarcoma arising from lymphadenopathy in the hilar and anterior mediastinal regions with literature review.

Case presentation: A 24 year old man was admitted to our institution for persistent cough, nocturnal diaphoresis, and weight loss of 6 kg. The chest X-ray displayed opacity of the left hilum at polycyclic contours. Chest Computed tomography scan confirmed supradiaphragmatic lymphadenopathy in the hilar and anterior mediastinal. Biopsy was performed. Histological and immunohistochemical analysis showed small and round cells tumor with positive staining for CD99 and vimentin, and negative staining of desmine, myogénine, actine muscle lisse, Protéine S-100, Chromogranine, CD56, pancytokeratin, myeloperoxidase and TTF1. Young age, morphological and immunohistological characters argued in favor of a tumor of Ewing group .We could not perform molecular cytogenetic analysis, because of the lack of technical structure. The staging was negative for any other metastatic disease or primitive bone tumor, and final diagnosis was primary localized Ewing sarcoma in mediastinal nodes. The patient received Ewing's sarcoma chemotherapy regimen. Complete response was achieved after six courses. Radiotherapy was prescribed, and the same chemotherapy regimen was continued totaling a period of one year. The patient was well with no evidence of local relapse or metastasis three years after diagnosis.

Conclusion: Extraskeletal Ewing sarcoma should be contemplated in the differential diagnosis of mediastinal lymphadenopathy. With multimodal treatment, the patients are potentially curable.

Keywords: Ewing's sarcoma; Extraskeletal; Mediastinum; Lymphatic; Chemotherapy

Abbreviations:

ES: Ewing's sarcomas; PNETs: Peripheral Primitive Neuroectodermal Tumors; LDH: *Lactate Dehydrogenase;* HIV: *Human Immunodeficiency Virus;* IDR: Intradermal Reaction; TTF1: Thyroid Transcription Factor 1; ESFT: Ewing Sarcoma Family of Tumors; EES: Extraskeletel Ewing Sarcoma; NCCN: *National Comprehensive Cancer Network;* EFS: Evenment Free Survival; OES: Osseous Ewing Sarcoma

Introduction

Ewing's sarcomas and peripheral primitive neuroectodermal tumors (ES/PNETs) are high grade malignant neoplasms, arising from bone and soft tissues and are grouped in the Ewing family of tumors. Primary localization of ES/PNET in the mediastinum is extremely rare and was treated in only a few case reports. Lymphatic localization has not studied. We present a case of an inoperable primary Ewing sarcoma arising from lymphadenopathy in the hilar and anterior mediastinal regions with literature review.

Case Report

A 24 year old man, without past medical, surgical history, history of tobacco, or concept of contagion tuberculosis was admitted to our institution for persistent cough, nocturnal diaphoresis, and weight loss of 6 kg. The patient denied any fever, exertional dyspnea, hemoptysis, joint pain, or occupational or travel related exposures. Physical examination was normal and no lymphatic nodes were palpable. The chest X-ray displayed opacity of hydric toning of the left hilum at polycyclic contours (Figure 1). In biology, the blood chemistry including inflammatory markers, LDH and serological tests for HIV were negative. Just as well, the tuberculin IDR was negative. Chest computed tomographic confirmed lymphadenopathy in the hilar and anterior mediastinal regions measuring 66 × 61 mm and 66 × 58 mm

respectively (Figure 2a and 2b). Biopsy was performed under radiological guidance, and a histological analysis showed that the tumor was composed of small and round cells with round nuclei, fine chromatin and scanty granular cytoplasm. Immunohistochemical analysis revealed positive staining for CD99 and vimentin (Figures 3a and 3b) and negative staining of desmine, myogénine, AML (actine muscle lisse), protein S-100, chromogranine, synaptophysine, CD56, pancytokeratin, myeloperoxidase, TTF1 and LCA (leucocyte antigen).

Based on these findings, an ES/PNET was diagnosed. Abdominal pelvic CT scan, bone scintigraphy and bone marrow biopsy were negative for any other metastatic disease or primitive bone tumor. Consequently, final diagnosis was primary localized ES in mediastinal nodes.

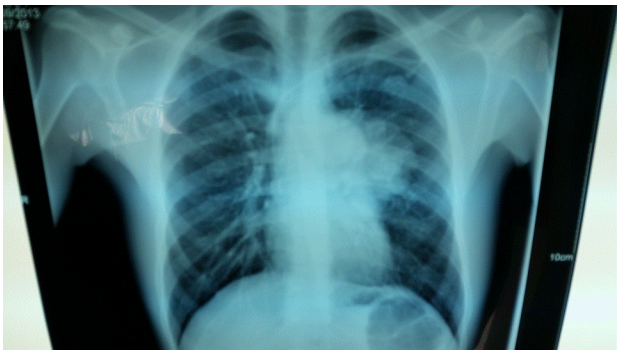

Figure 1: Chest X-ray showing left mediastinal opacity.

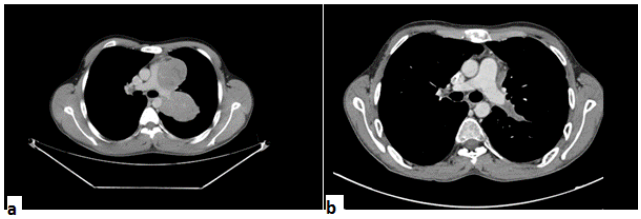

Figure 2: Lymphadenopathy in the hilar and anterior mediastinal regions (a) at diagnosis (b) after chemotherapy.

After a multidisciplinary decision-making approach, The patient received 3 courses of combined chemotherapy (one cycle every 3 weeks), including 2 mg/m^2 vincristine in day 1, 75 mg/m^2 adriamcin in day 1 and cyclophosphamide 1200 mg/m^2 in day 1, altering with 1, 8 g/m^2 ifosfamide from day 1 to day 5, 1,8g/m^2 mesna from day 1 to day 5, and 100 mg/m^2 etoposid from day 1 to day 5. The clinical response to the treatment was good with disappearance of the cough, weight gain and morphological partial response of 30%. After the sixth course of treatment, thoracoabdominal CT scan confirmed a complete response (Figure 2b). Radiotherapy was started, total dose of 54 Gray was administered with daily standard fractionation schedule of 2 Gray followed by the same chemotherapy regimens for one course totaling a period of one year. The patient was well with no evidence of local relapse or metastasis three years after diagnosis.

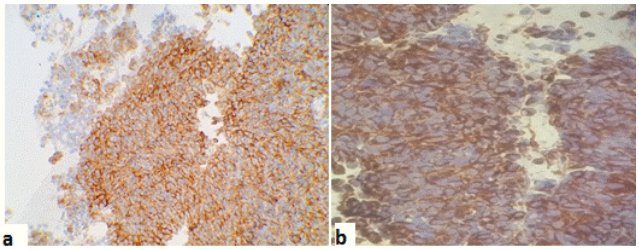

Figure 3: Immunohistochemical examinations for small cells tumors are positive for CD99 (a) and vimentin (b).

Discussion

Ewing sarcoma and PNET were the second etiology of bone cancers. It is a heterogeneous group of tumors, defined by histological and immunohistochemical similarities. It is a group of high-grade small round blue cell tumors, characterized by strong membrane expression of CD99 in a chain-mail pattern and negativity for lymphoid (CD45), neuroblastoma (neurofilament protein) and rhabdomyosarcoma (myogenin, desmin, actin) markers. Although separately described and although to be distinct malignancies, both these tumors arise from a common precursor cell: neuroectodermal cells, with variable differentiation (albeit in different degree). Ewing's sarcoma tends to be poorly differentiated, whereas PNET most often shows definite neuroectodermal differenciation.

Ewing's sarcoma, Askin's tumor, and PNET are now considered together as members of the Ewing sarcoma family of tumors (ESFTs) characterized by the presence of the pathognomonic translocation t (11; 22) (q24; q12) resulting from the fusion of the EWS gene on chromosome 22 and an ETS-type gene especially the FLI1 gene on chromosome 11, are implicated in the great majority of cases [1,2]. Ewing sarcoma is typically arising in the bones (called osseous Ewing's sarcomas OES), rarely in soft tissues defining what we call extraskeletal Ewing sarcoma (EES) or called extraosseous Ewing sarcoma.

First described by Tefft et al. in five young children, all of whom presented with signs and symptoms of epidural cord compression and a paravertebral soft tissue mass [3], extraskeletal Ewing sarcoma predominantly involves chest wall, lower extremities, retroperitoneum and paravertebral region [4]. Primary localization of EES in the mediastinum is extremely rare [5,6], and mediastinal nodal EES was not described in our knowledge.

Prognostic factors and outcomes of EES are similar to that of primary osseous Ewing's sarcomas [7,8]. Several studies demonstrated the prognostic impact of primary site and size at diagnosis. However, in recent studies, these two factors appear to have a non-significant prognostic value, probably related to the intensive neoadjuvant chemotherapy and improvement of local control therapy. Suboptimal histologic response to neoadjuvant chemotherapy, defined as less than 95% tumor necrosis, can be considered a good prognostic factor. Some studies demonstrated the prognostic impact of age, serum lactate dehydrogenase LDH rate, resection margins, type of local treatment and type of translocation [8]. Normal LDH, and absence of metastatic disease at the time of presentation are the indicators of favorable prognosis for this location that supported by the good response after chemotherapy alone.

The patient characteristics differ between EES and skeletal tumors. Patients with EES have a higher mean age, but also a bimodal distribution with EES more commonly found in those older than 35 and less than 5 years compared with skeletal tumors. Other important differences were noted. Patients with EES were less likely to be male, white or have pelvic primary tumors, though more likely to have tumors arising in other axial locations [9]. Patients often present with a painless mass or vague abdominal or chest pain depending on tumor site [1]. Those with metastatic disease may have fever, weight loss, fatigue, and elevated markers of inflammation [1,10]. Spontaneous hemorrhage can lead to rapid growth of a mass or mimic an acutely painful abdomen [10].

In our report ,we describe a case of a man with a symptomatic mediastinal and hilar lymphadenopathy for which multiple several diagnoses may be mentioned, the most common malignant causes are non–small-cell lung cancer (approximately 50%), small-cell lung cancer (approximately 25%), lymphoma, and metastatic lesions (each approximately 10%). This clinical and radiological setting can bring up other benign etiologies including: cheesy home tuberculosis (endemic countries), a hydatic cyst or an aneurism of the pulmonary artery. Only the biopsy with immunohistochemical studies affirms the diagnosis.

EES is an uncommon yet distinct clinicopathologic entity that should be considered in the differential diagnosis of a soft tissue tumor occurring in adolescents and young adults . The major histological differential diagnoses include Ewing's sarcoma of bone with extensive soft tissue extension and an in apparent intraosseous component, undifferentiated or primitive soft tissue sarcoma including rhabdomyosarcoma, metastatic neuroblastoma and rarely, other tumors such as peripheral neuroepithelioma, mesenchymal chondrosarcoma of soft tissue, hemangiopericytoma, synoviosarcoma, granulocytic sarcoma and metastatic small cell carcinoma of the lung. Expression of MIC2 can fully discriminate these tumors from other small-round-cell tumors aforementioned, although it is not exclusively specific for these tumors [11]. Demonstration of the chromosomal translocation t (11; 22) (q24; q12) is highly specific for ES/PNET, but it is not available in our institution. In our case, given the absence of cytogenetic analysis, the complete response after OES protocol confirmed retrospectively the diagnosis for ES/PNET in this localization. And normality of the bone scan allowed excluding bone primary tumor.

The standard treatment used in the bone Ewing's sarcoma can achieve a good therapeutic effect in EES [12], this is a typical example of the multimodality approach in cancerology including chemotherapy, surgery and radiotherapy based comprehensive treatment. A few retrospective studies showed that the treatment modality which patients accepted had a significant effect on the prognosis could improve the survival rate, the local control rate in margin positive patients by radiotherapy, and could eliminate micrometastasis by chemotherapy [6,13]. The treatment recommended by 2015 NCCN ESFT guidelines is the following protocol: multiagent chemotherapy followed by local control therapy (surgery and / or radiotherapy) and adjuvant treatment. Multidrug combination chemotherapy is recommended and the preferred regimens include vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide. The OES protocol improved survival rate and EFS of patients with EES probably because of the use of pulsed, more intensive anthracycline-containing [14].

Surgery and radiotherapy are the local control treatment modalities used for patients with localized disease. There have been no randomized studies that have compared these two modalities treatment. The choice of the local control therapy should be individualized and is dependent on tumor location, size, and response to chemotherapy, anticipated morbidity and patient preference.

These items have influenced the choice of local treatment of our patient; the first surgical difficulties of the mediastinal area, and complete response to chemotherapy were spared the patient a morbid surgery. Radiotherapy dose was found to influence local control in non-metastatic Ewing sarcoma treated with chemotherapy and definitive radiotherapy. In particular, patients who received RT doses >or = to 49 Gray for tumor size <or = to 8 cm and >or =54 Gy for tumor size >8 cm had improved local control [15] which justify radiotherapy of consolidation at dose of 54Gy in our patient.

Conclusion

Primary EES appears to be a distinct clinicopathologic entity that can be distingued from the other common round cell tumors arising in soft tissues of young adults. The localization of mediastinal node was never described and should be contemplated in the differential diagnosis of mediastinal lymphadenopathy. With multimodality treatment combined high-dose irradiation and chemotherapy, the patients are potentially curable.

Authors' Contributions

CE and MR K Conceived of the idea and drafted the manuscript, CE, MR K and MZ did the research and oncological data collection. CE, MT and RT did patient oncological follow up. HC and MO performed the histopathological examinations and pathological data collection. RT, HE and MI have contributed in supervision and guidance of manuscript. All authors read and approved the final version of the manuscript.

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References

1. Ludwig JA (2008) Ewing sarcoma: historical perspectives, current state-of-the-art, and opportunities for targeted therapy in the future. Curr Opin Oncol 20: 412-418.
2. Baldini EH, Demetri GD, Fletcher CD, Foran J, Marcus KC, et al. (1999) Adults with Ewing's sarcoma/primitive neuroectodermal tumor: adverse effect of older age and primary extraosseous disease on outcome. Ann Surg 230: 79-86.
3. Tefft M, Vawter GF, Mitus A (1969) Paravertebral "round cell" tumors in children. Radiology 92: 1501-1509.
4. Murphey MD, Senchak LT, Mambalam PK, Logie CI, Klassen-Fischer MK, et al. (2013) From the radiologic pathology archives. Ewing sarcoma family of tumors: radiologic-pathologic correlation. Radiographics 33: 803-831.
5. Ahmad R, Mayol BR, Davis M, Rougraff BT (1999) Extrakeletal Ewing's sarcoma. Cancer 85: 725-731.
6. Rud NP, Reiman HM, Pritchard DJ, Frassica FJ, Smithson WA (1989) Extraosseous Ewing's sarcoma. A study of 42 cases. Cancer 64: 1548-1553.

7. Lee J, Hoang BH, Ziogas A, Zell JA (2010) Analysis of prognostic factors in Ewing sarcoma using a population-based cancer registry. Cancer 116: 1964-1973.
8. Tural D, Molinas Mandel N, Dervisoglu S, OnerDincbas F, et al. (2012) Extraskeletal Ewing's sarcoma family of tumors in adults: prognostic factors and clinical outcome. Jpn J Clin Oncol 42: 420-426.
9. Applebaum MA, Worch J, Matthay KK, Goldsby R, Neuhaus J, et al. (2011) Clinical features and outcomes in patients with extraskeletal Ewing sarcoma. Cancer 117: 3027-3032.
10. Ibarburen C, Haberman JJ, Zerhouni EA (1996) Peripheral primitive neuroectodermal tumors: CT and MRI evaluation. Eur J Radiol 21: 225-232.
11. Olsen SH, Thomas DG, Lucas DR (2006) Cluster analysis of immunohistochemical profiles in synovial sarcoma, malignant peripheral nerve sheath tumor, and Ewing sarcoma. Mod Pathol 19: 659-668.
12. Gururangan S, Marina NM, Luo X, Parham DM, Tzen CY, et al. (1998) Treatment of children with peripheral primitive neuroectodermal tumor or extraosseous Ewing's tumor with Ewing's directed therapy. J Pediatr Hematol Oncol 20: 55-61.
13. Xie CF, Liu MZ, Xi M (2010) Extraskeletal Ewing's sarcoma: a report of 18 cases and literature review. Chin J Cancer 29: 420-424.
14. Castex MP, Rubie H, Stevens MC, Escribano CC, de Gauzy JS, et al. (2007) Extraosseous localized Ewing tumors: improved outcome with anthracyclines-the French society of pediatric oncology and international society of pediatric oncology. J Clin Oncol 25: 1176-1182.
15. Paulino AC, Nguyen TX, Mai WY (2007) An analysis of primary site control and late effects according to local control modality in non-metastatic Ewing sarcoma. Pediatr Blood Cancer 48: 423-429.

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