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Case Presentation

Indeterminate cell histiocytosis successfully treated with narrowband UVB

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Abstract:

We present a 47-year-old man with a sudden eruption of more than 100 reddish-brown papules, which histologically exhibited a dense dermal proliferation of large mononuclear cells with vesicular nuclei and abundant pale cytoplasm. Electron microscopy and immunohistochemistry revealed findings consistent with indeterminate cell histiocytosis and the patient responded well to treatment with narrowband UVB therapy.

Case synopsis:

A 47-year-old, otherwise healthy man with a history of mild plaque psoriasis presented to his dermatologist for evaluation of two asymptomatic, reddish brown, dome shaped papules on his abdomen. The lesions had been present and asymptomatic for several weeks and further evaluation and treatment was initially deferred given the banal appearance of the lesions. In ensuing weeks however, the number of similar appearing lesions increased and spread centrifugally from his trunk to his extremities and face. When the patient returned for a follow up several weeks later, he had over a hundred lesions involving his entire body, but most prominent on this trunk (Figures 1 and 2). Punch biopsies of representative lesions were obtained at this time. A systemic workup was also performed as even though the patient remained in good health, the sudden increase in the number of skin lesions raised concern for internal disease. A systemic workup including bone marrow biopsy, computed tomography scan of the chest, abdomen and pelvis, complete blood count, and complete metabolic panel was performed. The results of these evaluations were normal except for a mild thrombocytopenia. Given the negative systemic work up and the patient's continued overall good health, concern for systemic involvement was considered minimal.

Prior to histologic examination, a clinical differential diagnosis was contemplated and based on the eruptive nature of the disease consisting of hundreds of discrete dome shaped red brown papules. The differential diagnosis included a wide variety of papular entities. Mast cell disorders can present eruptively, but our patient demonstrated no urtication and only minimal itching, making this diagnosis seem unlikely. Lymphocytic disorders also seemed unlikely because the eruption consisted of hundreds of discrete firm papules; T cell disorders most often present as indolent patches or plaques, whereas B cell disorders more commonly present as solitary or localized lesions, often plum colored. Clinically, lymphomatoid papulosis can present as numerous papules, but the lesions have a tendency toward hemorrhage and crusting, which was lacking in our patient. The eruptive and discrete nature of the papules brought to mind the histiocytoses, such as Langerhans and non-Langerhans cell histiocytoses. Langerhans cell histiocytosis typically presents in a distribution favoring the flexures or similar to seborrheic dermatitis, which our patient did not demonstrate. The individual morphology of the lesions was reminiscent of multicentric reticulohistiocytosis. However, the sparing of acral surfaces was inconsistent with this diagnosis. Finally, the non-Langerhans cell histiocyte disorders were considered, of which, generalized eruptive histiocytosis and indeterminate cell histiocytosis seemed most likely considering the patient's age and truncal distribution were not consistent with the other non-Langerhans cell disorders of benign cephalic histiocytosis or juvenile xanthogranuloma.

The results of the punch biopsies were obtained and histologic evaluation revealed a dense dermal proliferation of large mononuclear cells with vesicular nuclei and abundant pale cytoplasm along with an admixed infiltrate of normal appearing lymphocytes. Epidermotropism was not present. Immunohistochemical evaluation showed diffuse CD1a and CD68 positivity, negative CD207 (langerin) staining, and weaker S-100 staining (Figures 3 – 8). Electron microscopy revealed a diffuse sheet-like

infiltrate in the papillary and reticular dermis without Birbeck granules in more than 95% of the histiocytoid cells. The patient was diagnosed with indeterminate cell histiocytosis (ICH).

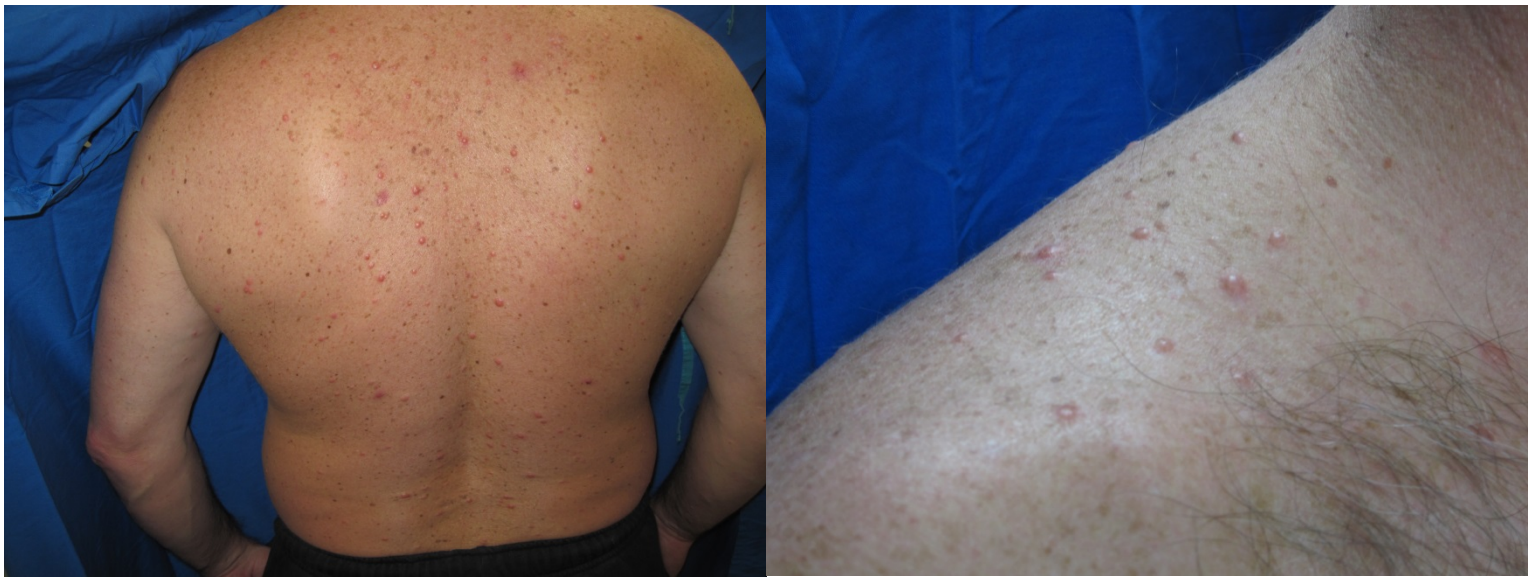


Figure 1. Trunk of our patient with indeterminate cell histiocytosis (ICH) demonstrating numerous discrete wide spread reddish brown dome shaped papules. This was his initial presentation.

Figure 2. On closer view of the dome shaped papules, many are showing an iridescent quality.

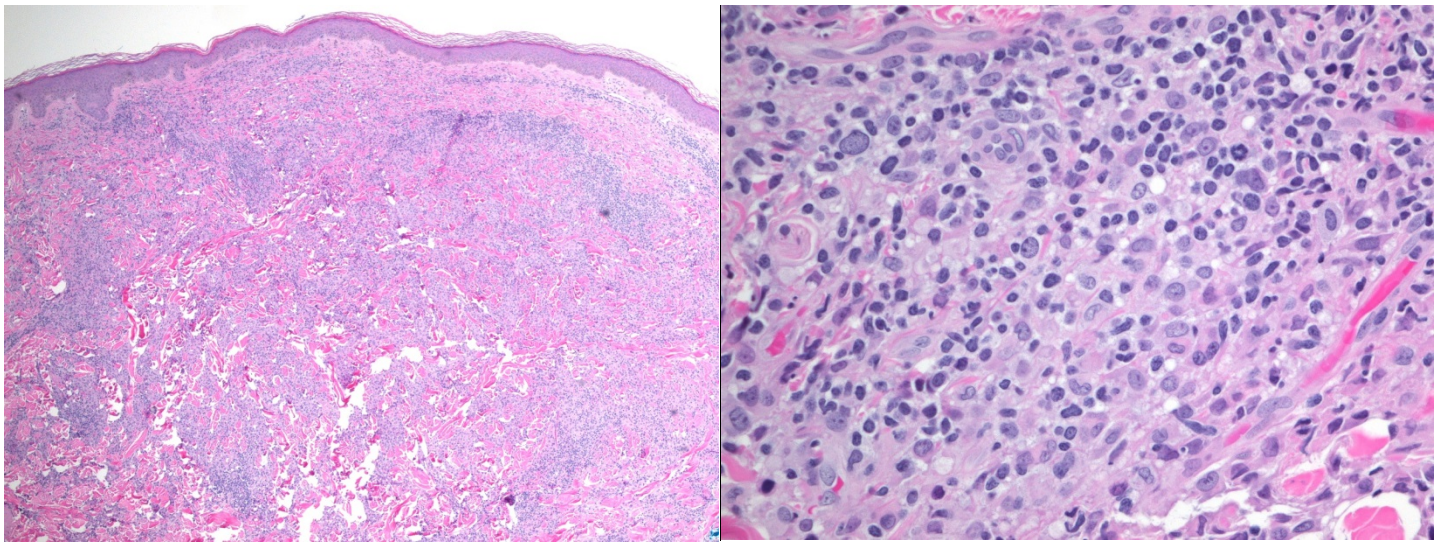
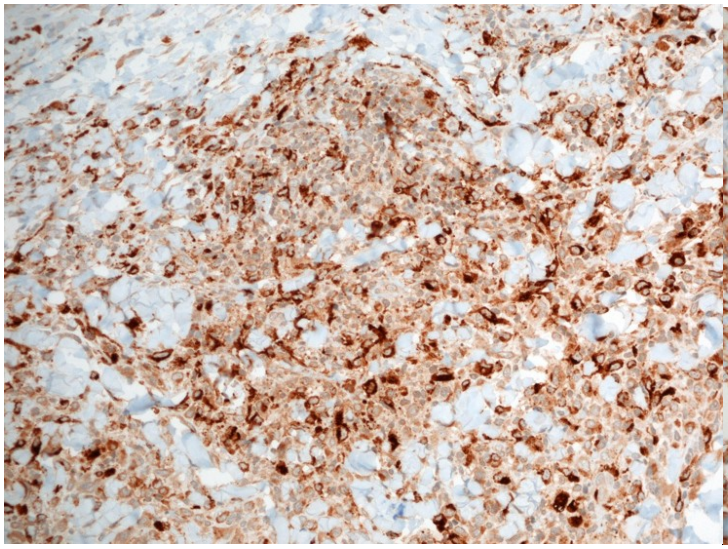


Figure 3. Low power H&E demonstrating the dense dermal proliferation of large mononuclear cells.

Figure 4. High power H&E demonstrating the dermal proliferation of mononuclear cells with vesicular nuclei and abundant pale cytoplasm. Note the lack of epidermal involvement.



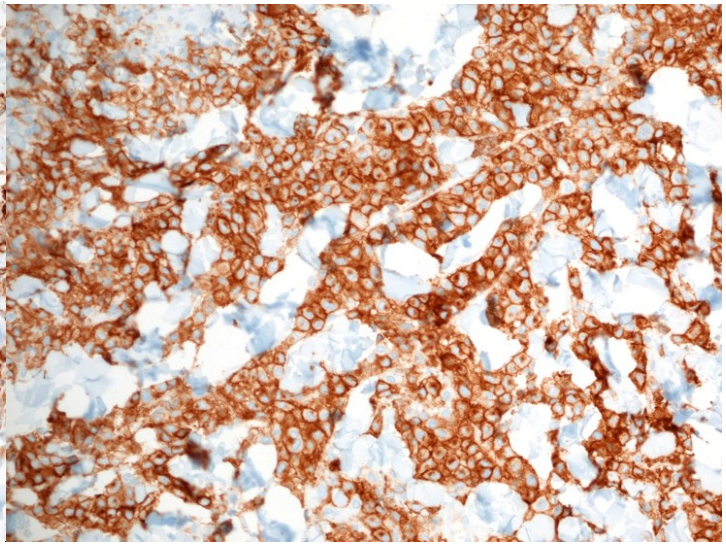
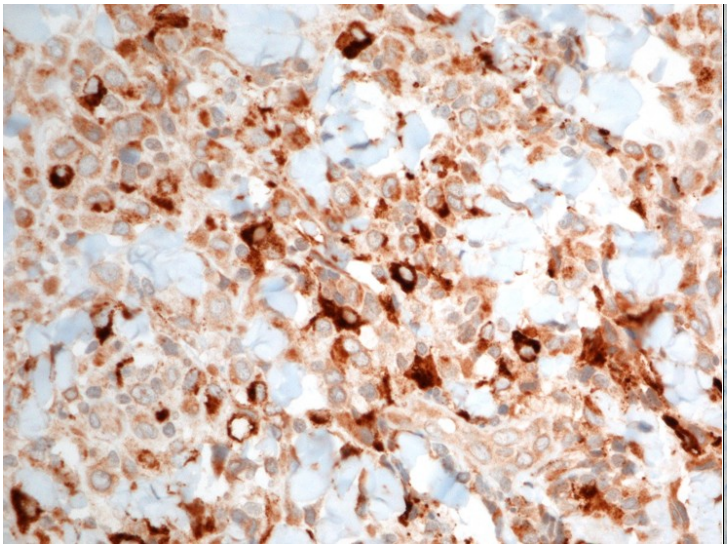


Figure 5. CD68 staining showing diffuse positivity. **Figure 6.** CD1a staining showing diffuse positivity.



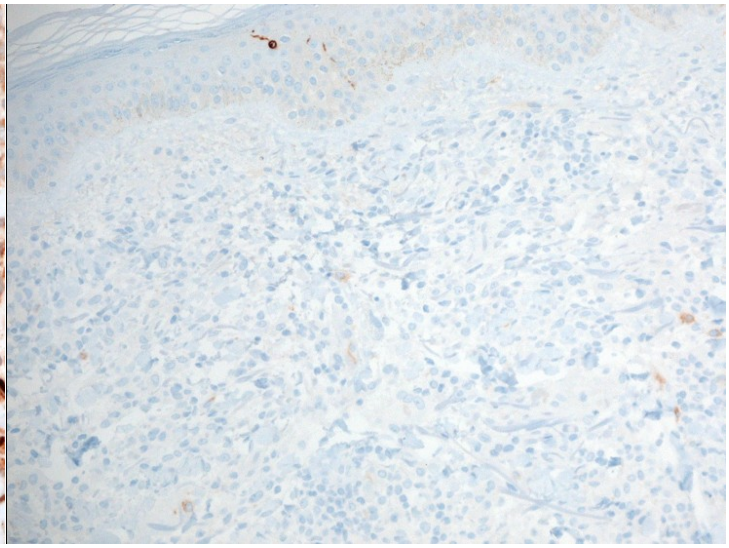
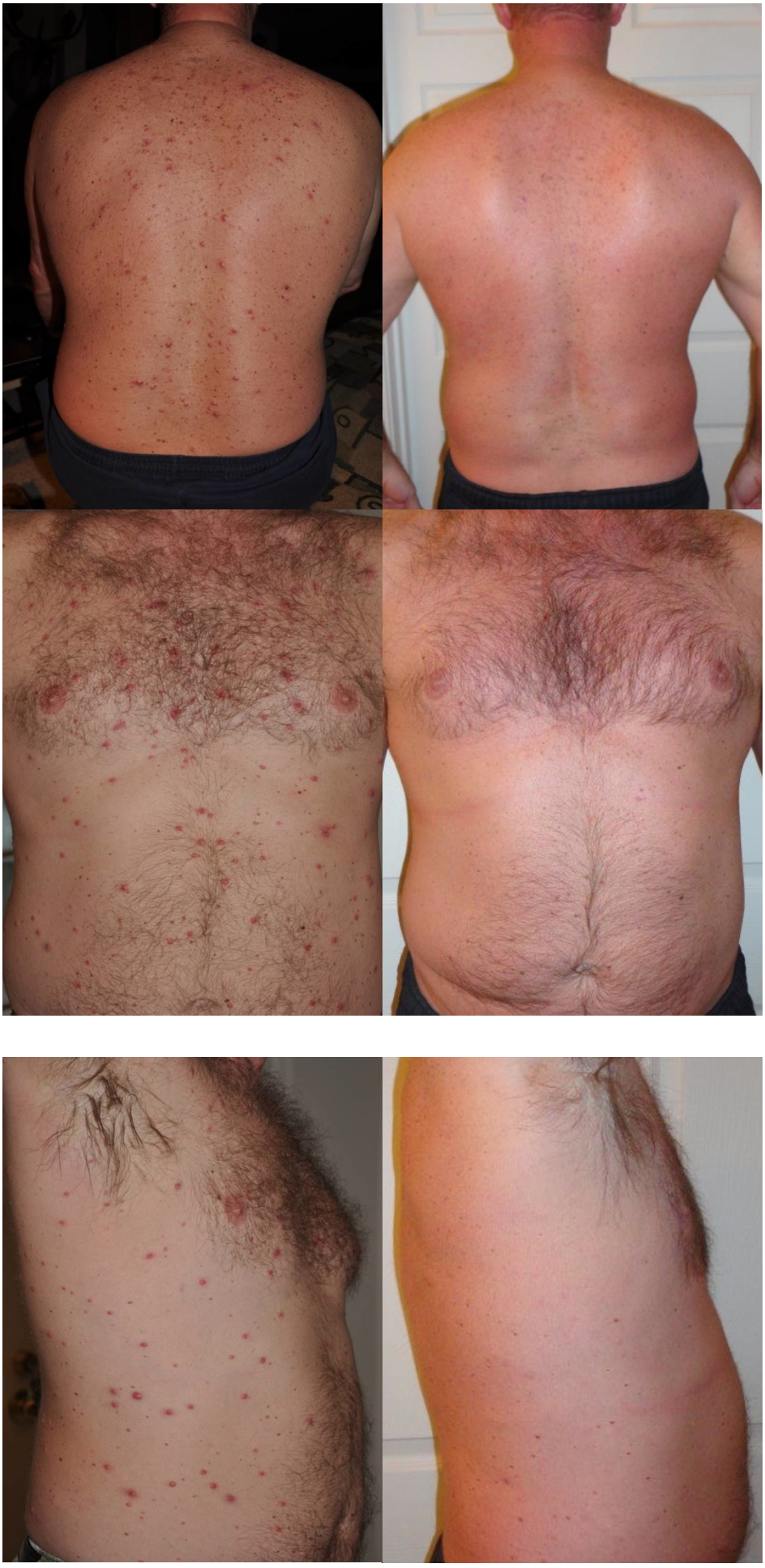


Figure 7. S100 positivity was more focal and demonstrated in this section.

Figure 8. Langerin staining is negative. Note the positive staining Langerhans cell within the epidermis demonstrating a positive internal control.

Given the aforementioned absence of systemic disease, narrowband UVB phototherapy (NBUVB) was initiated to treat the patient's skin lesions. He was started at a dose of 400mJ/cm^2 two to three times per week increased by 100mJ/cm^2 per session until a maximum of 1800mJ/cm^2 was reached. Over the course of thirty treatments, most of his skin lesions flattened, leaving only hyperpigmentation. After several months of office phototherapy, he procured a home phototherapy unit to ease the logistical burden of office phototherapy. He has continued his phototherapy at home with similar results. Throughout the course of his treatment he has remained in good health. Initially, in the first few months of phototherapy, he continued to develop a few new lesions in addition to having many recalcitrant papules. Several of these lesions were biopsied to exclude another process given their recalcitrant nature, but the histology continued to be consistent with ICH. Over the course of approximately one year, the patient reports essentially complete resolution of his lesions at his current phototherapy dose of 1800mJ/cm^2 several times per week (Figures 9 – 14). Despite having a diffuse erythema (sunburn type reaction) at one point, he has reported no adverse reaction from his phototherapy. His dose has since been titrated lower and he continues to have good control of his skin disease. His thrombocytopenia, felt to be unrelated to his skin disease, has resolved as well. We plan to titrate his phototherapy to the lowest dose possible to control his disease, perhaps even tapering off phototherapy completely, depending upon his response to the taper. We anticipate seeing him in our clinic every six to twelve months for ongoing monitoring not only of his skin lesions, as there are reports of ICH having a relapsing remitting nature, but also for monitoring of potential systemic disease, given that ICH has been associated with hematologic malignancies [1,10,11].



Figures 9 – 14. Figures 9, 11 and 13 demonstrate the extent of the patient's skin lesions prior to initiation of narrowband UVB. Figures 10, 12 and 14 demonstrate the almost complete clearing of the patient's skin lesions after approximately one year of narrowband UVB phototherapy.

Discussion

Although the true nosology of indeterminate cell histiocytosis (ICH) or indeterminate cell tumor (ICT) has been a subject of contention since Wood et al initially described this entity in 1985, in 2008 the World Health Organization (WHO) incorporated ICT officially into its Classification of Tumors of the Hematopoietic and Lymphoid Tissues [1,3]. It is also present in the 2006 version of the WHO Classification of Skin Tumours as indeterminate cell histiocytosis [14]. The terms indeterminate cell histiocytosis, indeterminate cell tumor, and indeterminate dendritic cell tumors are used interchangeably in the literature. ICH is perhaps best defined by its immunohistochemical staining, the pattern of which has features of both macrophages, with CD68 positivity, and Langerhans cells, with both S-100 and CD1a positivity [1,2]. Importantly, Birbeck granules, whose function remains unknown, have been classically absent on electron microscopy examination. More recently, langerin (CD207), an immunohistochemical stain for a transmembrane protein found in Birbeck granules, has been used in lieu of electron microscopy [1,2]. Staining for this marker is classically negative in ICH.

The true pathogenesis of ICH remains an enigma, although two theories are noted in review of the literature. The first is in regards to cases of ICH arising *de novo*. Because the cell of origin is thought to be the Langerhans cell, it is believed that indeterminate cells are a stage in the development of the Langerhans cell. However, it is uncertain as to whether or not the indeterminate cells are immature Langerhans cells not yet having developed Birbeck granules or Langerhans cells that have lost their Birbeck granules in migration towards a lymph node [2]. The second theory relates to those cases evolving from a preexisting B cell lymphoma. Although the cell of origin in ICH is from the common myeloid progenitor lineage, which does not given rise to B or T cells, cases of ICH have arisen in association with low grade B-cell lymphoma, leading some authors to speculate that ICH may be the result of B-cell dedifferentiation, caused by an as yet, unknown mechanism [2,13].

Clinically, the disease has no gender predilection and has occurred in all ages. It can present with multiple papules spread over the trunk and extremities or can occur as an isolated variant with a single or discrete group of lesions [1,2,4-13]. The multiple papular variant tends to occur as a spontaneous eruption, the course of which varies from different sources with spontaneous remission, stable disease, or remission and recurrence [1,2, 4-13]. ICH has also been reported without skin findings, occurring only in the lymphoreticular system [2]. Most of the reported ICH cases have followed an asymptomatic, benign course resolving without intervention. However, there are reports that describe extracutaneous manifestations that include ocular and bone involvement [1], leukemia [4] and low-grade B cell lymphoproliferative disorders [2, 13]. There have also been reports of ICH occurring after an inflammatory process. Specifically, ICH has been reported to occur after scabies and pityriasis rosea [1]. However, some sources suggest that this reactive form of ICH should be regarded as a distinct entity, separate from classic ICH [10].

The primary clinical entity in the differential diagnosis to consider is generalized eruptive histiocytosis, which can appear clinically identical. However, on immunohistochemical staining, the two diagnoses should be readily distinguished because the histiocytes of generalized eruptive histiocytosis are negative for CD1a and S100 protein, in contrast to their positivity in ICH. The primary histopathologic entity in the differential diagnosis to consider is Langerhans Cell histiocytosis (LCH). Previously, only electron microscopy could reliably distinguish ICH from LCH; Birbeck granules are present in LCH only. More recently, however, differential expression of langerin (CD207) has proven an effective surrogate for ultrastructural demonstration of Birbeck granules, thereby distinguishing LCH from ICH without the need for electron microscopy [1,2].

The overall course of the disease is not always entirely clear in the literature because many of the case reports have not included treatment or long term follow up [10, 13]. One study by Ratzinger et al reported on 18 patients with indeterminate cell histiocytosis who were followed up from six months to seven years after their initial diagnosis. In this study, the majority of patients with localized disease experienced complete resolution after excision (9 out of 10). Those with more widespread lesions tended toward stable disease, even without specific treatment. Only two patients developed slow progression of skin lesions. Two patients in this cohort did develop systemic disease, one with lesions of the eye and the other with lesions of the bone. No deaths or other serious illnesses were reported as related to ICH in this study, supporting the premise that ICH runs a benign course, regardless of the solitary or diffuse variant [1,2,10]. One case report documents remission and recurrence without treatment and there are reports of remission and recurrence with chemotherapy [10,11]. Even though it is uncommon, the most concerning outcome regarding the prognosis of ICH are the reports of evolution to hematologic disorders, with death having occurred in some instances even after treatment with chemotherapeutics [2,4,10].

There is no standardized treatment for ICH. Case reports describe a wide range of effective therapies to include, ultraviolet phototherapy [5,6], thalidomide [7], thalidomide and isotretinoin [11], methotrexate [8], oral cyclophosphamide [10], pravastatin [12], total skin electron beam therapy [9], and surgical excision for solitary lesions [1]. Partial remission of lesions can occur as was the case with our patient initially [1]. A systemic workup prior to initiation of therapy should be considered given ICH's association with extracutaneous manifestations because systemic involvement would have a bearing on the choice of treatment.

Consideration should also be given to routine follow up after the initial diagnosis of ICH, regardless of response to treatment; there are several documented reports of patients developing hematologic malignancies years after their initial diagnosis [2,4,10].

Conclusion

There appears to be consensus among experts that ICH exists as a defined entity [3,10,14]. The defining characteristics of ICH are in large part immunohistochemical, with positive staining for CD1a, CD68 and S100 and negative staining for langerin, a surrogate marker for Birbeck granules, which are classically absent on electron microscopy. Our patient presented with classic ICH, consisting clinically of widespread, eruptive discrete papules, histology demonstrating a lack of epidermotropism, and electron microscopy demonstrating a lack of Birbeck granules [10]. Although we believe the expected prognosis of our patient to be excellent given that his disease is limited only to the skin, we will continue to monitor his condition for any evidence of systemic disease. Although we used narrow band UVB, we have identified at least two other case reports in the literature using phototherapy successfully, one using narrowband and one using broadband UVB [5,6]. Finally, with regards to the treatment of ICH, we believe our case report adds additional support to the use of phototherapy in the treatment of ICH, not only for its demonstrated effectiveness, but also given its overall low side effect profile with very low risk of systemic toxicity, especially when compared to chemotherapeutics.

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