Langerhan's cell sarcoma: two case reports

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Abstract

Langerhan's cell sarcoma (LCS) is a rare neoplasm with a poor prognosis. To our knowledge, only sixty-six cases have been published. We discuss two patients who presented very differently with LCS, as well as a recently published review of all sixty-six cases. Our first case had a complicated history of metastatic, high-grade myxofibrosarcomas and presented with a single skin lesion of LCS which was treated with resection to a positive margin and adjuvant radiotherapy. The LCS recurred locoregionally and was again resected. The patient is alive two years after initial diagnosis. The second case presented with bone marrow and splenic involvement, leukocytosis, and thrombocytopenia. This patient had an excellent response to etoposide, prednisone, oncovorin, cyclophosphamide, and adriamycin, with normalization of the complete blood count, negative bone marrow biopsy at follow up, and splenectomy without viable neoplasm. This patient is alive without signs of disease at 16 months after initial diagnosis.

Introduction

Langerhan's cells are dendritic cells derived from CD34+ hematopoietic stem cells. They function as antigen presenting cells and are most commonly located in the epidermis, mucous membranes, and lymphatics.[1,2] Langerhan's Cell Sarcoma (LCS) is a rare, but aggressive tumor with a poor prognosis. It was first reported by Wood *et al*. in 1984 and at the time was labelled malignant histocytosis X.[3] To our knowledge only 66 cases have been previously reported in literature.

Langerhan's cells sarcoma is often difficult to diagnose by morphology alone and immunohistochemical markers play an important role in its diagnosis.[2,4] LCS stains positive for CD1a, CD4, CD207 (Langerin), lysozyme, and S-100 protein.[1,2,5,6] A high mitotic rate, cellular atypia, and the presence of Birbeck granules on electron microscopy are also present.[2]

Case Report #1

The first case is a 77 year old female with a complicated oncologic history of recurrent, metastatic high-grade myxofibrosarcomas previously treated with multiple resections and radiotherapy presented with a new scalp lesion. Prior to the diagnosis of LCS, the patient had 7 lesions develop between 2003 and 2015 revealed to be metastatic, high grade myxofibrosarcoma. Lesions were located in the left groin, the left vulva, the subcutaneous tissues of the left upper back, the parenchyma of the right middle lung lobe, multiple lymph nodes in the left neck, in the soft tissue of the right post-auricular area, the musculature of the right thigh and in the right triceps. These lesions were treated with resection alone, neoadjuvant chemotherapy followed by resection, or by resection and post-operative radiotherapy. A follow up positron emission tomography/computed tomography (PET/CT) scan in 2013 identified a right posterior auricular nodule as well as a lesion on vertex of the scalp. On physical exam, the scalp lesion was pink, raised and measured 2 cm. It was described as round and soft. Subsequently, both lesions were excised. The posterior auricular nodule was positive for metastatic myxofibrosarcoma and stained negative for S100, CD1a, CD21, CD45, CD163, Langerin, and lysozyme. The scalp lesion had a positive margin from 9 o'clock to twelve o'clock. The scalp lesion stained positive for CD1a, S100, Langerin, CD163, CD45, and lysozyme, consistent with Langerhan's cell sarcoma (Figure 1). The patient subsequently underwent post-operative radiation therapy to the scalp vertex at another institution totaling 1400 cGy in 7 fractions. She also received post-auricular radiotherapy to 6600 cGy in 33 fractions. In 2014, a follow up CT of the head and neck revealed enlargement of the right parotid gland and recurrence of the lesion on the vertex of the scalp. The patient underwent a right parotidectomy and wide local excision of the scalp lesion. All margins at this time were negative. Pathology was again consistent with Langerhan's cell sarcoma. The parotid tumor measured 1.3 cm and the scalp lesion measured 2×1.5 cm. Both specimens stained positive for Langerin, lysozyme, CD163, CD1a, and S100 and negative for desmin and actin. The patient is alive at 2 years after diagnosis of LCS and 12 years after initial diagnosis of high-grade myxofibrosarcoma.

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Case Report #2

A 66 year old male with a past medical history of stage 2 colon cancer, status post resection presented initially with diagnosis of sepsis and consequent diffuse intravascular coagulation with no apparent source of infection. A CT scan of the chest, abdomen and pelvis revealed diffuse bilateral alveolar infiltrates, pericardial effusion, and splenomegaly measuring 21.5 cm with heterogenous enhancement and multiple areas of mass like hypodensities without hepatomegaly or lymphadenopathy (Figure 2). Pertinent lab studies include white blood cell count of 27.6, hemoglobin of 14, and platelets of 10. Blood smear revealed neutropenia with left shift, thrombocytopenia, and no evidence of blasts.

A bone marrow biopsy was performed and pathology was consistent with Langerhan's cell sarcoma. Immunistochemical studies of tumor cells were positive for S100, fascin, and CD1a. Langerin stains were focally positive. LCA, CD34, CD8, cytokeratin, desmin, actin, CD31, PGM01, KP-1, CD61, CD45RO, CD21, Factor 8, vimentin, melanin A, CD30 stains were all negative. The patient received 6 cycles of chemotherapy with etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH). A post treatment bone marrow biopsy six months since initial bone marrow biopsy was negative for malignancy. Furthermore, complete blood counts were all within normal limits. A repeat CT of the chest, abdomen and pelvis revealed a decrease in splenomegaly

measuring 11.9 cm. No adenopathy, hepatomegaly, or alveolar infiltrates were noted (Figure 3). The patient underwent a splenectomy which revealed multifocal areas of necrosis without viable tumor. The patient is in remission 16 months after initial presentation without signs of recurrence.

Discussion

In 2015, Howard *et al.* performed a systematic review of literature for LCS and found 66 published cases. The median age of this series was 50, ranging from congenital development of the tumor to 88 years at diagnosis. Seventy-four percent of cases involved the lymph nodes, 49% involved the skin, 29% involved the lung, 17% involved the liver, and 15% had splenic involvement. Thirty-three percent of patients presented with single-site involvement, 26% with locoregional involvement, and 41% with >2 site disease. In this series, LCS was found to have a pattern of spread starting in the skin or mucosa, then moving to regional lymph nodes, and eventually to disseminated disease.[1] Treatments reported in this study included surgery alone, chemotherapy alone, radiotherapy alone, surgery plus chemotherapy, surgery plus radiotherapy, surgery plus chemoradiotherapy, and bone marrow transplant. The only complete responses occurred in patients with 1 or 2-site disease, with the exception of one patient with >2 site disease who received a bone marrow transplant.[1] Surgery was effective for single-site disease. With more extensive disease, the efficacy of surgery decreased. Chemotherapy alone was not considered an effective treatment. The addition of radiotherapy to chemotherapy improved the rate of complete response.[1] Bone marrow transplant is the only treatment that has been reported anecdotally as inducing a complete remission in a patient with >2 site disease.[1,6] Howard *et al.* reported that patients with increased disease burden had significantly worse outcomes with 5 year disease specific survival of 70% for one site, 15% for locoregional involvement, and 0% for disseminated disease. The mean disease free survival for all patients was 27 months. The disease specific survival for single site involvement, locoregional disease, and disseminated disease was 44 months, 29 months and 6 months, respectively.[1] In Howard *et al.*'s study, the majority of patients presented with greater than 1 site of involvement, which created a significantly worse prognosis. Wide local excision with negative margins was the most effective treatment for local disease control, and addition of a combination of chemotherapy and radiotherapy appeared to be beneficial. They reported that multimodality treatment without delay in adjuvant therapy appeared to have more favorable outcomes. Bone marrow transplant also appeared effective in 4 patients.[1]

In the first case presented in this report, after a history of multiple, recurrent, metastatic, high-grade sarcomas, our patient presented with unifocal LCS of vertex of the scalp with positive margins following resection. The area was treated with adjuvant radiotherapy to 1400 cGy in 7 fractions, a dose below that used typically for adjuvant treatment of soft tissue sarcomas. Fifteen months later the patient had recurrence on the scalp and in the parotid gland. Treatment was wide local excision of the scalp and parotid mass with negative margins. The patient is alive 2 years after initial diagnosis of LCS. This patient's locoregional recurrence suggests that resection to a positive margin with adjuvant radiotherapy to 1400 cGy, which would be an acceptable treatment for Langerhan's cell histiocytosis, is insufficient to treat LCS. Nakayama *et al.* treated a patient with single site disease that consisted of one involved lymph node to 59.4 Gy and achieved a complete response.[7]

We are not aware of any genetic disorders that would predispose to multiple, recurrent, metastatic sarcomas. No other cases of LCS had other high-grade sarcomas associated with them. We do not believe the patient's myxofibrosarcomas predisposed to his LCS.

The second case presented with leukocytosis, thrombocytopenia and splenomegaly, which resolved with chemotherapy. There are six other reported cases with bone marrow involvement, with 1 unknown outcome, 4 patients who died of their disease, and 1 patient was alive at 24 months.[1] EPOCH chemotherapy caused a clinical response with a decrease in splenomegaly, negative repeat bone marrow biopsy, and negative splenic involvement upon splenectomy. We do not believe EPOCH has been reported as a treatment for LCS in literature. This regimen led to an excellent response in this patient with 2-site disease who is alive without recurrence at 16 months after diagnosis. For single site disease, we recommend surgery to negative margins. If negative margins are not achievable, adjuvant radiation to doses commonly used for other sarcomas would appear to be reasonable. In patients with disseminated disease,

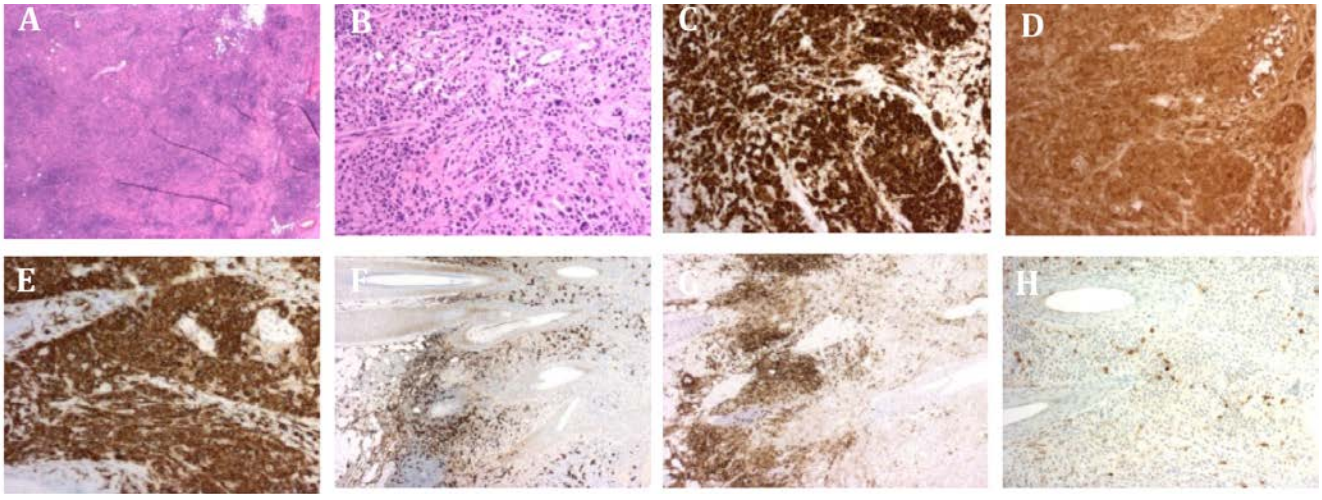

Figure 1. Surgical pathology of scalp lesion with various stains confirming diagnosis of Langerhans sarcoma. A) Low power hematoxylin and eosin (H&E) and B) intermediate power H&E stain reveal high population of large cells and prominent nucleoli with abundant eosinophilic cytoplasm. Tumor cells exhibit strong positivity for immunohistochemical stains C) CD1a, D) S100, E) Langerin, F) CD163, G) CD45 and H) lysosome.

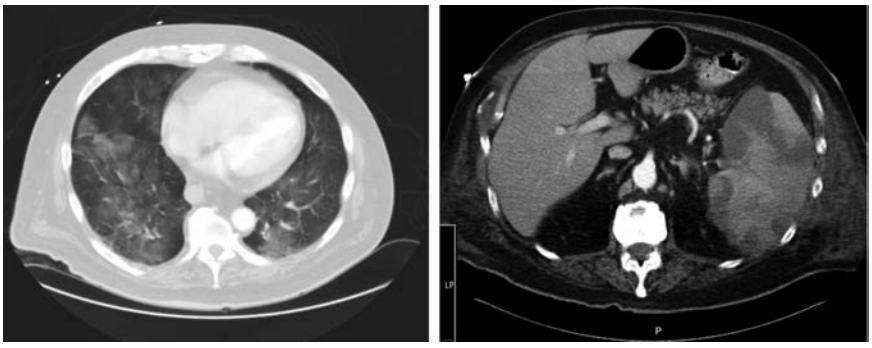

Figure 2. Initial computed tomography chest/abdomen revealing bilateral alveolar infiltrates, pericardial effusion and massively enlarged spleen with heterogeneous enhancement and multiple areas of mass like hypodensities.

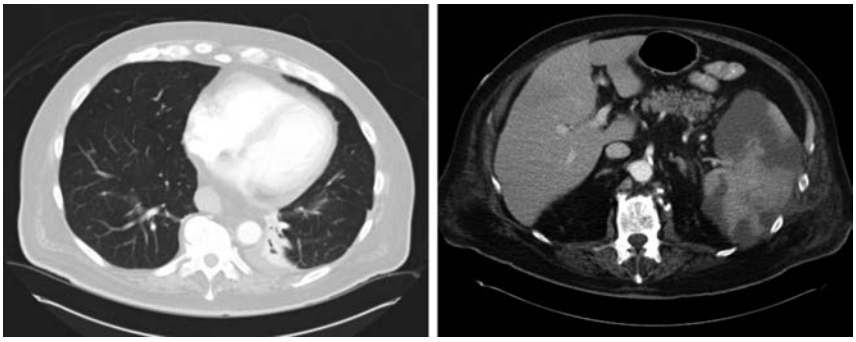

Figure 3. Post-chemotherapy computed tomography chest/abdomen with interval resolution of diffuse ground glass opacities and decrease in radiologically measured size of spleen and areas of heterogeneous enhancements.

systemic therapy and potentially bone marrow transplant have been associated with positive outcomes. However, since these are reported in isolated case report form, it is not possible to draw a sold conclusion given that data is lacking on the number of patients treated with bone marrow transplants that had negative outcomes. Development of targeted therapies may be considered in the future. Cellular markers such as Langerin, which is highly specific for Langerhan cells, may be used as a molecular target in the future. Antibodies have been developed to Langerin, which are rapidly internalized when they bind to Langerhan cells.[8,9] Perhaps this antibody could be used similarly to brentuximab, a CD30 antibody, which releases monomethyl auristatin E, a potent microtubule antagonist when internalized.

Conclusions

The longest analysis of Langerhans Cell Sarcoma includes only 66 cases and we have added two more to the literature. Patients with LCS have been treated with combinations of surgery, chemotherapy, radiotherapy, and bone marrow transplant. Due to a lack of available data, we are unable to reach a conclusion regarding optimal treatment regimens. However, patients who present with >1 site of disease have a significantly worse prognosis. Clinical judgments must be used when treating patients with LCS. If a patient presents with a single, resectable area of disease, it is reasonable to treat with wide local excision to negative margins. Radiotherapy can be added in cases of subtotal resections or in inoperable situations. Systemic therapy should be considered in patients with disseminated disease. More research is required to determine a systemic therapy that is effective for these patients. We encourage physicians to publish cases of LCS in order to compile additional data that will assist in developing optimal treatments regimens.

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