Indeterminate Cell Histiocytosis: A Case Report

Chun-Hua Wang and Gwo-Shing Chen
Department of Dermatology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.

Indeterminate cell histiocytosis is a rare neoplasm composed of cells with mixed characteristics of Langerhans cells and non-Langerhans cells. An otherwise healthy, 36-year-old woman presented with asymptomatic generalized papules and nodules that had appeared on all four extremities, the trunk, and cheeks in the previous 6 months. The lesions were firm, painless, non-pruritic, and slightly flesh-yellow or reddish-brown in color. Histopathologic, immunohistochemical examination and electron microscopic studies showed characteristic findings of indeterminate cell histiocytosis: diffuse proliferative histiocytes infiltrating the dermis without epidermotropism or atypia; neoplastic cells expressing markers characteristic of both Langerhans cells (CD1a, S-100) and focal monocytes/macrophages (Factor XIIIa, CD68); and no Birbeck granules within the cytoplasm of the neoplastic cells. Flow cytometry revealed more CD34+ cells in the peripheral blood of the patient than in peripheral blood from a control. Interestingly, the patient responded favorably to psoralen ultraviolet A-range treatment. Herein, we present this case and review the literature.

Key Words: indeterminate cell histiocytosis
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The histiocytic disorders cover a wide range of benign and malignant diseases and can be differentiated on the basis of clinicopathologic features, ultrastructural picture, and prognosis. According to the origin of the proliferating cells, these conditions have been classified as Langerhans, non-Langerhans, and indeterminate cell histiocytoses [1]. Indeterminate cell histiocytosis (ICH) was first described by Wood et al in 1985 as a neoplastic disease originating from dermal indeterminate cells that are characteristically positive for S-100 and CD1a but lack Birbeck granules on electron microscopy [2]. A few cases have subsequently been reported. Cases with a solitary lesion have also been described [3,4]. We now present the first case in Taiwan and propose a new treatment for this disorder.

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Address correspondence and reprint requests to: Dr. Gwo-Shing Chen, Department of Dermatology, Kaohsiung Medical University Hospital, 100 Shih-Chuan 1st Road, Kaohsiung 807, Taiwan.
E-mail: d700086@kmu.edu.tw

Case Presentation

An otherwise healthy, 36-year-old woman presented with a 6-month history of generalized, firm, asymptomatic, flesh-yellow to reddish-brown, partially coalesced papules and nodules over the four extremities, anterior chest, shoulder, lower abdomen, back, and cheeks (> 60 in number) (Figure 1). No ulceration or mucosal involvement was noted, and no lymphadenopathy was found on physical examination. There was no family history and no history of trauma or infection before the occurrence of the skin lesions.

The following laboratory data were within normal limits: complete blood count with differential classification; urinalysis; stool analysis; serum electrolytes; general biochemistry (including lipids); Venereal Disease Research Laboratory/*Treponema pallidum* hemagglutination; qualitative test for antinuclear antigen; rheumatoid factor; tumor markers including α-fetoprotein, squamous cell carcinoma (SCC), tumor polypeptide antigen (TPA), and carcinoembryonic antigen; and the numbers of all T cells, active T cells, all B cells, CD4/CD8 cells, and DR+ cells. The dinitrochlorobenzene test and challenge test (performed 1

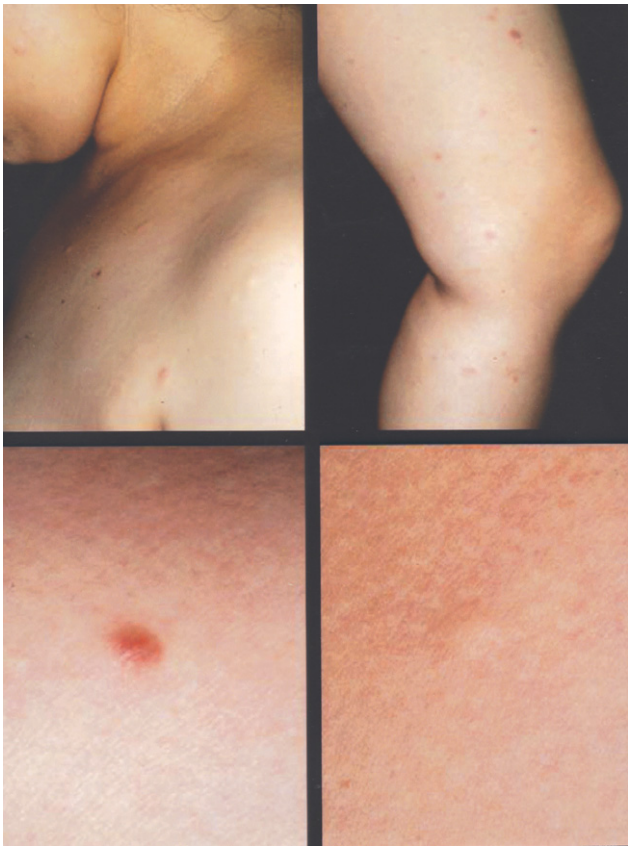

Figure 1. *Generalized asymptomatic flesh-yellow to reddish-brown papules and nodules on the four extremities, trunk, and face.*

week later) revealed erythema after 24 hours. Abdominal sonography, chest roentgenography, bone scan, and gallium-67 scan were not remarkable. The pathergy test and purified protein derivative test yielded negative results.

Multiple excisional biopsies were taken from the forearms and thighs. The specimens were fixed in formalin and embedded in paraffin for routine hematoxylin and eosin stain and immunohistochemical studies including S-100 protein, lysozyme, CD1a, human leukocyte antigen (HLA) DR, CD4, CD68, CD34, and Factor XIIIa. The histologic examination of all specimens revealed diffuse histiocytes infiltrating the entire dermis without subcutaneous fat involvement, as well as mild perivascular lymphocytic infiltration. The histiocytes were spindle or epitheloid in shape with round or oval nuclei and a pale cytoplasm. No kidney-shaped nuclei, intercellular edema, or epidermotropism were seen (Figures 2A and B). Staining with periodic acid-Schiff (PAS) and PAS diastase, specific for labeling neoplastic cells, was negative. Immunophenotypic studies revealed that the neoplastic cells were positive for S-100 and CD1a (Figures 2C and D) and focally weakly positive for CD4, CD68, Factor XIIIa, and CD34.

Slides for ultrastructural studies were processed using 2% paraformaldehyde and 2.5% glutaraldehyde, uranyl acetate/lead citrate staining, and epoxy resin (Epikote; Merck, Darmstadt, Germany) embedding. They were then examined using a goniometer-equipped transmission electron microscope (Jeol Jem-2000 EX II; JEOL Ltd, Tokyo, Japan). The cells had irregularly shaped nuclei, scanty chromatin, and abundant cytoplasm containing mitochondria, rough endoplasmic reticulum, ribosomes, and variable amounts of irregularly-sized dense bodies (Figure 3). Although an extensive search was carried out, Birbeck granules were not found in any specimen. Based on these clinicopathologic, immunohistochemical, and ultrastructural data, the diagnosis of ICH was made.

Mononuclear cells, which consisted mainly of lymphocytes and monocytes, were isolated from peripheral whole blood from the patient and from a normal control using Ficoll-Hypaque™ (Amersham Pharmacia Biotech AB, Uppsala, Sweden) centrifugation. Cells were analyzed by flow cytometry (Figures 4A–E). Interestingly, there were more CD34+ cells in the peripheral blood of the patient than in that of the control.

The patient then received oral 8-methoxypsoralen (8-MOP) plus ultraviolet A (UVA). Psoralen UVA (PUVA) treatment was administered three times a week for 4 months. UVA was given at an initial dosage of 2.0 J/cm^2 and, at every second or third exposure, 0.5 J/cm^2 was added to the previous dose (final dose, 5 J/cm^2). After 2 months of treatment, the skin lesions gradually regressed and PUVA therapy was continued over the next 2 months. No new skin lesions or side effects developed during or after treatment. The skin lesions regressed gradually, and left only some post-inflammatory hyperpigmentation (Figures 5A and B). After 4 months of PUVA, the patient discontinued treatment and received regular outpatient follow-up.

Discussion

ICH seems to show no gender- or age-specific predilection [5]. The clinical features of this disease include multiple, asymptomatic, cutaneous papules and nodules in otherwise healthy individuals [1]. Cases with a solitary lesion have also been described [3,4]. In most cases, lesions are located on the trunk and extremities or distributed as generalized eruptions. As in our patient, early lesions usually consist of flesh-yellow, firm subcutaneous nodules and papules that tend to become reddish-brown in the later stages.

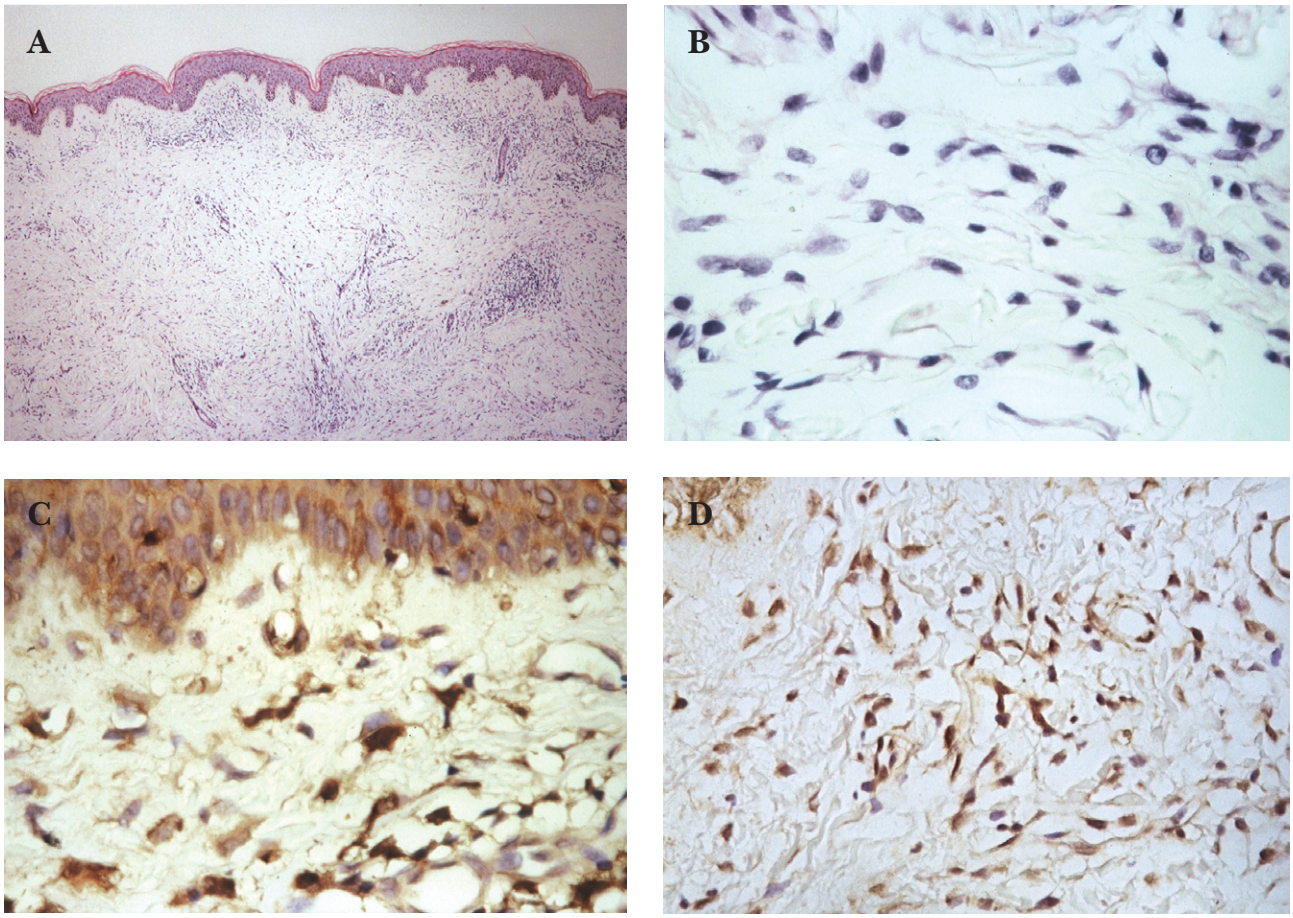

Figure 2. *(A) Diffuse histiocytes infiltrate throughout the dermis without subcutaneous fat involvement and mild perivascular lymphocytic infiltration (hematoxylin and eosin, × 40). (B) Histiocytes show large, round, or oval nuclei and pale cytoplasm (hematoxylin and eosin, × 400). (C) Neoplastic cells are positive for S-100 (× 400), and (D) for CD1a (× 200).*

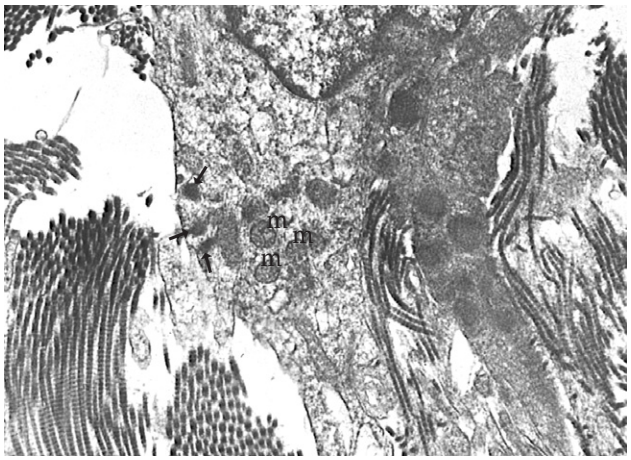

Figure 3. *Irregularly shaped nuclei, scanty chromatin, and abundant cytoplasm containing variable amounts of irregular-sized dense bodies (arrows) but no Birbeck granules (× 10,000). m = mitochondria.*

Because histiocytosis disorders cover a wide range of forms, some authors employ a modification of the scheme shown in the Table to diagnose histiocytosis. This scheme primarily uses the presence or absence of S-100, CD1a, and Birbeck granules to subdivide histiocytosis disorders, and a variety of other markers to provide an overview [6]. Our case was not likely to be histiocytosis X since we could not find its characteristic features, such as extracutaneous involvement, epidermotropism, or Birbeck granules [2]. Congenital self-healing reticulohistiocytosis, in which only a minority of the histiocytic cells are S-100 positive and Birbeck granules are found, is also distinctive for its appearance at birth or during the first few days of life, and for its rapid resolution [7].

Cutaneous non-X histiocytosis comprises a spectrum of disorders exhibiting proliferative histiocytic or macropha-

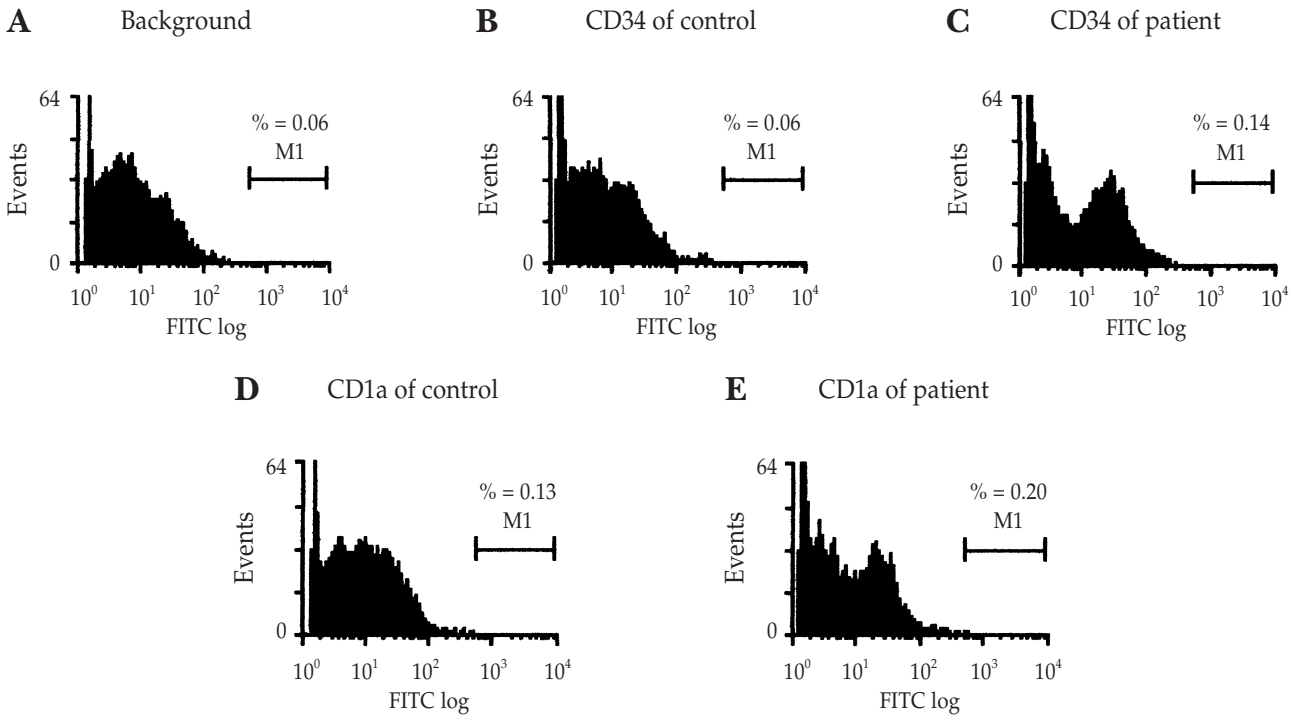

Figure 4. *Marker expression (% positive cells) in mononucleocytes from both a control and a patient detected by flow immunofluorescence. (A) Background. (B) & (C) There are more CD34+ cells in the patient compared with the control. (D) & (E) There are more CD1a+ cells in the patient compared with the control. FITC = fluorescein isothiocyanate.*

gic cells, such as generalized eruptive histiocytosis, benign cephalic histiocytosis, xanthoma, etc. These disorders are characterized by the absence of epidermotropism, negativity for both S-100 and CD1 antigens, and lack of Birbeck granules but positivity for monocyte/macrophage and dendrocytic markers such as CD68 and Factor XIIIa (Table) [6]. Clinically, our case had a similar presentation to generalized eruptive histiocytosis. Therefore, positivity for S-100 and CD1a was considered to be the main feature and helped to distinguish ICH from cutaneous non-X histiocytosis.

Regarding the origin of indeterminate cells in the dermis, Murphy et al have reported that indeterminate cells may

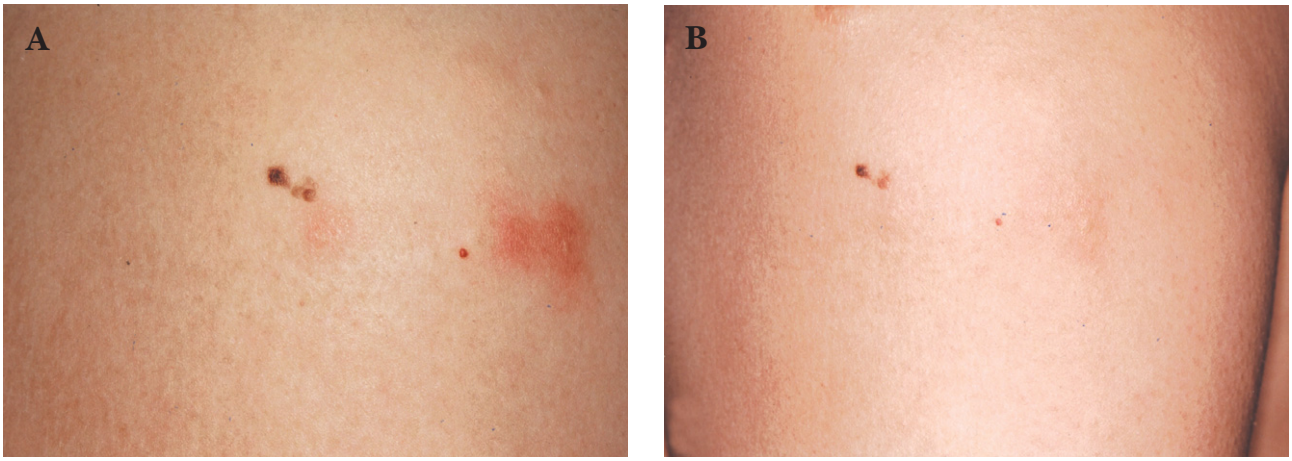

Figure 5. *The clinical picture (A) pre-psoralen ultraviolet A (PUVA), and (B) post-PUVA.*

Table. Antigenic markers in histiocytic disorders [6]

Disease	S-100	CD1a	Birbeck	MS-1	KP1 (CD68)	MAC387	CD34	Factor XIIIa
LCH	+	+	+	−	−	−	−	−
CSHRH	+	+	+	−	−	−	−	−
ICH	+	+	−	−	−	−	−	−
SHML	+	−	−	−	−	−	−	+/−
XD	−	−	−	+	+	−	−	+
PX	−	−	−	+/−	+/−	+	−	−
MR	−	−	−	+	+	−	−	−
GCRH	−	−	−	+	+	−	−	+/−
EH	−	−	−	+	+	−	+/−	−
BCH	−	−	−	?	?	?	?	?
Our case	+	+	−	ND	+/−	ND	+/−	+/−

LCH = Langerhans cell histiocytosis; CSHRH = congenital self-healing reticulohistiocytosis; ICH = indeterminate cell histiocytosis; SHML = sinus histiocytosis with massive lymphadenopathy; XD = xanthoma disseminatum; PX = papular xanthoma; MR = multicentric reticulohistiocytosis; GCRH = giant cell reticulohistiocytoma; EH = eruptive histiocytosis; BCH = benign cephalic histiocytosis; + = positive; − = negative; +/− = variable or conflicting data; ? = little or no data; ND = not done.

represent precursors of Langerhans cells that acquire Birbeck granules when they transfer from dermal to epidermal sites, as a result of the interaction between their cellular receptors and epidermis-specific ligands [8]. On the other hand, some consider that indeterminate cells may represent Langerhans cells that have left the epidermis and lost their Birbeck granules on their way to the lymph node [5].

The CD34 cell marker is selectively expressed on human lymphoid and myeloid hematopoietic progenitor cells. In an *in vitro* study, Caux et al used granulocyte macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor-α (TNF-α) to generate Langerhans cells from CD34+ human hematopoietic progenitors [9]. Another author claimed that Langerhans cells belong to the family of "myeloid" cells. They share common precursors with macrophages in bone marrow and probably blood, but the precise point at which Langerhans cells differentiate from the myelomonocytic lineage remains unclear [10]. According to one study, the level of CD34+ cells in the peripheral blood of patients with Langerhans cell histiocytosis was three times higher than that in normal controls. In addition, after 6 days of culture in GM-CSF and TNF-α, cells derived from CD34+ cells from peripheral blood were similar to "indeterminate cells" [11]. Our flow cytometry data from peripheral blood revealed that the percentages of CD34+ and CD1a+ cells in our patient were greater than those in the normal control. We therefore speculated that the indeterminate cells might be similar to Langerhans cells, which originate from CD34+ human hematopoietic progenitors. However, this hypothesis needs further investigation.

Because ICH is a rare disorder and has a variable clinical course, treatment has not been established. Total excision [3,4], intravenous vinblastine [2], electrodessication [12], topical pure coal tar, and 5% 5-fluorouracil cream [13] have all been proposed. In some patients, the process is clinically benign and may resolve spontaneously. Conservative management might be favorable for these patients [1,5,14, 15]. However, the disease can also be extensive and debilitating. For example, one adult female reportedly died of acute mast cell leukemia [16], and an infant had a malignant course leading to death despite aggressive chemotherapy and bone marrow transplantation [17].

In previous studies, PUVA has reduced the number of Langerhans cells as well as their function [18]. The beneficial effects of PUVA therapy on Langerhans cell histiocytosis have been previously described [19,20]. Interestingly, in our case (ICH), the cutaneous lesions responded well to PUVA therapy and almost complete remission was achieved. We concluded that PUVA therapy may be considered an effective treatment for ICH that is localized to the skin.

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