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Chronic cutaneous pustulosis due to a 175-kb deletion on chromosome 2q13: Excellent response to anakinra

Cristina N. Brau Javier, MD¹, Jose Gonzales-Chavez, MD¹, and Jorge R. Toro, MD²

¹Department of Dermatology, University of Puerto Rico, Puerto Rico, USA

²Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, NCI, NIH, Bethesda, MD 20852, USA

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Deficiency of interleukin-1 receptor antagonist (DIRA) is a newly described autosomal recessive autoinflammatory disease in which absence of interleukin-1 (IL-1) receptor antagonist allows unopposed IL-1 activation, resulting in life-threatening systemic inflammation with prominent skin and bone involvement. We present a case of chronic cutaneous pustulosis treated with anakinra, a recombinant IL-1 receptor antagonist, resulting in rapid and significant clinical improvement.

REPORT OF CASE

In May 2010, a 15-year-old Puerto Rican male with chronic cutaneous pustulosis was referred to the University of Puerto Rico dermatology clinic. He was born at term, weighing 7 lb with congenital hip dysplasia. At two weeks of age, he developed a cutaneous eruption on his neck and antecubitals that evolved into erythematous pustular plaques covering most of his body surface area (BSA). An older half-sister developed a similar cutaneous eruption starting at two weeks of age and died at 15 years of age. At 6 months of age, our patient was hospitalized for right femur osteomyelitis and was noted to have lytic lesions on the vault and right femur. At age 12, he was diagnosed with pustular psoriasis; treatment with daily soriatane 10 mg orally was initiated and extended for 2 years but it was not efficacious. He was diagnosed with dilated cardiomyopathy (treated with digoxin) and corneal lacerations and ulcers at the same age.

On examination, our patient had diffuse erythematous scaly plaques with overlying pustules involving 80% BSA and digital anonychia (Figure 1). Microscopic examination of the lesional skin revealed a psoriasiform dermatitis with subcorneal neutrophilic pustules (Figure 2). Skin bacterial cultures showed normal skin flora. His clinical exam was also

Address correspondence: Jorge R. Toro, M.D., Division of Cancer Epidemiology and Genetics, NCI, National Cancer Institute, 6120 Executive Boulevard, Executive Plaza South, Room 7012, Rockville, MD 20892-7231, toroj@mail.nih.gov.

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notable for severe growth retardation, joint contractures, muscle atrophy, abdominal distention with caput medusae, and knee widening. Laboratory evaluation was remarkable for chronic leukocytosis, microcytic anemia, thrombocytosis, and elevated erythrocyte sedimentation rate (ESR) of 58 mm/hr; liver function tests were normal. Radiological studies showed bowing of the long bones, broadened ribs, distal metaphyseal enlargement, and osteopenia. Chest CT did not show pulmonary fibrosis. Abdominal CT was notable for portal vein thrombosis with ascites.

The presence of neonatal onset pustulosis, lytic bone lesions, and a first-degree relative with similar cutaneous pustules were suggestive of deficiency of interleukin-1 receptor antagonist (DIRA). Genetic testing using a high density SNP chip array (Illumina) revealed a homozygous 175 kb deletion on chromosome 2q13 including the interleukin-1 receptor antagonist (*IL1RN*) gene and five adjacent related genes (*IL1F9*, *IL1F6*, *IL1F8*, *IL1F5*—also known as interleukin-36 receptor antagonist or *IL36RN*, and *IL1F10*).

THERAPEUTIC CHALLENGE

There is limited data on the treatment of DIRA as it is a newly recognized disease and only ten genetically confirmed patients have been reported—none of them in the dermatology literature.^{1, 2} Treatments reported include antibiotics, indomethacin and interferon- γ among others, none of them resulting in notable improvement.¹ Patients only achieve partial response to high doses of corticosteroids.¹ Six patients with DIRA have been successfully treated with anakinra achieving clinical remission.^{1, 2} However, a Puerto Rican patient with the 175 kb deletion on chromosome 2q13 treated with anakinra showed marked yet incomplete clinical response allowing corticosteroid dose reduction but not discontinuation.¹

SOLUTION

Since our patient had a deficiency of the IL-1 receptor antagonist, the most logical next step was to initiate therapy with anakinra, a recombinant IL-1 receptor antagonist, at 1 mg/kg subcutaneously daily. Our patient achieved rapid clinical resolution of all pustules after ten days; only minimally scaly patches persisted on exam (Figure 3). At eight months of treatment our patient sustained cutaneous remission along with improved yet not normalized ESR levels (32 mm/hr) despite titration of anakinra. We expect that our patient will require sustained therapy with anakinra. Reported anakinra-related adverse effects include: transient injection-site reactions (the most common—characterized by mild erythema, ecchymosis, inflammation, and pain lasting about 2–4 weeks), infection (primarily bacterial such as cellulitis, pneumonia, and bone and joint infections, rather than opportunistic, fungal, or viral infections), and small reductions in the mean values for total white blood count, platelets, and absolute neutrophil blood count (ANC). No medication side effects were noted in our patient.

COMMENT

DIRA is a newly described autosomal recessive autoinflammatory disease in which absence of IL-1 receptor antagonist allows unopposed IL-1 activation and an increased response to IL-1 α and β stimulation resulting in life-threatening systemic inflammation with prominent skin and bone involvement.¹ Germline mutations in *IL1RN* predisposes to the development of DIRA. Ten cases of DIRA have been reported in the English literature.^{1, 2} Most *IL1RN* mutations consist of point mutations and base pair deletions leading to a truncated protein.¹ Founder mutations have been reported in populations in Puerto Rico, the Netherlands, Canada, and possibly in Lebanon.¹ The 175 kb deletion on chromosome 2q13 is a founder mutation previously described in two Puerto Rican patients with DIRA with an estimated allele frequency of 1.3% and an incidence of 1/ 6,300 births in Puerto Rico.^{1, 2} It includes

the entire *IL1RN* gene and five adjacent related genes that share structural homology. An autosomal recessive condition shared by half-siblings would be very unusual in the absence of consanguinity. However, we believe that our case and his half-sister represent an extraordinary chance association due to the founder effect in a genetically isolated town in northwestern Puerto Rico.

Cutaneous manifestations of DIRA include generalized erythematous plaques with overlying pustules starting at birth or by 2.5 weeks of age. Nail changes (mostly manifested as pitting) have been frequently observed; yet our patient had severe anonychia.^{1, 2} While pyoderma gangrenosum was reported in a Puerto Rican patient with the homozygous 175 kb deletion on chromosome 2q13, it was not present in our patient.¹ Skeletal manifestations of DIRA include lytic bone lesions, periostitis, osteopenia, long bone epiphyseal ballooning and erosions, widening of clavicle and anterior rib ends, periosteal elevation, and heterotopic ossification.^{1, 2} Our patient had many of these skeletal features similar to the other two patients with the homozygous 175 kb deletion on chromosome 2q13.^{1, 2} Rare vascular manifestations such as thrombosis of the right common femoral and right external iliac veins and CNS vasculitis have been described in two DIRA patients (the former reported in a patient with the 175 kb deletion).^{1, 2} Our patient had portal vein thrombosis with ascites and severe abdominal distention. Hepatosplenomegaly has been reported in five patients with DIRA.¹ Interstitial lung disease has been described in patients with DIRA including a patient with the homozygous 175 kb deletion on chromosome 2q13 but it was not present in our patient.^{1, 2} Conjunctiva injection has been observed in DIRA, yet our patient had a history of corneal lacerations and ulcers.^{1, 2}

To our knowledge, our patient is the oldest living, and third Puerto Rican reported with genetically confirmed DIRA.^{1, 2} Reported causes of death associated with DIRA include multiorgan failure secondary to systemic inflammatory response syndrome and pulmonary hemosiderosis with progressive interstitial fibrosis.^{1, 2} It is of interest that monogenic homozygous and compound heterozygote pathogenic mutations in *IL36RN* gene (previously known as *IL1F5*), one of the five adjacent genes to *IL1RN* in the 175 kb deletion, have been recently reported associated with generalized pustular psoriasis and termed interleukin-36-receptor antagonist deficiency.^{3, 4} Therefore, our patient and other Puerto Rican patients with 175-kb deletion have at least two known mutated genes associated with pustulosis (*IL36RN* and *IL1RN*).

The differential diagnosis of DIRA includes other autoinflammatory syndromes with skin and bone manifestations such as Neonatal-onset multisystem inflammatory disease (NOMID) and Majeed syndrome.⁵⁻⁷ In contrast to DIRA, NOMID is caused by a gain of function mutation in *NLRP3*.⁸ While patients with NOMID commonly have short episodes of recurrent fever, it is rare in DIRA. NOMID dermatologic manifestations include urticaria-like lesions reported in about two-thirds of affected newborns.^{8, 9} Histologic examination of lesional skin in NOMID shows a superficial and deep perivascular infiltrate of lymphocytes, neutrophils and occasional eosinophils in contrast to the neutrophilic pustulosis associated with DIRA. Systemic manifestations characteristic of NOMID, but absent in DIRA patients, include cerebral atrophy, aseptic meningitis and high-frequency hearing loss.⁸ In contrast to the osteolytic lesions and other bone features associated with DIRA, patients with NOMID develop a unique arthropathy with epiphyseal radiological findings showing osseous overgrowth.⁸⁻¹⁰

Majeed syndrome is an autosomal recessive disease caused by mutations in *LPIN2*, characterized by early onset chronic recurrent multifocal osteomyelitis, congenital dyserythropoietic anemia, periodic fevers, and neutrophilic dermatosis (from sweets syndrome to chronic pustulosis).⁵⁻⁷ Microcytic congenital dyserythropoietic anaemia is

unique of Majeed syndrome and it is not seen in patients with DIRA. Physical examination and genetic testing can distinguish NOMID and Majeed syndrome from DIRA. It is possible that cases previously described in the literature as infantile generalized pustular psoriasis associated with lytic bone lesions represent DIRA.^{1, 11}

Daily treatment with anakinra 1–5 mg/kg has led to clinical resolution of skin and bone manifestations within days to weeks in all DIRA patients with truncating mutations.¹ However, of the two previously described Puerto Rican patients with the homozygous 175 kb deletion on chromosome 2q13 treated with anakinra, one showed significant yet incomplete response whereas the other had complete clinical resolution.^{1, 2} Our patient experienced marked clinical improvement with clearing of all pustules, however minimally scaly patches persisted on exam. His inflammatory markers improved but did not reach normal levels. We are unclear as to why the patient described by Reddy et al² experienced a complete clinical resolution of all skin lesions, yet our patient and the one described by Aksentijevich¹ did not. However, all three patients had significant clinical improvement with anakinra. Gene-gene interactions and/or environmental factors may account in part for the variability in treatment effect observed among Puerto Rican patients with the homozygous 175 kb deletion. Although *IL36RN* may contribute to the pustular phenotype in these patients, it is not clear whether the four additional deleted genes adjacent to *IL1RN* contribute to a more severe and resistant phenotype. Therefore, the role of the additional genes deleted in the clinical phenotype of these patients needs to be investigated in future studies. It is of interest that anakinra is also efficacious in the treatment of other autoinflammatory diseases including NOMID.⁸

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Figure 1.
A. Abdominal distention and erythematous plaques with overlying pustules. **B.** Close-up of abdominal lesions revealing pustules.

Figure 2.
Psoriasiform dermatitis with a subcorneal pustule. (Hematoxylin and eosin stain, original magnification 4X)

Figure 3.
Significant improvement in abdominal lesions at 10 days of follow-up after anakinra treatment.