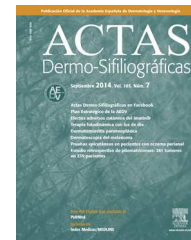




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## CASE AND RESEARCH LETTERS

### Neutrophilic figurate erythema of infancy associated with juvenile myelomonocytic leukemia



### Eritema figurado neutrofílico de la infancia asociado a Leucemia Mielomonocítica Juvenil

A 2-year-old girl presented with a 3-month history of asymptomatic annular erythematous skin eruptions. Each plaque began as a small erythematous papule that enlarged, acquiring an annular configuration with central clearing. During this time some lesions spontaneously disappeared, leaving hyperpigmentation. The patient did not present constitutional symptoms. At the age of 1, she had been diagnosed with Disseminated Juvenile Xantogranuloma, without neurologic, ophthalmologic or other visceral involvement. She was otherwise healthy, had neither allergies nor a significant family history. There was no history of insect bites or exposure to animals and she had not received any medications previous to the eruption.

Physical examination revealed multiple annular and polycyclic erythematous plaques, with indurated borders and petechiae on the rims. The plaques were devoid of vesicles, crusts, erosions or desquamation (Fig. 1) and were distributed on her upper chest, abdomen and upper back. There was no hepatosplenomegaly, lymphadenopathy, or arthritis.

Laboratory studies disclosed a normal white cell count with normal differential. Immunoglobulin G titers were slightly elevated; IgM, IgA, IgE, antistreptolysin O titers; serum levels of C3 and C4 were normal. Anti-SS-A (Ro) and anti-SS-B (La) antibodies were negative. A stool examination for parasites and serologic tests for *Toxocara*, *Bartonella henselae*, Epstein-Barr virus and hepatitis B virus infection were negative.

Histological examination of an annular plaque revealed superficial and deep perivascular and interstitial mixed-cell dermatitis. The deep dermal infiltrate was composed predominantly of neutrophils with abundant nuclear dust. Other vasculitis signs were absent (Fig. 2). Clinical and histopathological features were

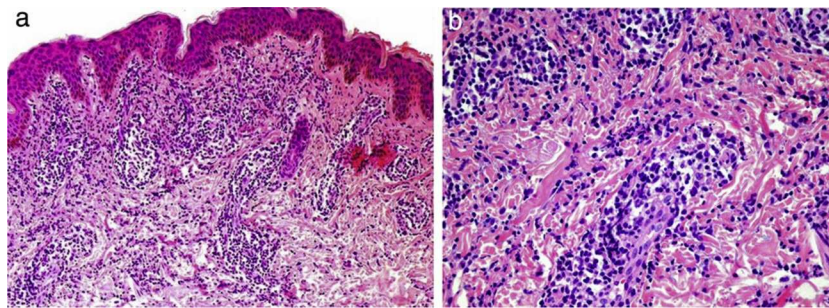
consistent with Neutrophilic Figurate Erythema of Infancy (NFEI).

Two months after the consultation, the patient presented clinical and laboratory findings suggestive of mononucleosis syndrome due to Epstein-Barr virus. During the infection, the lesions increased in size and number. No improvement was seen during febrile periods.

Ten months after the beginning of plaques, a complete blood count was performed, which showed leukocytosis: 28,600 WBC/mm<sup>3</sup> with 22% monocytes and blast cells. A myelogram showed hypercellularity and 12% blast cells with monocyte-like appearance. The immunophenotype showed 17% immature monocytoid cells. Her fetal hemoglobin concentration was 24%. The translocation study (t9:22, t8:1



**Figure 1** Multiple annular and polycyclic erythematous plaques with purpuric macules and indurated borders devoid of crusts, vesicles or desquamation distributed along her left chest and axillae.



**Figure 2** Histological examination of a biopsy specimen taken from an indurated border of one plaque, hematoxylin–eosin stain (a) superficial and deep perivascular and interstitial infiltrate, without epidermal changes (Hematoxilina-Eosina 80X). (b) The deep dermal infiltrate was composed predominantly of neutrophils, with abundant nuclear dust, without other signs of vasculitis (Hematoxilina-Eosina 100X).

and t15:17) was negative. Therefore, juvenile myelomonocytic leukemia (JMML) was diagnosed. She began oral chemotherapy with hydroxiurea, observing an important improvement in the cutaneous lesions.

## Discussion

Annular or figurate erythemas of infancy (AEI) are characterized by a primary annular, circinate, arcuate or polycyclic pattern of cutaneous lesions.<sup>1,2</sup> The lesions may be due to a known cause (rheumatic marginated erythema, neonatal lupus, erythema chronicum migrans) or may be idiopathic<sup>3</sup> and may present with a localized or broad distribution.<sup>2,3</sup>

NFEI belongs to those figurate erythemas of unknown etiology.<sup>3</sup> It is characterized by papular erythematous eruptions with rapid centrifugal enlargement to annular or polycyclic asymptomatic plaques with indurated borders devoid of vesicles, crusts or desquamation.<sup>4,5</sup> Frequently, the eruptions begin on the face and then spread centrifugally to the limbs. The patches tend to disappear within 2–4 weeks, but the disease course is chronic.<sup>1,3</sup>

Histologically, NFEI is characterized by a superficial and deep, perivascular and interstitial infiltrate of neutrophils associated with leukocytoclasia but without other signs of vasculitis.<sup>1,2,4,5</sup>

Differential diagnosis of NFEI includes annular erythemas of infancy and dermatoses with a prominent neutrophilic infiltrate such as Sweet syndrome (SS) and pyoderma gangrenosum, urticarial lesions of dermatitis herpetiformis or linear IgA dermatosis, early lesions of bullous lupus erythematosus, Still disease, Sjögren's syndrome and early leukocytoclastic vasculitis.<sup>2</sup>

Sweet syndrome (SS) was very important in our differential diagnosis, considering the association with JMML presented in this case. However, our patient lacked typical manifestations of SS, as the lesions were asymptomatic and neither fever nor neutrophilia were present.<sup>2</sup> Furthermore, paraneoplastic SS in children usually presents mucosal involvement, anemia and thrombocytopenia, and the neoplasm is concomitant with skin eruptions.<sup>7,8</sup> Finally, SS histological findings differ from NFEI, as SS is characterized by a dense nodular or diffuse dermal infiltrate of neutrophils

with nuclear dust with a variable amount of lymphocytes, histocytes, extravasated erythrocytes and a Grenz zone,<sup>2,7,8</sup> findings not found in NFEI descriptions or in this patient.

Some authors have described cases of recurrent annular neutrophilic dermatosis in adulthood<sup>9</sup> and have included this condition in the spectrum of neutrophilic dermatoses.

Although NFEI has been considered a benign chronic condition, only three pediatric cases have been reported.<sup>2,4,6</sup> The association with a hematological neoplasm and its response to its treatment in our patient suggest that NFEI may be among the group of neutrophilic dermatoses. Cytokines and other biochemical mediators produced by blast cells could be involved in the development or maintenance of the skin lesions.

A standard treatment for NFEI has not been established. Previous reported treatments include topical steroids, systemic corticosteroids, hydroxychloroquine and colchicine, with poor responses.<sup>1,5</sup>

We present the first case of NFEI associated with JMML. Histological findings and the association with a hematological neoplasm suggest that NFEI may be in the spectrum of neutrophilic dermatoses. Therefore, after a diagnosis of NFEI an exhaustive study to exclude inflammatory diseases and neoplasms is warranted.

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## Bilateral Ossification of the Auricular Cartilage<sup>☆</sup>



### Osificación bilateral del cartílago auricular

We present the case of a 45-year-old man who was admitted for hyponatremia of unknown etiology. He was referred to Dermatology by Internal Medicine for evaluation of an induration of the auricles of the ears. On examination, the ears were of normal appearance, with no visible changes in the skin. Palpation revealed diffuse rigidity of the cartilaginous part of the auricle bilaterally, with no changes in the ear lobes (Fig. 1 A). The patient stated that the changes had started 2 years earlier and had been progressive and asymptomatic. Skin ultrasound revealed a hypoechoic area corresponding to the normal auricular cartilage, superficial to which there was a linear hyperechoic image suggestive of transformation of the cartilage by mineralization (Fig. 1 B). On cranial x-ray, the auricles of the ear showed a diffuse and homogeneous increase in density, similar to that of bone (Fig. 1 C). Histopathology of the skin and of the auricular cartilage showed no significant changes in the epidermis or dermis, but there were fragments of elastic cartilage with foci of ossification and the formation of mature bone trabeculae (Fig. 2, A and B).

In the blood tests, the basal cortisol levels were almost undetectable (<0.4 µg/dL; normal range, 4.3–22.4 µg/dL), with corticotropin levels in the lower range of normal (9.5 pg/mL; normal range, 8–46 pg/mL) and an inadequate cortisol response in the corticotropin stimulation test (cortisol, 1.11 µg/dL). The prolactin level was slightly elevated (47.8 ng/mL; normal range, 2.6–13.1 ng/mL). Studies of calcium metabolism, other hormonal markers, autoimmunity, and serology for infectious diseases were normal or negative. No changes were observed on abdominal ultrasound, cerebral computed tomography, or magnetic resonance imaging of the hypophysis. A diagnosis was made of bilateral ossification of the auricles secondary to central adrenal insufficiency of unknown origin.

Auricular ossification is a very rare cause of petrified auricles, a condition first described by Bochdalek<sup>1</sup> in 1866 and which has now been reported in the literature in more than 160 cases. The most common cause of petrified

auricles is auricular calcification, which is associated with numerous diseases and, as occurs with calcinosis cutis, it can be metastatic, dystrophic, or idiopathic. In auricular ossification, ectopic bone formation is a response to the release of bone morphogenetic protein by damaged tissue.<sup>1</sup> New bone forms over tissues that do not normally ossify; this occurs by the deposition of calcium and phosphorus salts in a proteinaceous matrix of hydroxyapatite crystals. Severe or recurrent hypothermia is the most common cause of auricular ossification,<sup>2,3</sup> though the condition has also been described secondary to trauma and local inflammatory conditions. The systemic disease most commonly associated with auricular ossification is adrenal insufficiency, although the pathophysiological mechanism is unclear.<sup>4–6</sup> It has been suggested that an acute or chronic fall in cortisol levels may induce a reactive hypercalcemia that could lead to calcium deposition in tissues, such as acral tissues, made susceptible by a poor peripheral circulation; however, this hypothesis is still in doubt because many patients have no detectable hypercalcemia.

The disorder mainly affects men. On examination there is a typically asymptomatic, partial or complete induration of the auricle of the ear with sparing of the ear lobe; there are no visible alterations of the skin. Some patients present pain on pressure and, in a few cases, pressure ulcers may develop.<sup>4</sup> In addition, alterations of the external auditory canal can lead to secondary otalgia and hearing impairment. The rigidity is most commonly bilateral and progressive. The clinical findings enable a provisional diagnosis to be established and this will be supported by the radiologic findings; however, the definitive diagnosis of auricular ossification is established on histology, which reveals replacement of the auricular cartilage by true lamellar bone, with the presence of bone trabeculae and osteocytes.<sup>7,8</sup> The etiologic diagnosis is based on a full medical history including possible inflammatory disorders and trauma. Only when no local cause can be identified should laboratory screening studies be performed to exclude underlying metabolic or endocrinologic diseases. There is no specific treatment for this condition and its course is irreversible.<sup>7,8</sup> In patients who report pain, some authors favor treatment by surgical reduction of the affected auricle.<sup>8,9</sup>

Twenty cases of histologically documented auricular ossification have been reported to date in the literature (Table 1). Of these, 4 cases were associated with systemic diseases: 3 with primary adrenal insufficiency<sup>4,5</sup> and 1 with adrenal insufficiency secondary to postpartum hypopituitarism.<sup>6</sup> We have reported the second case of

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