SHORT COMMUNICATION

A Rare Soft Tissue Presentation of Mixed Histiocytosis with Multiple Disseminated Subcutaneous Masses

Fumi MIYAGAWA[1*], Kohei OGAWA[1], Maiko TAKEDA[2], Akihiko YOSHIZAWA[2] and Hideo ASADA[1]
[1]Department of Dermatology, Nara Medical University School of Medicine, Kashihara, Nara 634-8522, Japan, and [2]Department of Diagnostic Pathology, Nara Medical University School of Medicine, 840 Shijo, Kashihara, Nara 634-8522, Japan. Email: fumim@naramed-u.ac.jp
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The concomitant occurrence of Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD) in the same patient (mixed histiocytosis) is rare. Approximately 20% of patients with ECD also have LCH lesions, sometimes within the same biopsy sample (1). A recent study demonstrated that in patients with mixed histiocytosis, both the LCH and ECD lesions carried the BRAFV600E mutation, suggesting a common progenitor cell for these diseases (1, 2). LCH is now considered to be of neoplastic origin and to be derived from bone marrow-derived monocytes (3, 4), and ECD is suggested to belong to the same class of neoplastic disorders (5).

We report an unusual case of mixed histiocytosis (LCH+ECD), in which the patient presented with multiple disseminated subcutaneous masses as well as crusty erythematous lesions in skin folds and the genital area, which to the best of our knowledge have not been reported previously.

CASE REPORT

A 29-year-old female presented with crusty and erosive erythema/papules in intertriginous areas, such as the submammary regions, axillae, inguinal regions, buttocks and genital area, which had lasted for 1 year (**Fig. 1**a), and bone pain in the left forearm, which had persisted for 3 months. She also had a low-grade fever of around 37.5°C. Histopathological samples of erythematous lesions in the submammary region and two perianal regions all revealed the infiltration of mononuclear cells with grooved nuclei into the superficial dermis and epidermis (Fig. 1b). Immunohistochemical staining showed that these mononuclear cells were positive for CD1a, CD207 (Langerin) (Fig. 1c), S-100, CD68 and mutated BRAF (V600E). A diagnosis of LCH was made. Computed tomography (CT) showed multiple soft tissue masses in the subcutaneous and intermuscular regions of both shoulders, axillae and the chest wall. Multiple subcutaneous masses were also found on the outer sides of the pelvis, perineum, buttocks and inner sides of the thighs. Masses were also present around the heart, the aortic arch, the descending aorta and the kidneys. Multiple lytic bone lesions were found in the skull, pelvis, vertebrae and extremities. A biopsy from the ulna demonstrated prominent infiltration by foamy histiocytes, which were positive for CD68, admixed with mononuclear cells, which were positive for CD1a, S100, CD207 and CD68; neutrophils; and eosinophils. These findings suggested a diagnosis of LCH and ECD (mixed histiocytosis). A bone marrow biopsy was negative, with no infiltration of LCH or ECD observed. The patient was treated with a combination of methotrexate, vinblastine and interferon (IFN)-α for 2 years at the orthopaedics department, and IFN-α alone weekly thereafter, which led to remission of the disease although residual masses remained in the axillae. However, due to the patient's busy work schedule, the interval between IFN-α doses increased to once every 2 to 4 weeks.

Six years later, she noticed erosive lesions in her genital area. Subcutaneous nodules subsequently appeared on both thighs, and she was referred to us again 7 years after the initial presentation. A physical examination revealed multiple erosive and ulcerating subcutaneous nodules or tumours in the axillae, inguinal regions, thighs, buttocks and genital area (**Fig. 2**a). No erythema was found in intertriginous areas. Histopathology

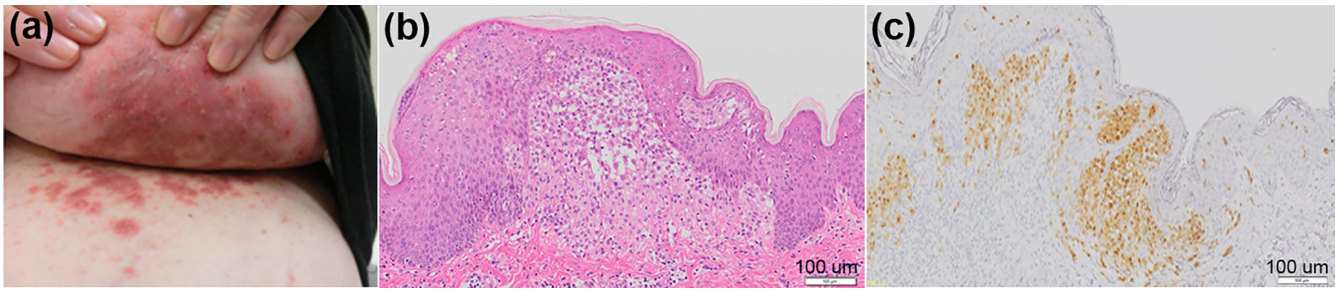

Fig. 1. (a) Erosive and crusty erythema and red papules were seen in the submammary area. (b) A skin biopsy taken from thesubmammary erythema revealed the infiltration of mononuclear cells with grooved nuclei and pale-eosinophilic cytoplasm beneath the epidermis and in the epidermis (hematoxylin-eosin; x100) (c) Immunohistochemical staining of (b) demonstrated that the tumour cells were positive for CD207 (Langerin) (x100).

of a subcutaneous tumour in the thigh revealed diffuse infiltration by foamy mononuclear histiocytes admixed with mononuclear Langerhans cells as well as small lymphocytes, neutrophils and eosinophils. Multinucleated histiocytes or Touton cells were also observed (Fig. 2b and c). Immunohistochemical staining showed foamy histiocytes and Touton cells, which were positive for CD68, CD163, S100 and mutated BRAF, and negative for CD1a and CD207, suggesting a diagnosis of ECD (Fig. 2d). The mononuclear Langerhans cells were positive for CD1a, CD207, S100, CD68 and mutated BRAF, suggesting a diagnosis of LCH (Fig. 2d). A diagnosis of mixed histiocytosis (ECD+LCH) was made. CT demonstrated similar findings to those seen at the initial presentation (Fig. 2e and f). Axillary lymph node ultrasound demonstrated multiple swollen lymph nodes. Treatment with weekly IFN-α treatment was resumed, and multiple masses have gradually decreased in size.

DISCUSSION

Histopathology is key to diagnosing LCH and ECD. The histological diagnosis of LCH involves the morphological identification of LCH cells (mononuclear cells with grooved and folded nuclei) and positive immunostaining for CD1a and CD207 (5). LCH cells can also be positive for CD68 (6). In contrast, ECD is characterized by foamy histiocytes that are positive for CD68 and CD163 and negative for CD1a and CD207. A few multinucleated giant cells or Touton cells are also frequently observed. Some ECD histiocytes may be positive for the S100 protein (5, 7). These criteria confirm that the histopathological findings of the skin biopsy sample obtained at recurrence in our case indicated the coexistence of LCH and ECD.

The cutaneous manifestations of LCH commonly include crusty erythematous papules and nodules, predominantly in the folds of the skin, such as the submammary fold (8, 9). A predilection for the mucous membranes of the axillae and anogenital erosions and crusts may also be seen (9). Our patient demonstrated crusty reddish papules and patches in intertriginous areas, including the submammary folds, anogenital region and axillae at the initial presentation, which is consistent with the reported cutaneous manifestations of LCH.

In contrast, the most frequent cutaneous manifestations of ECD are multiple yellowish patches on the eyelids or periorbital spaces (xanthelasma-like lesions). Other ECD lesions include erythematous or brown patches or papulonodular lesions (10). Subcutaneous soft tissue masses have been described in rare cases. To the best of our knowledge, only nine such cases have been reported (11–14), and 8 cases presented with one or several localized subcutaneous

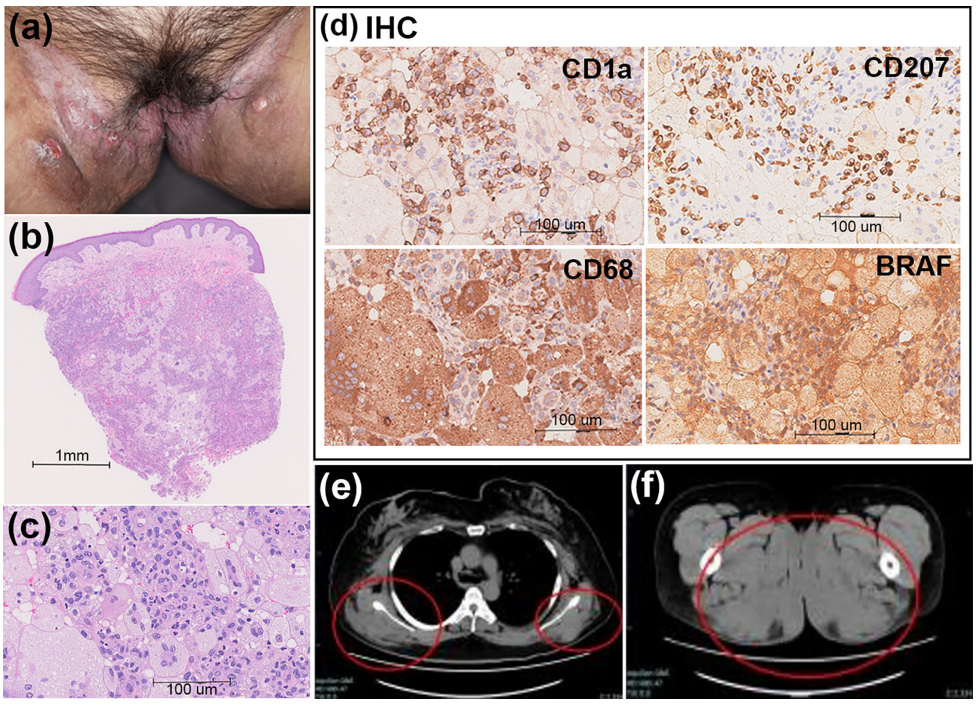

Fig. 2. (a) Multiple erosive and ulcerating subcutaneous nodules or tumours were present in the genital and inguinal regions. (b) A skin biopsy taken from a subcutaneous tumour in the thigh revealed diffuse infiltration by large foamy histiocytes and mononuclear Langerhans cells (hematoxylin-eosin;×25). (c) Higher magnification of (b) showed infiltration by foamy mononuclear histiocytes and multinucleated giant cells or Touton cells admixed with mononuclear Langerhans cells with grooved nuclei as well as small lymphocytes, neutrophils, and eosinophils (hematoxylin-eosin;×400). (d) Immunohistochemical staining (IHC) of (c) showed that the mononuclear cells were positive for CD1a, CD207, CD68 and mutated BRAF (V600E). The foamy histiocytes and Touton cells were positive for CD68 and mutated BRAF, but negative for CD1a and CD207 (×400). (e,f) CT showed multiple soft tissue masses in the subcutaneous and intermuscular regions (red circles).

nodules or tumours (11, 13, 14). The other case, which was reported by Pivkova-Veljanovska et al., presented with multiple nodular subcutaneous tumours in the back, including tumours all over the spinal cord and in the retroperitoneal soft tissue region (12). The clinical presentation of our case is similar to the latter case in that the tumours were distributed from the subcutaneous tissue to soft tissue (12). However, our case is distinct in that the tumours were disseminated all over the body, including the shoulders, axillae, chest wall, buttocks, perineum, and thighs. Tumours were also found around the heart and kidneys, although there was no involvement of risk organs (the liver, spleen, or bone marrow) (5). It is known that perinephric and periaortic infiltrations are frequent in ECD (7). Our case is also distinct in that histopathologically, the tumours showed characteristic features of both LCH and ECD, rather than ECD alone. The cutaneous manifestations of mixed histiocytosis have rarely been reported. To the best of our knowledge, only one case report that provided a detailed description of the cutaneous lesions seen in mixed histiocytosis described histopathological features of both LCH and ECD, in which the patient presented with lightly scaly, pink-red macules, which occasionally coalesced into patches on the abdomen and back (13). The clinical manifestations of mixed histiocytosis seen in our case have not been reported previously and their prognostic significance needs to be elucidated.

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Data Availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

The authors have no conflicts of interest to declare.

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