

Indeterminate Cell Histiocytosis – Case Report and Review of Literature

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Abstract

Introduction. Indeterminate cell histiocytosis is a rare proliferative disorder of indeterminate dendritic cells, reported in only 50 case reports so far. It is clinically presented as yellow, red or brown papules and nodules that appear in otherwise healthy adult individuals. Indeterminate cells are distinct dendritic cells of the skin that have ultrastructural similarities to the epidermal Langerhans cells but do not contain the characteristic Birbeck's granules and they are also langerin-negative, unlike LCH. Indeterminate cell histiocytosis is an exceptional entity with variable clinical, histopathologic or immunohistochemical findings, sharing morphologic and immunophenotypic features with both Langerhans- and non-Langerhans cell histiocytoses. **Case Report.** We present a case of indeterminate histiocytosis in a 77-year-old man with 3-year history of asymptomatic, multiple reddish and brown papules and nodules over the entire body, including the oral mucosa. Skin biopsy was done, and histopathological analysis with immunohistochemistry was performed. The positive ICH staining of cells for CD68, CD1a, and S-100 enabled us to diagnose ICH in our patient. Also, *BRAF V600E* mutation was detected in tumor tissue. The treatment was started with methotrexate that was effective for 6 months, but due to the disease recurrence, further therapy with thalidomide was advised, without effect. **Conclusion.** Indeterminate histiocytosis is a rare disease, therefore no standardized treatment has been established and the treatment options are limited.

Key words: Histiocytosis; Dendritic Cells; Langerhans Cells; Skin Neoplasms; Rare Diseases; Treatment Outcome

Introduction

Indeterminate cell histiocytosis is an extremely rare variant of cutaneous histiocytosis which can be distinguished from Langerhans cell histiocytosis by three important characteristics: the lack of Birbeck granules on ultrastructural study, the absence of epidermotropism on histopathology, and the lack of extracutaneous involvement. These cells evidently express both Langerhans cell and monocyte/macrophage markers (1). It is clinically characterized by multiple asymptomatic yellow, red, or reddish brown papules and nodules that can be found in otherwise healthy individuals (2).

Indeterminate cells may present as dendritic cells histologically and immunohistochemically resembling Langerhans cells because of their expression of CD1a and S-100, but without the definitive Birbeck granules (3). The real relationship between the two types of cells has been a matter of controversy

since their original finding. Because of the fact that indeterminate cells migrate into the epidermis, some authors share an opinion that their organelles may modify and may become LC (1). On contrary, in cell culture, LC usually lose Birbeck granules, resembling indeterminate cells and therefore some authors have also postulated that finding of the indeterminate cells may represent a more mature form of LC (2-4). Because of their immunophenotypic similarity, indeterminate cells are considered to be related to Langerhans cells. By definition, they express S-100 protein and CD1a, but in contrast to LCh, they do not express langerin (CD207). Furthermore, these tumors do not express any of other histiocytic and dendritic specific markers including CD163, CD30, CD21, CD23, and CD35. They are variably positive for CD45, CD68, lysozyme, and CD4 (4-6).

ICHs are extremely rare neoplasms of indeterminate cells and have only been re-

ported in less than 50 cases. In most cases the patients have been presented with one or more papules, nodules, or plaques on the trunk, face, neck or extremities. Diagnosis is established based on the histopathological analysis of the lesion. In case of localized disease, further work-up with systemic CT scans and bone marrow biopsy is not indicated (5, 6). Treatment of the disease is not standardized due to its rarity. The treatment options include: systemic chemotherapy, PUVA, narrowband ultraviolet B phototherapy, thalidomide, pravastatin and low dose methotrexate. The disease course is usually not progressive. Recently, BRAF mutations were found in patients with certain forms of histiocytoses and treatment with BRAF inhibitors was found to be effective in some of these patients.

Case Report

A 77-year-old man presented with a 3-year history of asymptomatic multiple brown and reddish papules and nodules over the trunk and extremities and in the oral mucosa



Figure 1. Asymptomatic multiple brown and reddish papules and nodules over the trunk



Figure 2. Reddish papules and nodules

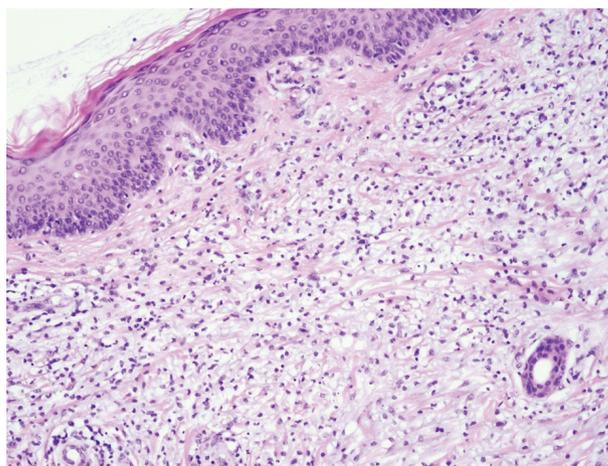


Figure 3. Histopathology revealed a diffuse, moderately mononuclear, monomorphous, nonepidermotropic infiltrate of large epithelioid cells in the upper dermis (stain type–Hematoxylin and eosin; original magnification: 100).

(Figures 1, 2, 3). The first skin biopsy was nonspecific with superficial dermal infiltrate of lymphocytes. The patient was treated with systemic corticosteroids and colchicine without response, and then with indometacin, desloratidine, dapson and azathioprine, again without effect. The patient's history, physical examination, and routine laboratory tests did not show any systemic involvement. The erythrocyte sedimentation rate (ESR) was increased and the C-reactive protein was elevated (SE 125 mm/h; CRP 36,1 mg/l), as well as the level of lactate dehydrogenase (256 U/L). The results of serum protein electrophoresis (SPEP), ANA, anti-HIV antibody, complete blood count, total proteins, serum albumin, bilirubin, cholesterol, triglycerides,

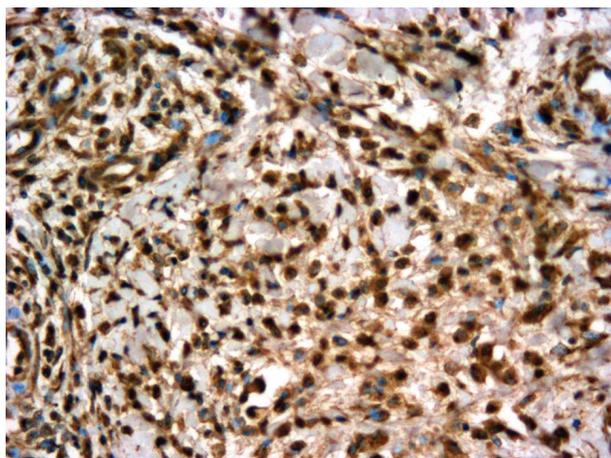


Figure 4. Immunohistochemical examination showed expression of S-100 (original magnification: 300)

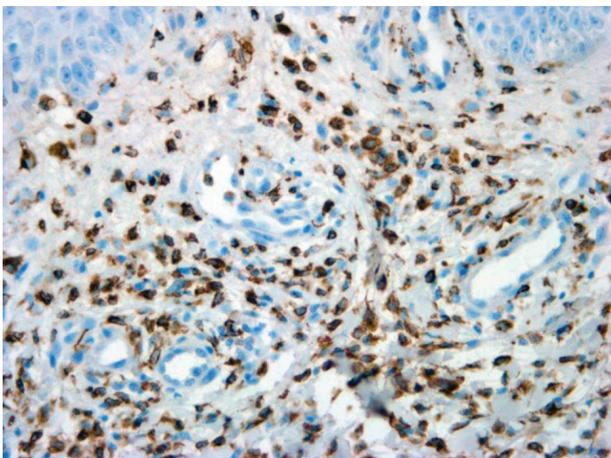


Figure 5. Immunohistochemical examination showed expression of CD 68 (original magnification: 300)

AST, ALT, CK, RF, a-CCP, IgM, IgA, IgG, C3, C4, PSA, f/t PSA were within normal range. Chest radiography, radiography of the joints of hands and feet, and ultrasound imaging of the abdomen and peripheral lymph nodes showed normal results. Skin biopsies were repeated and histological findings of the second and the third skin biopsies were also non-specific, while diffuse, moderately active mononuclear infiltrate of small histiocytic cells was found in the upper dermis on the fourth biopsy. Histiocytes were kidney-shaped, segmented and partly with the light nucleus. Immunohistochemical examination showed histiocyte cell expression of S-100 protein and CD68, while no expression was found for

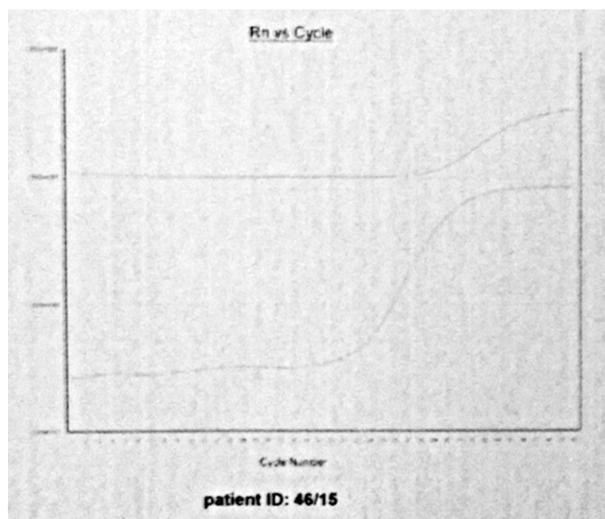


Figure 6. The genetic analysis of BRAF mutation was done using real-time PCR

CD3, CD4, CD8, CD10, CD20, CD30 and CD1a (Figures 4, 5). Also, somatic mutation in the *BRAF* gene (*BRAF^{V600E}*) was identified (Figure 6). Bone marrow biopsy was done and showed normal result, and TCR and BCR rearrangement analysis revealed polyclonal pattern in the bone marrow. B clonality testing in the skin tissue showed IgH monoclonal B cell infiltrate, while it was polyclonal in the peripheral blood. TCR rearrangement in the skin and peripheral blood revealed polyclonal pattern. CT of the chest, abdomen and pelvis showed normal results.

The diagnosis of indeterminate cell histiocytosis was made based on clinicopathologic and immunohistochemical findings. The patient was treated with methotrexate with regression of skin lesions (Figures 7, 8). However, after six months, a new flare-up of generalized reddish nodules was evident, so the treatment with thalidomide was advised, but with no response. The patient was lost to follow-up and died one year later.

Discussion

Histiocytoses are a heterogeneous group of disorders characterized by the proliferation and accumulation of the cells of mononuclear-macrophage system and dendritic cells, originating from neutrophil/macrophage lineage CD34⁺ progenitor cells in the bone marrow (3-7). Langerhans cells (LC), the proto-



Figure 7. After treatment with methotrexate



Figure 8. After treatment with methotrexate

type of dendritic cells are characterized by strong immunoreactivity for S100 protein and CD1a. In addition, they show Birbeck granules, a defining ultrastructural feature of LC.

Monocytes/macrophages are defined by markers, such as KP1 (CD68) or Ki-M1p.2 Ultrastructurally, they show phagolysosomes, but no Birbeck granules. Occasionally, LC stain for KP1 (CD68), but then with less intensity than macrophages. Conversely, macrophages are usually negative for the LC markers, S-100 protein and CD1a. Various hypotheses regarding the relationship between LC and IC have been proposed – i.e. ICs are either immature precursors of LC and LC are precursors of IC or both are independent types of dendritic cells.

Less than 50 cases of ICH have been reported so far. The disease is a proliferative disorder of dendritic cells that has both immunophenotypic features of Langerhans cells (CD1a and S-100-positive) and macrophages (CD68-positive). Birbeck granules that characterize Langerhans cells cannot be detected by electron microscopy in ICH histiocytes. Nowadays, it is proposed that ICH could be a non-Langerhans' cell histiocytosis variant, but its pathogenesis has remained unknown (5-8).

Two theories on pathogenesis of this rare disorder have been presented in the literature. The first is in regard to the cases of ICH arising de novo. Since the cell of the origin is thought to be the Langerhans cell, it is believed that indeterminate cells are a phase in the development of the Langerhans cell. However, it is still uncertain whether or not the indeterminate cells are immature Langerhans

cells that have not developed Birbeck granules or that they are Langerhans cells that have lost their Birbeck granules in their migration towards a lymph node. 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, some 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 a so far unknown mechanism (8, 9).

Histologically, there is a diffuse dermal infiltration of cells with irregular nuclear grooves and clefts that resemble Langerhans cells. These cells are without Birbeck granules on electron microscopy and desmosomes; however they contain cell processes. On immunohistochemistry, these cells are S100 and CD1a positive and are negative for CD21, CD23, CD35, langerin, and B and T cell markers (13). Although langerin immunostaining was not available at the time of diagnosis, the histopathological analysis with immunohistochemical profiling was consistent with the diagnosis of ICH in our patient.

Recently, a somatic mutation in the *BRAF* gene (*BRAF V600E*) was identified in Langerhans cell histiocytosis and Eredheim-Chester disease tissue infiltrates, suggest-

ing a common origin of both histiocytoses and leading to the reclassification of these disorders (12-14). The presence of *BRAF* mutation in indeterminate cell histiocytosis was also described in case reports, as well as in our patient (5, 10).

ICH is a localized or generalized, and almost exclusively cutaneous disease (9-12). A study done 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 the localized disease experienced complete resolution after excision. The disease tended to become stable in the patients having more widespread lesions, even without specific treatment. Only two patients developed a slow progression of skin lesions. Two patients in this cohort developed a systemic disease, one with lesions of the eye and the other with lesions of the bone. Neither deaths nor other serious illnesses were reported as related to ICH in this study, thus supporting the premise that ICH runs a benign course, regardless of the skin lesion distribution (solitary or diffuse variant). One case report documents the remission and recurrence without treatment but there are reports of remission and recurrence also with chemotherapy. Even though it is rare, there are cases with systemic involvement,

Table 1 Treatment modalities for ICH and their effects in previous case reports

Number of patients	Immunostaining of the dermal cell infiltrate	Treatment modality	Treatment efficacy	Reference
1	CD1, CD68, S100	nbUVB	Short term	Nogueira Zerbini MC, 2016. (20)
1	CD1, S100	nbUVB	Complete	Ishibashi M, 2008. (21)
1	S100-	nbUVB	Complete	Bard S, 2011. (22)
1	S100, CD68	methotrexate	Complete	Fornier J, 2011. (23)
1	S100, CD 1-	thalidomide	Complete	Toth B, 2012. (24)
1	CD1, S100, CD68	thalidomide	Complete	Ventura, 2010. (27)
1	CD1, S100	EBT+ 2-chlorodeoxyadenosine	Complete	Adam Z, 2017. (26)
1	CD1, S100	PUVA	Without effect	Adam Z, 2017. (26)
1	CD1, S100, CD68	pravastatin	Complete	Burns MV, 2011.(28)
1	S100, CD68	methorexate thalidomide	Short term Without effect	Vojvodic A, 2018.

Abbreviations: nbUVB- narrowband UVB, PUVA- psoralen and UVA, EBT- electron beam therapy

resistant to the chemotherapy with the lethal outcome. Our patient was treated for 6 months with methotrexate with a temporary resolution of skin lesions, but with a further relapse and unsuccessful treatment with thalidomide. He was lost to follow-up and he died a year later, and further details from his medical history were unavailable.

There is no standardized treatment for ICH (Table 1) (14-17). As ICH has a benign clinical course, conservative management is the best approach. In some cases, skin lesions were resolved spontaneously. Some treatments that have been used with various success include systemic chemotherapy, PUVA, narrowband Ultraviolet B, thalidomide, pravastatin and low dose methotrexate with a generally good therapeutic response. Chemotherapy must be used for aggressive cutaneous ICH, which involves over 50% of the body surface area and lasts for at least 6 months with no spontaneous resolution and new appearing lesions. There are four reports of ICH association with malignancies: one case of mast cell leukemia, another patient with myelomonocytic leukemia, and two cases with low grade B-cell lymphomas (8, 14, 18). Our case was not associated with hematologic malignancy, which was ruled out. Our patient's clinical history, physical examination and routine laboratory tests did not show any systemic involvement. TCR and BCR rearrangement analyses revealed polyclonal infiltrate in the bone marrow. Monoclonal IgH B cell infiltrate was found in a skin sample, while it was polyclonal in the peripheral blood, which was described previously in these entities (19).

Conclusion

Indeterminate cell histiocytosis is a rare disorder of cutaneous histiocytic/dendritic system development, but the true pathogenesis is still unknown. It can be found mostly in adults and must be diagnosed only on the basis of a thorough clinical investigation, repeated skin biopsies, histopathological, immunohistochemical and molecular analysis. In our patient, treatment with methotrexate led to transient resolution of lesions, while further thalidomide treatment was inefficient. Targeted inhibition of *BRAF-V600E* with combined *BRAF* and *MEK* inhibitors could be a

good option and might be a promising therapy for patients with treatment resistant disease. Further research in these groups of rare disorders is needed to widen the treatment options for these patients.

Abbreviations

LCH, LC – Langerhans cells
Lh – Langerhans
ICH – Indeterminate cell histiocytosis
IC – Indeterminate cell

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Histiocitoza indeterminantnih ćelija – prikaz slučaja i pregled literature

Sažetak

Uvod. Histiocitoza indeterminantnih ćelija je retko proliferativno oboljenje histiocita koje je opisano u literaturi kao pojedinačni slučajevi kod oko 50 pacijenata. Javlja se u vidu žuckastih, crvenih ili smeđih papula i nodusa kod zdravih odraslih osoba. Indeterminantne ćelije su različite dendritične ćelije kože koje imaju ultrastrukturne sličnosti sa epidermalnim Langerhansovim ćelijama, ali ne sadrže karakteristične Birbekove granule, niti ekspimiraju langerin u poređenju sa Langerhansovom histiocitozom. Histiocitoza indeterminantnih ćelija je redak entitet sa promenljivim kliničkim, histopatološkim ili imunohistohemijskim nalazima, koji dele morfološke i imunofenotipske karakteristike histiocitoza Langerhansovih i non-Langerhansovih ćelija. Prikaz slučaja. Predstavljamo slučaj indeterminantne

histiocitoze kod 77-godišnjeg muškarca sa trogodišnjom istorijom asimptomatskih, multiplih, crvenkastih i smeđih papula i nodula na celom telu, uključujući i oralnu mukožu. Histopatološkom analizom bioptata kože uz imunohistohemiju ukazao je na pozitivno bojenje ćelijskih infiltrata na CD68, CD1a i S-100 što je omogućilo postavljanje dijagnoze histiocitoze indeterminantnih ćelija. Osim toga, detektovana je *BRAF V600E* mutacija u tumorskom tkivu. Lečenje je započeto metotreksatom uz regresiju promena na koži, ali su se posle 6 meseci promene ponovo javile, te je savetovana terapija talidomidom, zbog nedostupnosti *BRAF* inhibitora. Zaključak. Indeterminantna histiocitoza je retka bolest, što onemogućava standardizovani pristup dijagnostici i terapiji.

Ključne reči: Histiocitoza; Dendritske ćelije; Langerhansove ćelije; Kožne neoplazme; Retke bolesti; Ishod Terapije