First Clinical Description of an Infant With Interleukin-36-Receptor Antagonist Deficiency Successfully Treated With Anakinra

YM is the first son of Tunisian consanguineous parents who developed, at 2 weeks of life, an erythematous and scaly eruption, with subsequent rapid evolution toward generalized pustular psoriasis. Afterward, cutaneous flares of diffuse erythematous rash and pustules involving the whole body appeared, with a once weekly periodicity. Intense irritability was present during flares without fever. Moreover, since 1 month of age the infant presented with diarrhea, dysphagia, and reduced feeding rate, with failure to thrive. Laboratory tests during acute flares showed marked leukocytosis, thrombocytosis, and anemia without C-reactive protein elevation. Skin biopsy and clinical presentation were consistent with pustular psoriasis; nevertheless, the patient did not respond to high-potency topical corticosteroids and retinoid acid. As the patient presented with repeated skin flares early after birth, as well as serious constitutional distress with failure to thrive, an autoinflammatory syndrome like interleukine-1-receptor antagonist deficiency or interleukin-36-receptor antagonist deficiency (DITRA) was considered. The hypothesis was reinforced by parental consanguinity, and absence of skin lesion improvement under standard topical treatment. Genetic analyses showed a homozygous mutation in the IL36RN gene (L27P), which represents the same mutation recently described in DITRA patients. At age 6 months we started treatment with the recombinant interleukin-1 receptor antagonist anakinra with efficacy both on constitutional symptoms and skin involvement. DITRA is a recently described autoinflammatory disease characterized by repeated flares of generalized pustular psoriasis, high fever, asthenia, and systemic inflammation. We report herein the first exhaustive clinical description of an infant with DITRA who was successfully treated with anakinra. Pediatrics 2013;132:e1–e5

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ABBREVIATIONS: CRP—C-reactive protein, DITRA—interleukine-1-receptor antagonist deficiency, IL-36Ra—interleukin-36-receptor antagonist, GPP—generalized pustular psoriasis, IL—interleukin, IL-36Ra—interleukin-36-receptor antagonist.

Dr Rossi-Semerano conceptualized and drafted the initial manuscript; Drs Piram, Chiaverini, De Ricaud, and Smahi reviewed and revised the manuscript; Dr Koné-Paut critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Interleukin-36-receptor antagonist deficiency (DITRA) is a novel hereditary autoinflammatory disease characterized by repeated flares of generalized pustular psoriasis (GPP) associated with high fever, asthenia, and systemic inflammation.

This condition is caused by homozygous missense mutation in the IL36RN gene, encoding the interleukin-36-receptor antagonist (IL-36Ra), an anti-inflammatory cytokine. The consequent reduction of IL-36Ra function results in excessive activity of IL-36α, IL-36β, and IL-36γ, 3 cytokines belonging to the interleukin-1 (IL-1) family involved in several pro-inflammatory signaling pathways. The high physiologic expression of IL-36R and the 3 agonists in epithelial tissues like skin justifies GPP, representing the main clinical feature in all affected patients.

**CASE REPORT**

YM is the first son of Tunisian consanguineous parents (double-first cousins) without family history of GPP or other autoinflammatory disorders.

The mother’s pregnancy and delivery were unremarkable. YM’s physical characteristics at birth were: Apgar (vitality) score 8–10/10, weight 2.9 kg (15th percentile), height 50 cm (60th percentile), and head circumference 33 cm (15th percentile).

At 2 weeks of life, he developed an erythematous and scaly eruption over the scalp and the perineum, with subsequent rapid evolution toward GPP. Exacerbations of the erythematous scaly dermatitis (Figs 1 and 2) studded with pustules involving the whole body, palms, and soles (Fig 3), were noticed every week and progressed to generalized exfoliative dermatitis. Intense irritability with generalized tenderness on physical examination was present during flares without fever.

Since 1 month of age the infant presented with diarrhea, dysphagia, and reduced feeding rate, with failure to thrive, justifying hospitalization. Physical examination revealed persistent erythematous scaly dermatitis, geographic tongue, diffuse pain, and intense irritability requiring analgesic treatment with opioids; there was no joint swelling or evidence for any other organ involvement.

Laboratory tests during acute flares showed marked leukocytosis with neutrophilia up to 21 000/mm³, thrombocytosis (platelets up to 819 000/mm³), and mild anemia (hemoglobin 9.1 g/dL). C-reactive protein (CRP) levels were normal; no liver or kidney abnormalities were found.

Chest and skeletal radiographs and echocardiography were normal.

Skin biopsy showed an epidermal hyperplasia with acanthosis and irregular papilomatosis, spongiform pustules, compact orthokeratosis, and an exos-thosis of inflammatory cells (neutrophils, lymphocytes, and eosinophils) into the epidermis. The underlying dermis exhibited superficial perivascular polymorphous inflammatory cells. Although skin biopsy and clinical presentation were consistent with pustular psoriasis, the patient did not respond to high-potency topical corticosteroids and acitretin (retinoid acid).

The following causes were ruled out: bacterial, viral, or fungal infection (negative skin, blood, and stool cultures), nutritional deficiency (no zinc, biotin, or vitamin B₁₂ deficiency), cow’s milk proteins allergy (both skin prick and radioallergosorbent tests were negative), Netherton syndrome (neither hair defect at light microscopic examination nor expression of the serine protease Lekti at immune histochemical analysis), and immunodeficiency (normal lymphocytes subsets).

As this patient presented with repeated skin flares early after birth, as well as serious constitutional distress with failure to thrive, an autoinflammatory syndrome like interleukine-1-receptor antagonist deficiency (DIRA)² or DITRA was considered. The hypothesis was reinforced by parental consanguinity, and absence of skin lesion improvement under standard topical treatment. At 3 months of age, he had not gained weight for several weeks, despite enteral nutrition, and his growth failure was worsening (weight <3rd percentile, height <3rd percentile, and head circumference 3rd percentile).

Standard laboratory tests confirmed high white blood cell count and thrombocytosis with normal CRP and erythrocyte sedimentation rate. He had hypoalbuminemia (31.5 g/dL), probably related to malnutrition, but no other biochemical abnormalities. Two severe episodes of diarrhea with hypernatremia and dehydration appeared, followed by persistent feeding difficulties and
failure to thrive. Esophagogastroduodenoscopy showed minimal gastric ulcers, and colonic fibroscopy was normal. Histologic findings were as follows: focal inflammatory infiltrates (with predominant lymphocytes) were found in gastric body specimens; no abnormalities were found in duodenal and rectal specimens.

Intestinal malabsorption was ruled out (stool analyses, fecal elastase, and α-1 antitrypsine clearance were normal).

Blood IL-1β, IL-6, and TNFα were normal, whereas a high IL-1β level (206 pg/L), with normal levels of IL-6 and TNFα, were found in the cerebrospinal fluid. Aseptic meningitis was not present and cerebral magnetic resonance was normal.

A whole-body magnetic resonance did not identify any skeletal involvement. Genetic analyses were performed showing homozygous mutations in the IL36RN gene (substitution of a proline for a leucine at amino acid position 27 [L27P] of the IL-36Ra protein), the same mutation retrieved in the original description of DITRA patients who originated from the same country. Heterozygous IL36RN mutation (L27P) was present in both parents.

No mutations for DIRA in the IL-1RN gene were found in our patient.

As soon as the diagnosis of DITRA was confirmed at 6 months of age, recombinant IL-1-receptor antagonist, anakinra at 2 mg/kg/day was started with rapid effectiveness on constitutional symptoms (disappearance of irritability with discontinuation of opioid treatments in a few days), but not on skin involvement. At day 8 of treatment, anakinra was increased to 4 mg/kg/day. After dose increasing, the efficacy on skin involvement was noticed in ∼1 week (Fig 4) and no new cutaneous flares were observed at 2 months’ follow-up. Food intake progressively increased, with marked weight gain (+1560 g over 2 months, 15th percentile) and height (+6 cm, 15th percentile).

White blood cell count, platelets, hemoglobin, and albumin normalized after 2 weeks of treatment at 4 mg/kg/day of anakinra. No side effects occurred after a 2-month follow-up, except pain at the injection site without erythema.

**DISCUSSION**

To the best of our knowledge, we report the first detailed clinical description of an infant with DITRA. We even report, for the first time, a favorable clinical response of this disease to anakinra treatment.

DITRA is a hereditary autoinflammatory disease recently described in 16 patients from 9 Tunisian multiplex families, characterized by repeated flares of GPP, high fever, asthenia, and systemic inflammation (marked leukocytosis and elevated CRP). The disease developed in 12 of the affected subjects during childhood and in 4
controlled activity of IL-36α, IL-36β, and IL-36γ, involved in several proinflammatory signaling pathways. In physiologic conditions, IL-36R, IL-1Rrp2, and the 3 agonist cytokines are highly expressed in epithelial tissues like skin, trachea, and esophagus.4 Marrakchi et al1 demonstrated an overexpression of IL-36α, IL-36β, and IL-36γ in skin lesions from 4 patients homozygous for the L27P mutation.

Besides his psoriasiform dermatitis, our patient had prominent gastrointestinal complaints (dysphagia, anorexia with reduced food intake, diarrhea, with pathologic findings at esophagogastrroduodenoscopy), growth impairment, and marked irritability. The gastrointestinal signs might be related to excessive activity of the proinflammatory cytokines IL-36α, IL-36β, and IL-36γ in the digestive epithelium. Interestingly, 3 patients from the Tunisian series developed cholangitis during disease course.

The severe growth impairment (significant inflection of weight, height, and head circumference curves) could be related to accelerated bowel transit (diarrhea), excessive cutaneous water loss, and systemic effects of proinflammatory cytokines. The levels of expression of the IL-36 (α, β, and γ) could not be assessed on the gut biopsy. The intense irritability with diffuse tenderness on physical examination that required strong analgesic treatment was probably owing to a systemic involvement and was peculiarly similar to that reported in DIRA patients.2 Surprisingly, during cutaneous flares, he did not present with fever or elevated inflammatory markers (CRP and erythrocyte sedimentation rate), which were conversely reported in all patients carrying the same mutation.

Our patient showed several clinical characteristics described in infants affected by DIRA2,5; pustular eruption started during the first weeks of life with no fever during flares but with other systemic signs and symptoms as described previously. A significant response to the anti-IL1 treatment anakinra, with prompt decrease in systemic involvement and improvement of dermatitis, gastrointestinal complaints, and growth, was noticed. Interestingly, the patient had very high IL-1β levels in cerebrospinal fluid before anakinra treatment; we decided not to perform lumbar puncture on anakinra to avoid repeated invasive procedures. If IL-36R and IL-36Ra are restricted to epithelial cells,4 IL-1R and IL-1Ra are ubiquitously expressed,5 which can explain the bone and central nervous system involvement found only in DIRA and not in DITRA patients.

Dramatic response to IL-1 blockade in DIRA led some authors to test anakinra in resistant neutrophilic dermatosis. A good response of skin involvement with normalization of inflammatory markers has been recently reported in 2 patients with GPP on anakinra treatment.7 Anecdotal reports have also evidenced the efficacy of this agent in neutrophilic dermatosis such as Sweet syndrome,8 neutrophilic panniculitis,9 and neutrophilic urticarial dermatosis.10 Conversely, anakinra showed no significant efficacy in psoriatic arthritis in an open-label pilot study.11 Anakinra was effective in our patient on both cutaneous and systemic involvement, with major improvement in growth, which was severely affected. Nevertheless, we had only a 2-month follow-up; therefore we cannot conclude on long-term efficacy and tolerance of anakinra in infants with DITRA.

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