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DEFICIENCY OF INTERLEUKIN-1 RECEPTOR ANTAGONIST RESPONSIVE TO ANAKINRA

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Abstract

We describe a 3-month-old infant who presented to our institution with interleukin (IL)-1 receptor antagonist deficiency (DIRA), which consists of neutrophilic pustular dermatosis, periostitis, aseptic multifocal osteomyelitis, and persistently high acute phase reactants. Skin findings promptly improved upon initiation of treatment with anakinra (recombinant human IL-1 receptor antagonist), and the bony lesions and systemic inflammation resolved with continued therapy.

CASE REPORT

Atwin girl of Puerto Rican descent was born at 37 weeks to consanguineous parents with a healthy twin A. At 7 days of age, she developed pustules on her left ankle that resolved with topical antibiotics. The pustules later recurred on extremities, with gastroesophageal reflux and failure to thrive. At 7 weeks, she was admitted with an abscess over her left index finger, nail shedding, and high C-reactive protein, erythrocyte sedimentation rate, and white blood cell count. Bone scintigraphy showed bone lesions in the right hip, and a bone biopsy was performed. Cultures of blood, urine, cerebrospinal fluid, skin, and bone were negative for bacterial or fungal pathogens. The hip pain persisted despite antibiotic treatment, and the pustular lesions increased and demonstrated pathergy over areas of minor trauma.

At 3 months of age, she was transferred to our institution, where a complete immunologic and genetic examination was normal. Radiographs again showed multifocal periostitis and osteomyelitis. Skin biopsy showed epidermal acanthosis with intracorneal and intraepidermal neutrophilic microabscesses, mild papillary dermal edema, and a superficial interstitial infiltrate of neutrophils and occasional eosinophils (Fig. 1). Direct immunofluorescence, periodic acid Schiff and potassium hydroxide staining were negative. Therapy with methylprednisolone (2 mg/kg) was started, but the pustular lesions spread to the entire body; finally, generalized erythroderma and skin erosions developed, and the bullae became confluent (Fig. 2A,B). With an increase in corticosteroids and skin

debridement, the patient developed a systemic inflammatory response syndrome (SIRS) requiring mechanical ventilation.

Because of a suspicion of deficiency of the interleukin (IL)-1 receptor antagonist (DIRA), treatment with anakinra (recombinant human IL-1 receptor antagonist) was started. Within 1 week of starting anakinra, the patient showed rapid improvement of her pustular lesions and respiratory distress and normalization of the acute-phase reactants. After 6 weeks of treatment, she had caught up on her developmental milestones, and radiographs showed resolution of lesions. Genetic analysis at the National Institutes of Health confirmed homozygosity for the Puerto Rican variant of DIRA, which consists of a 175 kb deletion on chromosome 2q encompassing *IL1RN*, the interleukin-1 receptor antagonist (IL-1Ra) locus, and five other members of the IL-1 gene family IL-1F5–9 (1).

DISCUSSION

DIRA is a rare autosomal-recessively inherited autoinflammatory disease (1) that presents with neutrophilic pustular dermatosis, periostitis, aseptic multifocal osteomyelitis, and high acute-phase reactants (1,2). A growing number of monogenic autoinflammatory diseases involving IL-1 dysregulation are being described (3). The presence of a neutrophilic dermatosis characterized by intraepidermal pustules, marked edema of the papillary dermis, and dense dermal and subcutaneous neutrophilic infiltrates should raise the suspicion of an autoinflammatory disorder of this group.

Mutations in *IL1RN* result in deficiency of the IL-1Ra, which leads to unopposed signaling of IL-1 (1,2,4,5), leading to an inflammatory “escalation” in response to various triggers, including mechanical skin stimulation, catheter placement, and intubation. Approximately one-third of children with DIRA are symptomatic at birth, presenting with intrauterine growth retardation, but approximately two-thirds of individuals with DIRA develop pustular skin rashes, gastrointestinal reflux, and multifocal osteomyelitis within the newborn period. The development of systemic inflammatory response syndrome resulting in death has been described (1).

Other manifestations of DIRA include vesicular stomatitis, mouth ulcers, widening of ribs, periosteal reaction, joint swelling, cervical vertebral fusion, hepatosplenomegaly, and vasculopathy (1,2). Antibiotics and conventional disease-modifying antirheumatic drugs including steroids are of limited benefit, but blocking IL-1 signaling with anakinra dramatically improves clinical symptoms within days, normalizes acute-phase reactants, and permits appropriate growth (1,2).

Patients with DIRA need to remain on lifelong IL-1 inhibitory therapy; previous attempts at stopping or weaning anakinra have led to disease flares. Long-term efficacy and safety of anakinra treatment are under investigation, and it is not established whether longer-acting IL-1 inhibitors, such as canakinumab, are as effective as anakinra in the treatment of individuals with DIRA.

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Figure 1.

Skin biopsy shows epidermal acanthosis with intracorneal and intraepidermal neutrophilic microabscesses, mild papillary dermal edema, and a superficial interstitial infiltrate of neutrophils and occasional eosinophils (hematoxylin and eosin stain, original magnification, $\times 100$).

Figure 2.
(A) Periorificial redness and crusting, widespread erythema with pustules, bullae, and skin erosions. (B) Widespread, coalescing pustules on the dorsal foot.