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Langerhans Cell Sarcoma: Treatment with Dose-adjusted EPOCH

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Abstract

Background: Langerhans cell sarcoma (LCS) is a rare malignancy with no specific defined treatment strategy. Chemotherapy is the preferred option in cases with systemic involvement, though no consensus exists on the preferred regimen.

Case: A sixty-six year old male presented with advanced-stage LCS involving the bone marrow (BM) and spleen. Immunohistochemical analysis of the BM-sample confirmed the diagnosis of LCS. The patient was treated with chemotherapy utilizing dose-adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide and Doxorubicin (DA-EPOCH). The patient achieved complete remission and was able to tolerate the entire course (6 cycles) of chemotherapy with continued response at 10 months.

Conclusion: Due to the rarity of the disease no standard treatment modality exists; most successful treatment options described are anecdotal reports. Due to the paucity of such data and inability to include enough patients on clinical trials, various combination chemotherapy options have been used for best clinical response. The unattractive response rate to CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in previously described case series and the benefit of Etoposide in treating Langerhans cell histiocytosis and primitive sarcoma regimens along with an acceptable adverse effect profile, had us chose DA-EPOCH for our patient. We demonstrate that DA-EPOCH is a tolerable and an efficacious treatment regimen for LCS.

Keywords: Langerhans cell sarcoma; EPOCH; Treatment

Case report

A sixty-six year old Caucasian male was diagnosed with stage two colon cancer with no nodal involvement in December 2013 and was treated with surgical resection with good recovery. He did not receive any adjuvant chemotherapy. Three months later, he presented to the hospital with complaints of sudden onset diarrhea, weakness and shortness of breath. There was no history of nausea, vomiting, hematochezia or abdominal pain. Blood work revealed a total white blood count, 13.1 × 10^9/L with some left shift (but no blasts) on the peripheral smear and thrombocytopenia; 10 × 10^9/L. Computed tomography (CT) scan of the chest showed diffuse bilateral interstitial infiltrates and the patient had to be managed in the ICU for sepsis without any identified organism. He had a history of hypertension and atrial fibrillation.

The initial CT scan of the abdomen revealed an enlarged liver and splenomegaly (17 cm × 11 cm × 17 cm) with hypo-echoic nodules in the spleen suggestive of tumor lesions versus infarct (Figure 1a). No colonic lesions were identified and carcinogen embryonic antigen (CEA) was within normal limits. A bone marrow (BM) aspirate and biopsy was performed due to persistent thrombocytopenia after recovery from sepsis and resolution of chest infiltrates. He did not have any preceding hematological malignancy. BM biopsy revealed a hypercellular marrow demonstrating nodular involvement with large epithelioid pleomorphic cells containing abundant eosinophilic cytoplasm, hyperchromatic longitudinally grooved nuclei, prominent nucleoli and increased mitotic figures (Figure 2a). Immunohistochemical studies were positive for CD1a (Figure 2b), S100 (Figure 2c) and Fascin, and focally positive for Langerin (CD207) stains. LCA, CD34, CD8, cytokeratin, desmin, actin, CD31, PGM-1, KP1, CD61, CD45RO, CD21, Factor 8, vimentin, melan A, CD30 stains were all negative, thus establishing the diagnosis of Langerhans cell sarcoma (LCS). The splenic hypo-echoic lesions were not biopsy proven, however repeat imaging in 2 weeks had shown increase in number of the lesions, without an increase in spleen size (Figure 1b). There were no other sites with disease involvement. The patient's performance status on the Eastern Cooperative Oncology Group (ECOG) scale was assessed as 3 [1].

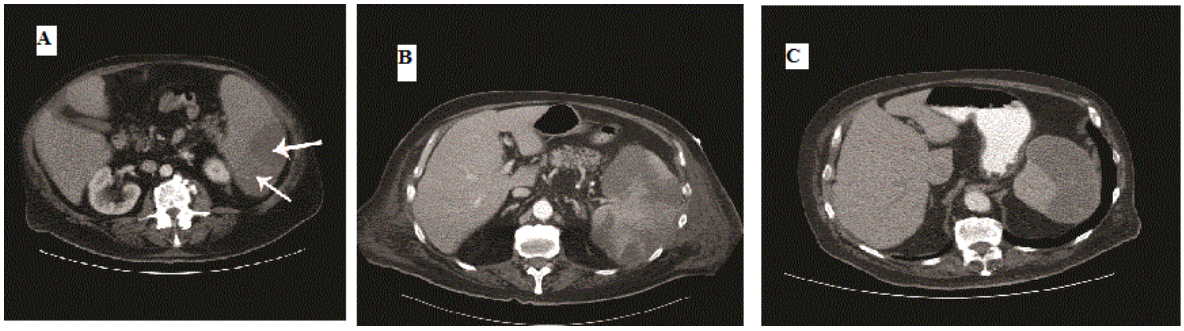

Figure:1(A): Initial CT scan at presentation with splenomegaly (17 cm × 11 cm × 17 cm) and two hypo-echoic nodules in the spleen suggestive of infarct versus tumor lesions.(B) Interval 2 weeks CT scan (prior to chemotherapy initiation) demonstrating an increase in number of the splenic lesions without an increase in spleen size.(C) CT scan on completion of chemotherapy with resolution of all splenic nodules but persistent defect consistent with splenic infarct.

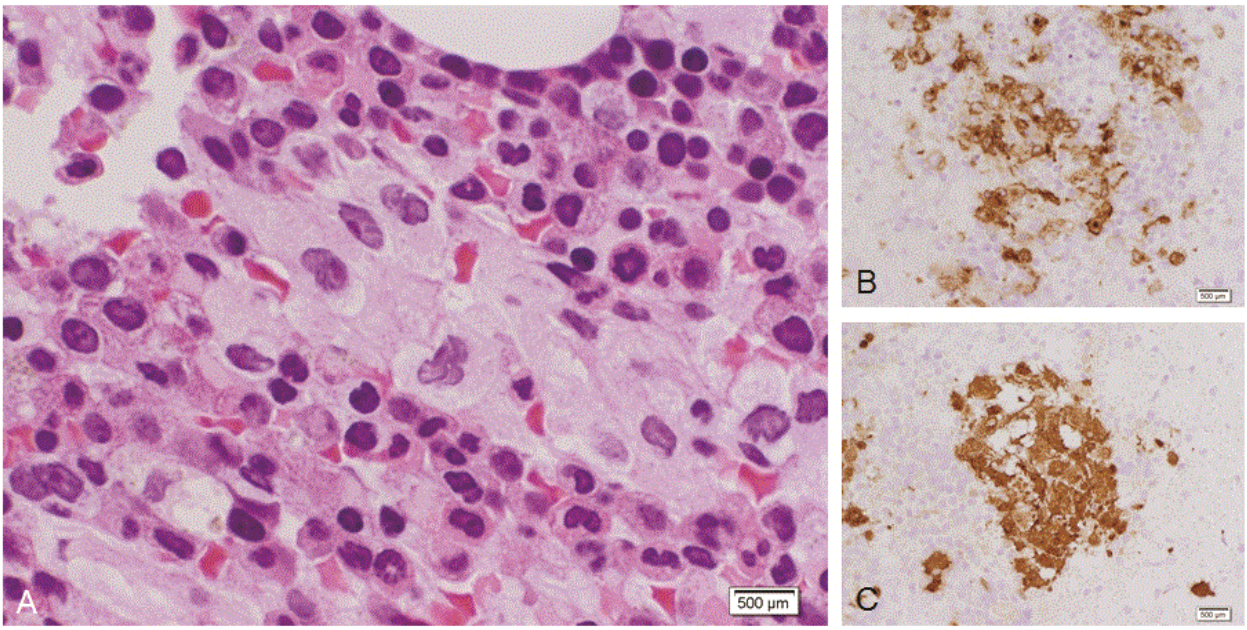

Figure: 2(A) BM biopsy (H&E) with a hypercellular marrow demonstrating nodular involvement with large epithelioid pleomorphic cells containing abundant eosinophilic cytoplasm, hyperchromatic longitudinally grooved nuclei, prominent nucleoli and increased mitotic figures consistent with malignant LCS cells. (b) Positive CD1a stains. (C) Positive S100 stains.

The patient was started on dose-adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide and Doxorubicin (DA-EPOCH) chemotherapy. There was a dramatic improvement in his functional status within five days of chemotherapy initiation. He did require granulocyte-colony stimulating factor (G-CSF) support with each cycle and dose increase was not possible after the second cycle. His blood counts stabilized with significant improvement in his platelets with only two episodes of transfusional support. An interim CT scan after 2 cycles revealed significant improvement in his splenic lesions with a marked decrease in the spleen size. He completed six cycles of DA-EPOCH without interruptions and tolerated the treatment remarkably well with continued improvements in his clinical status, recovery of blood counts (negative BM biopsy after 6 cycles) and resolution of the majority of splenic nodules. He underwent a splenectomy for a persistent CT finding (Figure 1c), consistent with splenic infarct on the postoperative pathology assessment. Patient declined evaluation for an allogeneic bone marrow transplant. He continues to be in complete remission at 12 months with stable counts and no new lesions on 3 monthly surveillance scans. An initial BRAF V600E mutation analysis on the BM biopsy specimen was inconclusive.

Discussion

Langerhans cell (LC) is a specialized epidermal dendritic cell which functions as an antigen presenting cell to T cells. Langerhans cell tumors comprise of the clinically benign Langerhans cell histiocytosis (LCH) and its malignant counterpart, LCS [2,3]. LCS can either arise

from LCH or develop de novo [4].There are also reported cases of LCS originating from transdifferentiation of pre-existing myeloid and lymphoid lineage malignancies [5-8]. LCS is an extremely rare and aggressive neoplasm with a very dismal prognosis and short survival. There is lack of enough evidence to establish standard treatment protocol with most of the therapy being empirical since only 66 cases have been reported so far [9].

In a recent systematic literature review, the median age at presentation was 50 years with a male to female ratio of 1.3:1 [9]. The most common primary site at diagnosis was skin and lymph nodes while the advanced disease also involved the lung, liver, bone and spleen. Disseminated disease was seen in 40.9% of the cases, as was the case with our patient involving the bone marrow and spleen [9].

The gold standard for diagnosis is mainly through pathological assessment of the tumor samples. Malignant cytological features of atypia, hyperchromatic and characteristically longitudinally grooved nuclei, prominent nucleoli, mitotic figures along with immunohistochemical expression of CD1a, S100 protein and Langerin (CD207) on the tumor cells confirm the diagnosis [2,3,10]. Proliferation of typical Birbeck granule containing tumor cells is also identified [11].

The extent of involvement expectantly predicts the prognosis, with disseminated forms correlating to the most dismal outcomes [9]. The management of LCS has also differed widely ranging from single modality (generally in cases with localized involvement); to combination therapy including surgery and/or chemo-radiotherapy, albeit no consensus exists on the sequence of the choice of therapy. In one reported case, Lucas et al noted a relapse after 3 months of therapy with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) and thereafter successfully treated the cutaneous lesions and nodal masses with palliative radiotherapy [12]. Bone marrow transplant has also been attempted and correlates to good outcomes in carefully selected patients, generally in the relapsed setting [13]. Due to the rarity of the confirmed cases and the diversity of applied treatments, the definition of optimal strategy has been nearly impossible, and most treatment data are based out of case reports and small case series. A recent analysis by Howard et al comprehensively summarized the different therapeutic options utilized so far in the published literature [9].

Traditionally, patients with LCS have been treated in accordance with the common lymphoma chemotherapy protocols, mostly using the CHOP regimen and its variants (adding cytarabine and mitoxantrone) [9,14,15]. Outcomes have however been poor with this reported approach. This could possibly be due to advanced disease state and poor patient selection or due to an inadequacy of the regimen to induce effective responses.

Recently, a trend towards increased utilization of adapting the soft tissue sarcoma regimens has been noticed with better outcomes. Uchida and colleagues used the MAID (Mesna, doxorubicin, ifosfamide and dacarbazine) regimen as neoadjuvant chemotherapy before surgical excision of localized LCS [16]. Another case with localized LCS was reported to be in complete remission for 4 years with a combination of doxorubicin, ifosfamide, mesna (AIM) chemotherapy along with involved field radiation [17]. Similarly, Kwong et al achieved a complete remission in a patient with relapsed disseminated LCS with the novel regimen of etoposide, cisplatin, ifosfamide (with Mesna) and gemcitabine (EPIG) for 6 cycles [18]. Such good responses are marred by the profound cytopenias, which can be treatment limiting in most cases especially with pre-existing cytopenias due to marrow involvement, hypersplenism or a preceding hematological malignancy. A similar outcome (ICU admission for neutropenic sepsis) was also noted in the patient who achieved a good response to a modified ESHAP regimen (etoposide, carboplatin, cytarabine, methylprednisolone) as second-line therapy after progression of disease on the CHOP regimen [19].

The mainstay of sarcoma treatment are the anthracycline (doxorubicin) and the alkylating agent (ifosfamide) [20]. Etoposide has also demonstrated efficacy in primitive sarcomas and is a defined treatment option for LCH along with prednisolone and vinca alkaloids (vinblastine) [21,22]. DA-EPOCH chemotherapy regimen with G-CSF support has shown a promising outcome in the treatment of diffuse large B-cell lymphoma and produces more cell kill than CHOP-based regimens with a well-tolerated safety profile [23-25]. The unattractive response rate to CHOP in previously reported cases of LCS and the presumed benefit of including etoposide made us chose the DA-EPOCH regimen as middle ground between highest efficacy and best tolerability. We hypothesized that a common ground was necessary for our patient who had just recovered from an infectious complication and had baseline cytopenias due to marrow involvement and splenomegaly, while not compromising on the efficacy due to the aggressive nature of the disease.

Our approach proved to be highly efficacious with good tolerability and easily manageable toxicities. Patient had complete recovery of his counts, with complete eradication of disease in his marrow and spleen. Although observed in a single patient, such a response with minimal toxicity has not yet been reported with other regimens in LCS. Standard combination chemotherapy regimen is still undefined in aggressive and advanced LCS due to the rarity of this disease type, thus preventing a prospective randomized trial. Our case suggests the benefit of a well-defined option as a therapeutic strategy in such selected patients. Further research on molecular pathogenesis to discover oncogenic mutations (such as BRAF) will help pursue novel therapeutic strategies in this rare tumor subtype.

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