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Secondary Histiocytic Sarcoma in a Pre-B-Acute Lymphoblastic Leukemia

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Abstract

Histiocytic sarcoma (HS) is a rare malignancy with grave prognosis. Adult acute lymphoblastic leukemia (ALL) patients developing HS as a secondary malignancy reported in the literature is even rarer. Through our case report, we aim to describe an adult pre-B-ALL patient who subsequently developed extensive HS while on maintenance therapy. We present the course of the disease, the management, and the resultant outcome. Active reporting of the course and management of secondary HS in adult ALL patients need to be emphasized to gain better insight into the presentation and the course of the disease, incidence as well as molecular pathology, especially given the relative silence of the literature in this regard.

Keywords
- secondary HS
- adult pre-B-ALL
- secondary malignancies

Introduction

Cancer survivors who have previously been treated with chemotherapy and/or radiotherapy find themselves at higher risks of developing secondary malignancies,[1,2] but only a handful cases of histiocytic sarcoma (HS) in adult acute lymphoblastic leukemia (ALL) have been reported in the literature.[3,4] HS is an extremely rare malignancy originating from non-Langerhans histiocytic cells of the monocyte/macrophage system that has a poor prognosis and limited treatment options.[5] Advancements in molecular and genetic sequencing techniques have made it possible to discover a shared clonal ancestry connecting malignant leukemia or lymphoma with cases of secondary HS.

In this case report, we discuss a case of a 37-year-old lady diagnosed with pre-B-ALL who subsequently developed extensive HS while on maintenance therapy for ALL.

Case Report

A 37-year-old female presented with a history of dysmenorrhea, backache, and bilateral lower limb swelling for 1 week. Physical examination revealed pallor, absent lymphadenopathy, moderate ascites, and decreased breath sounds with dull percussion notes on right side of the chest and bilateral pitting pedal edema. Ultrasonogram (USG) abdomen showed bilateral endometriotic ovarian mass with ascites. Computed

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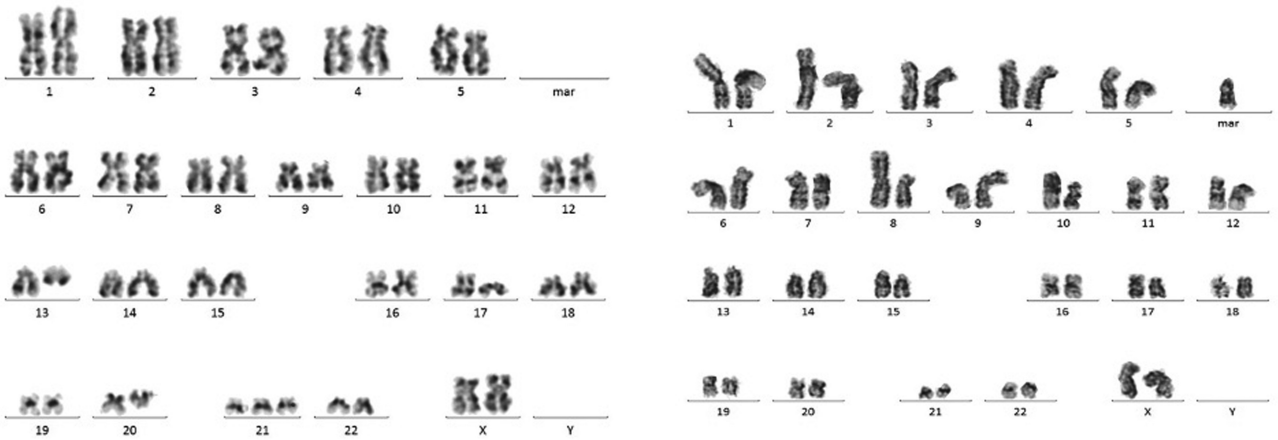

Fig. 1 Karyograms showing complex karyotype (>3 abnormalities) dic (8;9), iso 9q, del 13q, del 17p, del 20q and +21.

tomography of abdomen showed a homogenously enhancing soft tissue density retroperitoneal mass encasing the aorta and inferior vena cava, bulky uterus, ascites, and a bulky solid right adnexal space occupying lesion. USG-guided biopsy from the adnexal mass was performed and immunostaining showed tumor cells to be strongly and diffusely positive for terminal deoxynucleotidyl transferase (TdT) and CD20 and negative for CD3, chromogranin, synaptophysin, and desmin. Bone marrow examination revealed 70% blasts and cytogenetic analysis revealed complex karyotype (>3 abnormalities) which also included TP53 deletion (►**Fig. 1**). Reverse-transcription polymerase chain reaction for ALL panel (RNA) was negative for *BCR-ABL, E2A-PBX, MLL-AF4*, and *TEL-AML1* fusion transcripts. The patient was categorized as high-risk pre-B-ALL and was administered chemotherapy based on Berlin-Frankfurt-Munster protocol (BFM 95). Following induction, patient was clinically well and had no organomegaly. Her peripheral blood count was normal, and bone marrow was in complete morphological remission.

After 1.5 years on maintenance therapy, the patient presented with a new onset limp of left side along with pain in the left hip; there were no other constitutional symptoms. On focused physical examination, left hip flexion was limited to 40 to 45 degrees; rest of the movements were unrestricted. Rest of the systemic examination was normal. Magnetic resonance imaging of pelvis was suggestive of focal erosions of the left iliac blade with a large collection in the left iliac fossa. A subsequent bone marrow aspirate was conducted, revealing no indications of ALL relapse. A core biopsy of the left iliac bone showed sheets of atypical oval-to-spindle cells with abundant eosinophilic cytoplasm with fine vacuoles and pleomorphic vesicular, ovoid to elongated nuclei diffusely positive for CD163, CD45, CD68, OCT-2 and negative for CD43, Ki-67 - 60%, S-100, and CD1a negative, negative for TdT and CD34 with no intervening reactive cells thus favoring a diagnosis of a secondary HS with no signs of ALL relapse (►**Fig. 2**). Positron emission tomography scan showed disseminated multiple visceral deposits in lung, pleura, peritoneum, tail of the pancreas and uterus, parietal deposits in anterior abdominal wall, right gluteal region and right arm, internal mammary, retrocrural and pelvic lymph nodes, periarticular deposits involving both hip joints and large expansile lesion in left iliac blade, all of which were fluorodeoxyglucose-avid (►**Fig. 3**).

She was initiated on salvage chemotherapy with etoposide, cyclosporine, and dexamethasone for 1 month following which she developed severe urinary tract infection with sepsis requiring intensive care management.[6] Patient and family opted for best supportive care and palliative treatment. Subsequently, the patient succumbed to disseminated HS.

Discussion

Mathé et al was the first to describe HS as "tumors composed of free cells having variable morphology and form, in which nuclei were often distorted, monocytoid with coarse chromatin, often containing one or several nucleoli; the cytoplasm often contained vacuoles, and was slightly basophilic; the nuclear cytoplasmic ratio was that of blood monocytes which the tissue histiocytes closely resembled."[7] The rarity of this condition and the limited availability of detailed phenotypic data in the past posed significant challenges in accurately diagnosing HS. Consequently, it frequently led to misdiagnoses as non-Hodgkin lymphoma or other lymphoproliferative disorders due to the morphological resemblance shared among these conditions. Recent developments in immunohistochemistry and molecular analysis have enhanced the identification of this condition as a separate and distinct entity and have also enabled demonstration of genotypic relation between secondary HS and the primary malignancy. The current diagnosis of HS relies on histological and immunohistochemical findings that confirm histiocytic differentiation and the absence of epithelial, melanocytic, and lymphoid phenotypes. In our patient, genotypic analysis to detect a relation between the primary and secondary malignancies could not be performed due to resource limitations.

The International Lymphoma Study Group has reported the largest collection of accessible follow-up data succumbed to death. Majority of the patients were adult males (median

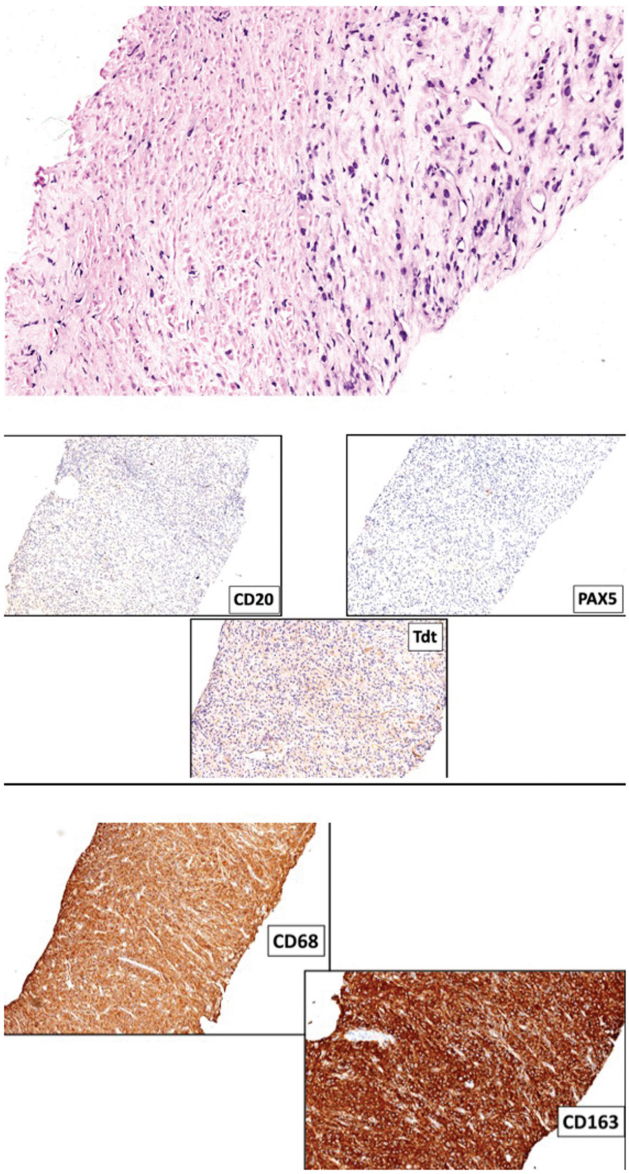

Fig. 2 Immunostaining shows tumor cells positive for histiocytic markers CD68 and CD163.

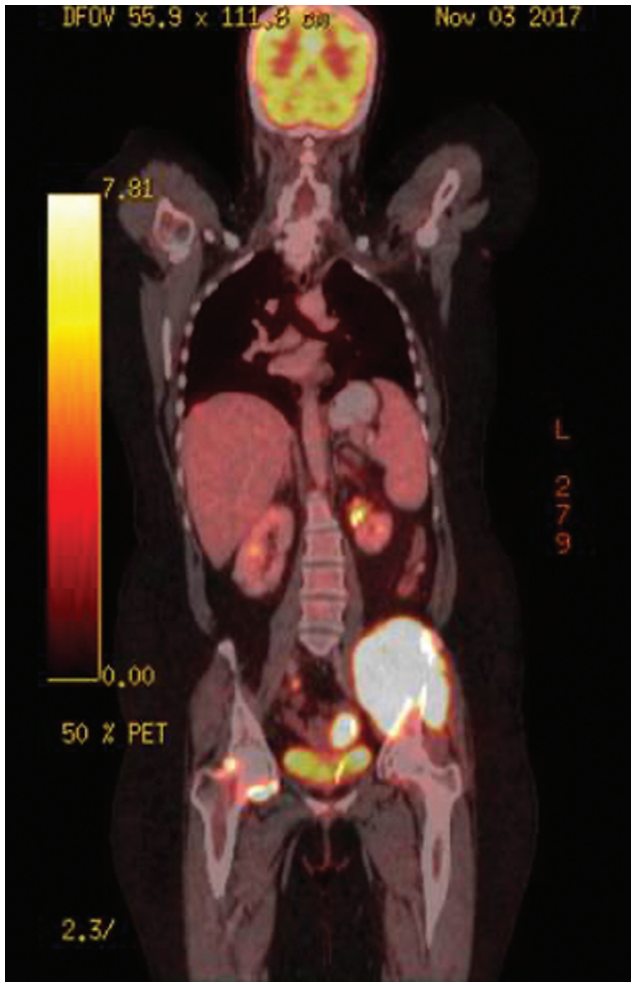

Fig. 3 Positron emission tomography-computed tomography demonstrating a hypermetabolic lesion at the left iliac blade. Multiple metabolically active deposits are seen in the lungs, abdomen, and hip joints also.

age of 46 years). Thirteen of 18 patients had extranodal presentation with lytic bone lesions, pancytopenia, and splenic enlargement.[8] In our case, HS was disseminated and involved multiple extranodal and nodal sites. From a histopathological perspective, HS exhibits distinctive features, including the proliferation of histiocytes with positive immunostaining for the macrophage-associated antigen CD68 and the histiocyte-specific marker CD163. Conversely, it is marked by negative immunostaining for the T-cell-associated and Langerhans cell antigen CD1a, as well as for the S-100 protein and the dendritic cell-associated antigens CD21 and CD35.[8–10] In our patient, the biopsy of pelvic mass showed a convincing morphological and immunophenotypic evidence of secondary HS as demonstrated by sheets of atypical oval to spindle cells with abundant eosinophilic cytoplasm with fine vacuoles and pleomorphic vesicular, ovoid to elongated nuclei and immunoreactivity for CD68, CD163 and negative for CD1a and S-100.

In the series reported by Castro et al, of 15 histiocytic lesions that developed following diagnosis of ALL of which four were HS, the interval between the initial diagnosis of ALL and development of the histiocytic lesion varied from 3 months to 10 years.[11] Our patient developed secondary HS 2.2 years from initial diagnosis of B-ALL. The proposed hypothesis to explain the development of histiocytic lesion in an ALL patient is (1) dedifferentiation of B/T cells to early progenitors and subsequent redifferentiation to histiocytic lineage, (2) transdifferentiation from lymphoid to myeloid lineage, and (3) therapy-related: Secondary malignancy is a known complication of many antineoplastic regimen. Among the handful case reports of secondary HS following ALL that has been reported in literature, adult ALL with secondary HS such as our case is a rare find. Soslow et al documented the occurrence of two instances of HS in pediatric patients following treatment for.[12] In a case study authored by van der Kwast et al, a 19-year-old male was documented with T-lymphoblastic lymphoma, which ultimately transformed into malignant histiocytosis featuring rearrangement of the immunoglobulin heavy chain gene.[13] Bouabdallah et al detailed a similar case of a 19-year-old

male who presented with a true histiocytic lymphoma 1.75 years after completion of treatment for B-ALL.[4] Both the reports demonstrated identical IgH gene rearrangements between the primary lymphoma/leukemia and the histiocytic lesion. Feldman et al also demonstrated lineage plasticity through a common clonal origin between secondary splenic HS and primary pre-B-ALL in a pediatric patient.[14] The authors suggested that HS can develop following chemoradiotherapy treatment of ALL, where the B-ALL cells could act as progenitor cells and transdifferentiate by the virtue of hematopoietic plasticity.

Due to the uncommon nature of this condition, there is no established standard treatment for HS. While complete surgical removal can lead to a cure for patients with localized disease, the majority of individuals present with widespread disease and unfortunately do not survive despite intensive treatment involving chemotherapy, radiation, and surgical interventions.[15] Although long-lasting remissions are not achieved, the most popular regimen still used in the management of advanced HS is the cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) regimen. Additionally, etoposide has been incorporated to the CHOP regimen to treat it as an aggressive form of lymphoma.[16] In selected cases, innovative strategies employing medications like thalidomide, alemtuzumab, and vemurafenib have been explored and have demonstrated favorable therapeutic outcomes. Autologous stem cell transplantation is primarily considered for cases of relapsed HS, and only a limited number of individuals have attained a complete response through this approach.[15,16] With the recent advances in immunotherapy, targeted therapies might become the standard in the near future. However, at present, it is advisable to approach HS as a high-grade lymphoma and initiate treatment with an induction regimen, followed by consolidation involving high- dose chemotherapy and subsequent allogenic hematopoietic stem cell transplantation based on the performance status of the patient.[17]

Conclusion

HS is a diagnosis of exclusion, however, in the setting of an ALL patient who is undergoing or has completed chemoradiotherapy treatment; it is important to consider HS as one of the differentials. There is no standard protocol for treatment of HS, and it has a poor prognosis. Therefore, active reporting of such cases needs to be emphasized to better comprehend the time and pattern of occurrence, incidence as well as molecular pathology.

Patient Consent

The name of the department(s) and institution(s) to which the work should be attributed:

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1. The manuscript has been read and approved by all the authors and the requirements for authorship have been met by each author. Each author believes that the manuscript represents honest work to the best of their knowledge.

2. There are no source of funding and conflict of interest to be declared.

Statement of Ethics

Ethical approval to report this case was obtained from Institutional Review Board (EC/WV/TMC/19/22).

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