

## CORRESPONDENCE

# Langerhans cell histiocytosis in IPEX syndrome: Possible role for natural regulatory T cells?

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To the Editor,

Langerhans cell histiocytosis (LCH) is generally accepted as a disorder characterized by Langerhans cell (LC) accumulation in single or multiple organs. Nevertheless the pathogenesis of the disorder is not completely understood and it has not yet been precisely clarified whether it is a malignancy or a immunodysregulation (1). The diagnosis is based on the evaluation of the clinical picture with histopathological features, that identify LC's reactivity to CD1a and S100 immunohistochemical staining (2).

The heterogenous clinical course of the LCH -from benign single organ involvement to life-threatening multi-system disorder- suggests that, LC accumulation may be the result of different diseases or conditions, each one caused by a different mechanism. Although the available data strongly suggest a relevant genetic component in the development of the disorder, to our knowledge, there is only one known relationship between LCH and a specific monogenic disease, that is, X-linked lymphoproliferative disease type 1 (XLP) (3, 4).

A 50-day-old boy was admitted to our Pediatric Gastroenterology Department with a history of bloody diarrhea for 10 days. He had erythrodermia in his trunk and extremities and a few papules in the trunk. Additionally, a few cervical (one of them 1 × 1 cm) and axillary lymph nodes were palpable. Laboratory results showed no abnormalities. After cow milk elimination was initiated, the symptoms improved

moderately over 2 months, but then the patient readmitted with the complaints of intractable watery diarrhea and maculopapular rash. Lymph node biopsy was performed at the 5 months of age due to the persistence of lymphadenopathy and skin rash. The biopsy revealed LC accumulation as shown in Fig. 1; the patient was eventually diagnosed with LCH as a result of the clinical and pathological findings. The lymphadenopathy and skin rash were resolved soon after the beginning of chemotherapy. On the other hand, during the first 2 months of therapy, the high-volume watery diarrhea did not improve, although several formulas and nutrients were tried. On investigation, no infectious or metabolic causes of the diarrhea were found. The secretory nature of the diarrhea directed us to suspect autoimmune enteropathy and its prototype immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. Sequence analysis of the coding region of the FOXP3 gene revealed a mutation within exon 11 that encodes for a portion of the forkhead DNA binding domain of the protein: c.1157G>A(p.R386H), that has been identified only in one another patient to date (5). The mother was found to be a carrier for the same mutation. The patient was diagnosed with IPEX syndrome and hematopoietic stem cell transplantation was recently performed.

An accumulation of regulatory T cells (Tregs) in LCH lesions was previously described by two independent groups, moreover, whether the Tregs in the LCH lesions were natural

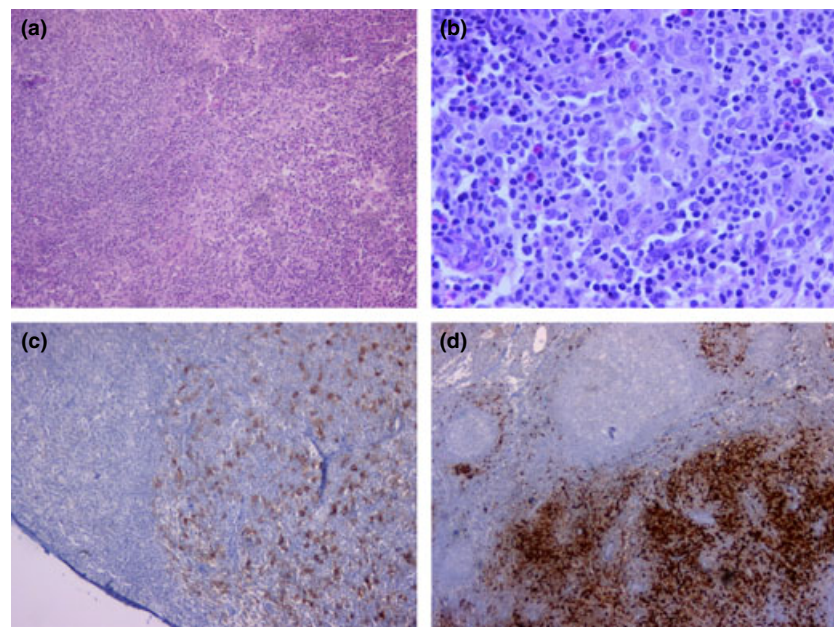


**Figure 1** Low-power (100X) hematoxylin-eosin staining of lymph node biopsy reveals mononuclear cell infiltration (a), while high-power (400X) exhibits large cells, that distend the interfollicular area, with moderately abundant cytoplasm and indented nuclei (b). These cells demonstrate strong immunoreactivity for CD1a (c) and S100 (d).

or acquired was also debated (6, 7). On the other hand, IPEX syndrome is caused by mutations of FOXP3 gene, which results in an absence of natural Tregs (8, 9). Natural Tregs play an essential role in the maintenance of self-tolerance, and thus, in preventing autoimmune diseases (9). Indeed, a recently published article showed that peripheral autoreactive B cells accumulate in the absence of Tregs, explaining the mechanism of autoimmunity in IPEX patients (10). Like in IPEX syndrome, a predisposition to autoimmunity -related with the impairment of Tregs-mediated self-tolerance- was also found in XLP (11). In addition, some time ago, a lack of T cell-mediated immunosuppression was observed in some patients with LCH. In that article, it was asserted that LCH could be related with an immunodeficiency syndrome because of the presence of thymic dysfunction and the disease's good response to thymic hormone therapy (12). Taking these findings into account, it is easy to suggest that natural Tregs plays an important role in the development of LCH. In this respect, LCH would add to the list of autoimmune phenomena evident in IPEX syndrome.

Digestive tract involvement in LCH is extremely rare and has been associated with poor prognosis. Diarrhea, with or without blood, is the main symptom. Usually, this has an association with cutaneous involvement. The peak incidence is under the age of 2 yr with a male predominance (13). Similarly, without treatment, IPEX is usually an early-onset and rapidly fatal disease within first year of life. There have only been reports of approximately 140 patients published in the literature. Severe cases are characterized by a triad of clinical manifestations in the first month of life specifically intractable watery diarrhea, type 1 diabetes mellitus, and cutaneous manifestations (8). In conclusion, we want to point out that, because of the similar clinical pictures, IPEX syndrome should be considered in patients with LCH, especially if gastrointestinal

symptoms present. Furthermore, we should be aware of the development of LCH in patients with primary immunodeficiencies, particularly those characterized by autoimmunity such as IPEX syndrome.

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### Conflict of interest

No conflicts of interest to disclose.

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