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Case Report

We Won the Battle but did we win the War? A Rare Case of Perianal Langerhans Cell Histiocytosis Complicated by Myelodysplastic Syndrome

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Abstract

Langerhans cell histiocytosis is a rare group of proliferative histiocytic disorders of the bone-marrow derived langerhans cell. Largely a pediatric disease, it has a wide clinical spectrum ranging from a single lesion commonly found in skin and bones to multisystemic organ involvement. Adult-onset Langerhans cell histiocytosis as a perianal lesion is an uncommon presentation reported in a few case reports. The concurrence of Langerhans cell histiocytosis and myelodysplastic syndrome has been reported in four other adult cases in the English literature. Here we report a rare case of an 81 year old male with thrombocytopenia and a recurrent perianal lesion diagnosed as Langerhans cell histiocytosis with myelodysplastic syndrome. We highlight the importance of considering Langerhans cell histiocytosis in the differential when working up perianal lesions. We also review the literature to determine an underlying mechanism of association between langerhans cell histiocytosis and myelodysplastic syndrome and other hematologic malignancies and the need to monitor for these hematologic disorders in patients with Langerhans cell histiocytosis.

Keywords: Langerhans cell histiocytosis; Perianal; Adult; Myelodysplastic syndrome; Hematologic malignancy; Hematologic disorders

Abbreviations

LCH: Langerhans Cell Histiocytosis; MDS: Myelodysplastic Syndrome; IHC: Immunohistochemistry

Introduction

The literature on adult Langerhans cell histiocytosis (LCH) is largely based on pediatric cases making the need for research on its presentation and workup essential in further understanding LCH in the adult population. LCH has a heterogeneous clinical presentation ranging from benign eosinophilic granuloma in skin and bones to fatal multisystem involvement [1]. The cutaneous lesions of LCH commonly present as papules on the trunk and eczematous, seborrheic dermatitis-like lesions on the scalp and flexures [2-4]. Adult onset LCH presenting as a perianal lesion is a rare initial presentation leading to its frequent misdiagnosis. As we further understand this rare disorder, we continue to discover its association with other conditions. Literature review shows a possible association between LCH and hematologic disorders such as myelodysplastic syndrome (MDS) and hematologic malignancies. Concurrence of MDS and LCH has only been reported in four other cases in the English Literature and one in the French Literature to the best of our knowledge [5-8] (Table 1). Here we present the fifth case of perianal LCH complicated by myelodysplastic syndrome in the English Literature.

Case Presentation

Our patient is an 81 year old gentleman with a past medical history of coronary artery disease. He was first seen and evaluated for complaints of perianal fullness and pruritus of 6 weeks duration that had been intermittently worsening over the past 3 ½ years. On exam, he was noted to have a flat sessile non-bleeding, non-ulcerated lesion in the perianal region. His labs were significant for a platelet count ranging between 70,000 to 90,000/ UL (Normal: 140,000 – 400,000). There were no other significant chemical or radiological abnormalities. The patient underwent surgical excision. Immunohistochemistry (IHC) was positive for CD1a and S-100 protein confirming the diagnosis of LCH. The patient was treated with adjuvant radiation therapy and was found to be symptom and lesion free on subsequent follow up.

About a year after the patient's initial presentation, he returned with recurrence of perianal pruritus and fullness. Examination revealed a reemergence of his prior perianal lesion which was once again resected. IHC demonstrated CD1a and S-100 reactivity consistent with recurrence of his perianal LCH.

Patient was now treated with vincristine over a 15 week period. He was followed for 2½ years without noted recurrence. The asymptomatic thrombocytopenia; however, persisted with no clear etiology. Patient then underwent a bone marrow biopsy and aspiration which revealed myelodysplasia with myeloproliferative activity and absent iron stores. No cytogenetic testing was performed. No further action was taken in view of patient's age and comorbidities.

Discussion

LCH is a rare group of proliferative histiocytic disorders of the

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Table 1: Adult Cases of LCH associated with MDS.

Age	Sex	Presentation	Morphology	Biopsy/IHC	Follow up
80	M	Pruritic upper back lesion in patient with MDS [5]	Pruritic papule	Proliferation of cells with reniform nuclei and eosinophilic cytoplasm in epidermis and dermis. Immunoreactive for S100 protein and CD1a.	Death from complications of CHF 4 months after diagnosis
75	M	2 year history of erythematosus lesions over trunk and extremities with prior biopsy diagnosed as Para-psoriasis/early mycosisfungoides in patient with MDS [5]	Papules	Proliferation of cells with reniform nuclei and eosinophilic cytoplasm in epidermis and dermis. Immunoreactive for S100 protein and CD1a.	Death from an unrelated cardiac event 12 months later.
71	F	4 month history of pruritic, non-tender lesions on trunk, abdomen, and proximal limbs [6]	Red to brownish papules	Large ovoid cells containing abundant eosinophilic cytoplasm and reniform nucleus diagnosed as LCH	Treatment with prednisone and vinblastine x 2 months with noted worsening lesions. Patient developed pancytopenia with bone marrow aspirate showing LCH and MDS. Patient was started on azacitidine but died from pancytopenia and bacterial infection 8 months later.
53	F	Several months of cutaneous vasculitis (no histological specificity) in patient with MDS [7]			Complicated by development of cutaneous LCH and acute monobasic leukemia (no further details available in English literature). Rapidly fatal from disease.
64	M	Perianal itch [8]	Anal fissure and polyps	Histological features consistent with LCH	Treatment with topical steroids and antibiotics provided temporary relief but new skin lesions noted. Bone marrow biopsy done two months later consistent with MDS. Repeat biopsy 4 months thereafter with acute myelomonocyticleukaemia. Treatment with cytarabine started but patient died of leukemia 8 months later.

bone marrow derived Langerhans cells which constitutes 2-4% of the resident epidermal cells [9]. They function as immunologic cells presenting foreign antigens to T-cells and can present any wherein the body [9]. Among the different organs involved, a cutaneous presentation is seen in 40% of cases with the most common areas involving the trunk and scalp [2,3,9].

Here we review some of the published case reports of perianal LCH in adults (Table 2). Perianal lesions diagnosed as LCH ranged from one to multiple eczema-like lesions, ulcerations, fissures, ulcerated plaques, and fistulas with the most common lesion being papules [3,4,10]. They presented either asymptomatically or as a pruritus perianal rash as seen in our patient [11,12]. The diagnostic criteria on biopsy is uniform regardless of age or initial presentation and is based on IHC revealing histiocytic infiltrates with positive s100 protein and positive CD1astaining [2]. Birbeck granules are present in varying amounts seen on electron microscopy and further confirm the diagnosis [2]. The standardized guidelines for treatment follow up, and surveillance protocols are largely based on pediatric research and case studies further necessitating ongoing research to understand LCH.

The stimulus for the abnormal proliferation of Langerhans' cells and its inherent pathophysiological nature remains a topic of debate. LCH has a heterogeneous clinical course from a benign spontaneously regressing lesion to multisystem organ failure [13]. Higher cytokines have been identified in LCH lesions suggesting an overall inflammatory response with self-remission leading some to believe that LCH is a reactive process [13]. However, more recent data has identified over expression of p53 in the clonal proliferating cells of LCH suggesting a neoplastic process [13].

Although mainly an isolated disorder, LCH has been associated with hematologic malignancies prior to, concurrent with, and after diagnosis of LCH [14]. Recurrent BRAF V600E mutation has been found in LCH suggesting a possible clonal relationship between LCH and myeloid neoplasms and another venue for treatment via BRAF V600 E inhibitors [14]. A study looking at 18 adults with initial cutaneous presentations of LCH were collected from five centers and reviewed [8]. Two of eighteen patients had MDS [8]. During follow-up, 5 developed hematologic malignancies including monocytic leukemia (2 cases), histiocytic sarcoma (1 case), diffuse large B-cell lymphoma (1 case) and peripheral T-cell lymphoma (1 case) [8]. This study suggests that LCH has an inherent reactive process that predisposes patients to the development of hematologic malignancies. Studies have suggested a potential therapy related neoplastic phenomenon as well given the latency in development of the hematologic malignancies post-treatment of LCH [8,15].

There have been a few pediatric cases with diagnosed MDS prior to diagnosis and treatment of LCH [16]. In accordance with Billings et al, we suggest that LCH is a myeloid-stem cell disorder that may be related to myelodysplastic disorder and review the cytogenetic abnormalities shared by these disorders that may explain their association [5,13].

A review of four pediatric histiocytic tumor lesions with confirmed diagnosis of LCH noted cytogenetic abnormalities in all of the cases including an abnormal clone in LCH showing t(7;12)(q11.2;p13) translocation [17]. We reviewed other disorders with chromosome 7 abnormalities including MDS, familial syndromes associated with MDS and acute myeloid leukemia including Fanconi anemia, familial pediatric MDS, and severe congenital neutropenia [6]. Chromosome 7 may be one of the potential links between LCH and MDS and hematologic malignancies.

Table 2: LCH presenting as Perianal Lesions.

Age	Sex	Presentation	Morphology	Diagnosis 1.Skin Biopsy: 2.IHC	Treatment	Response	Associated malignancy
20	M	Painful perianal lesion x 1 year [2]	Well-demarcated, erythematosus, and ulcerated plaque surrounding the anal orifice. Infiltrated and tender.	1. Rich dermal infiltration with large histiocytes with reniform nucleus. 2.CD1a and S100 +	Thalidomide 100 mg nightly to 200 mg nightly x 4 months followed by 100 mg x 2 months. Maintenance dose of 50 mg/d.	Remission	
38	M	Painful genitoanal ulcerating lesions x 6 months [3]	Ulcerated malodorous plaques, covered with slough (also noted systemic involvement including buccal mucosa and fingernails).	1. Dense perivascular and interstitial infiltrate with large histiocytic cells. 2. + S100 and CD1a. Electron Microscopy: Birbeck Granules	1. Cladribine 10 mg i.v per day x 5 days monthly for half year. 2. Thalidomide 200 mg oral per day x 3 months followed by 100 mg x 9 months.	1. Partial remission without improvement of perianal lesions. 2. Remission.	Non-Hodgkin's Lymphoma with bone- marrow involvement (initial biopsy negative at time of LCH diagnosis) s/p 6 cycles of CHOP with development of acute lymphatic leukemia (B-ALL) 9 months later.
64	M	Perianal itch [8]	Anal fissure, polyps	Histological features of LCH	Topical antibiotics and steroids	Temporary relief but then development of new skin lesions.	Acute myelomonocytic Leukemia
19	M	Friable perianal lesion x 2 years [10]	Two flat sessile, granulomatous, friable lesions on each buttock.	1.Ulceration of the epidermis and underlying histiocytic cells	Excision	Remission	
69	M	Persistent multiple ulcers around anus and perineum failing treatment for HSV [11]	Well-defined punched out ulcers without lymphadenopathy.	1.Dense cellular infiltrate of eosinophils, lymphocytes, histiocytes around ulcer 2.+S100 EM: Birbeck granules	Tacrolimus ointment 0.1% x 3 weeks and later 30 sessions of high dose (130 J/cm2) UVA1 phototherapy	No improvement	
34	M	Bleeding, painful ulcer x 19 months diagnosed as Crohn's disease [18]	Ulcerated lesion located in posterior commissure of the anus, jagged edges, slightly elevated, friable.	2.Third biopsy revealed CD1a and S100 +	Six doses of intralesional triamcinolone and oral thalidomide for three months.	Remission	
69	F	Erythematosus lesions in the anogenital region. Failed antifungals and steroids [19]	Pale red, infiltrated erythema with marginal flat papules localized in the perianal region and on the labia major.	Typical pattern of LCH	Radiation	Remission x 5 years. 1 year later developed acute respiratory failure 2/2 LCH.	
69	M	Perianal fistula and eczema [20]		1.Mixed histiocytic and eosinophilic infiltrates 2. CD1a and S100 +.	Prednisolone 1 mg/kg	Remission	
34	M	Perianal infiltrate [21]	Condylomata acuminate in appearance		Luestatin in 4 cycles	Regressed 50%. Complete remission with local radiation and adiuretin	

Did our patient have a myelodysplastic syndrome prior to his LCH or did this develop or progress after his chemotherapy? Our patient had a noted thrombocytopenia prior to his diagnosis and treatment of LCH suggesting that the patient may have had undiagnosed MDS prior to initiation of chemotherapy for LCH. Our patient would have benefited from undergoing a bone marrow biopsy at time of diagnosis of LCH given his thrombocytopenia and in light of a possible association of MDS and LCH. He would have also benefited from frequent follow up to monitor for development of hematological disorders.

Conclusion

Adult onset LCH as a perianal lesion is a rare presentation. The association of adult LCH with MDS and other hematologic disorders has been reported with studies showing a possible cytogenetic relationship linking these two diseases together. Here we presented an adult with recurrent perianal lesion diagnosed as LCH complicated by MDS. Our case highlights the importance of including LCH on the differential for perianal lesions and need to monitor for MDS and other hematologic disorders given the likely underlying pathogenetic relationship between these diseases. Although our patient's LCH was in remission for 2 ½ years, there was a likely dwelling undiagnosed MDS that lay untreated requiring further workup and monitoring. We recommend close follow up of LCH patients despite complete remission to identify malignancy at an early stage. We won the battle, but did we win the war?

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