Interleukin-1 receptor antagonist deficiency with a novel mutation; late onset and successful treatment with canakinumab: a case report

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Abstract

Introduction: Interleukin-1 receptor antagonist deficiency is a rare autoinflammatory disease involving neonatal onset of pustulosis, periostitis, and sterile osteomyelitis. The underlying genetic abnormality involves a recessive mutation in IL1RN, which encodes interleukin-1 receptor antagonist. In this case report, we describe a case of a 12-year-old Turkish girl who initially was presented at 1 year of age, older than previously reported children with interleukin-1 receptor antagonist deficiency, and with a novel mutation, p.R26X, in IL1RN.

Case presentation: Our patient developed pustular cutaneous lesions at 1 year of age. At the age of 12 years, she was hospitalized for arthralgia of her knees, elbows, and ankles and arthritis of the left knee, with simultaneous pustular cutaneous lesions. She was admitted to the intensive care unit because of septicemia and respiratory insufficiency during follow-up. A skin biopsy of hyperpigmented lesions demonstrated neutrophil infiltration in the epidermis and subepidermal pustular dermatosis. Interleukin-1 receptor antagonist deficiency was suspected, and genetic analysis revealed a homozygous mutation (p.R26X) in IL1RN, which led to a diagnosis of interleukin-1 receptor antagonist deficiency. Treatment with canakinumab (recombinant human anti-human interleukin-1β monoclonal antibody) 150mg subcutaneously once every 6 weeks was initiated. Our patient did not experience further cutaneous lesions or arthritis. Her post-treatment inflammatory markers were normal; she gained weight; and she was able to walk independently.

Conclusions: In this case report, we describe a patient with interleukin-1 receptor antagonist deficiency who responded excellently to canakinumab treatment. We believe more awareness is warranted for interleukin-1 receptor antagonist deficiency in children. It is possible that the mutation in our patient was a founder mutation that may lead to diagnosis of additional cases in Turkey.

Keywords: Autoinflammation, Canakinumab, Interleukin-1 receptor antagonist deficiency
which encodes for the interleukin-1 receptor antagonist (IL-1Ra) [1, 2, 11]. The radiological manifestations of DIRA syndrome include multi-focal osteitis of the ribs and long bones, heterotopic ossification, and periarticular soft tissue swelling [10]. Treatment with anakinra leads to a rapid clinical improvement [1, 2, 7–9, 11–13].

In this report, we describe a case of a 12-year-old girl who was initially presented at 1 year of age. She is considered to have a late-onset presentation in comparison to previously reported children with DIRA. She has a novel mutation in IL1RN and, to the best of our knowledge, is the first reported patient with DIRA who has had an excellent response to canakinumab (recombinant human anti-human IL-1β monoclonal antibody) treatment.

Case presentation
A 12-year-old Turkish girl, born at 38 weeks of gestational age to unrelated healthy parents, was well until 1 year of age, when she developed pustular cutaneous lesions that responded to corticosteroid and antibiotic treatment with healing and scar formation. Various treatments of these lesions had required four hospitalizations during the previous 11 years. No other family member had similar skin conditions. She was hospitalized at the age of 12 years for arthralgia of her knees, elbows, and ankles and arthritis of her left knee, with concomitant pustular cutaneous lesions. She developed septicemia and was admitted to the intensive care unit of a public hospital with respiratory insufficiency during her follow-up. After recovery, she was referred to our pediatric immunology department for further evaluation.

A hyperpigmented scar lesion on the right side of the face; bilateral inguinal, paraumbilical hyperpigmented scar lesions; and paronychia of the thumbs were noted on admission (Fig. 1). Additionally, the patient had contracture of the left knee limiting her motion, episcleritis, and failure to thrive [25kg (below third percentile), 132cm (below third percentile)]. The results of her laboratory studies revealed iron deficiency anemia, hypergammaglobulinemia, and elevated acute-phase reactants (red blood cell count 4.2 million/mm$^3$, hemoglobin 9.1g/dl, hematocrit 27.8%, mean corpuscular volume 81fl,

**Fig. 1** a Inguinal and pubic hyperpigmented scar lesions. b Paronychia of the toes
logic investigations yielded C-reactive protein, mutation, p.R26X, confirming the clinical AID can present with different skin or bacteria. Splenomegaly was sonography. Skin biopsy of CARD14 et al. Journal of Medical Case Reports (2015) 9:145–Acute-phase reactants upon admission and during follow-up while receiving canakinumab treatment SAA and IL-1β stimulation results in life-IL1RN – ESR or) were negative. She was erythrocyte sedimentation rate, IL1RN ı αcytes were normal. Autoanti- and the IL1RN.

|                | Reference ranges       | On admission | After first administration of canakinumab | Last visit |
|----------------|------------------------|--------------|------------------------------------------|------------|
| CRP            | 0-0.1mg/dl             | 6.5mg/dl     | 1mg/dl                                   | <0.33mg/dl |
| ESR            | 0-20mm/hr              | 100mm/hr     | 30mm/hr                                  | 10mm/hr    |
| SAA            | 0-8mg/L                | 123mg/L      | 13.3mg/L                                 | 6.9mg/L    |

CRP C-reactive protein, ESR erythrocyte sedimentation rate, SAA Serum amyloid A

Table 1 Acute-phase reactants upon admission and during follow-up while receiving canakinumab treatment

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have been approved: anakinra, rilonacept, and canakinumab [16]. Anakinra, a recombinant human IL-1Ra that blocks the proinflammatory effects of IL-1-β, rapidly relieves the symptoms of systemic inflammation in patients with DIRA [1, 17]. Anakinra is usually given subcutaneously at an initial dose of 1mg/kg/day. Most of the patients with DIRA are reported to have a good response to anakinra treatment. Unfortunately, our patient lived in a rural area where application of daily subcutaneous injections is unavailable, owing to inadequate sanitary conditions. Thus, canakinumab, a human anti-IL-1β monoclonal antibody that can be administered every 6 to 8 weeks, was the treatment of choice. We obtained full clinical and laboratory remission with canakinumab treatment applied every 6 weeks. To the best of our knowledge, ours is the first patient with DIRA treated with canakinumab.

Conclusions
Patients with DIRA may present with systemic inflammation, respiratory distress, joint swelling, pustular rash, multi-focal osteomyelitis, and periostitis. DIRA must be considered in the differential diagnosis of children with these symptoms. Treatment with IL-1-β blockage is accepted to be lifesaving, because the disorder mimics severe bacterial infections and may result in death from development of systemic inflammatory response. A prompt and accurate diagnosis is of utmost importance to avoid improper management of patients with antibiotics alone, as effective treatment options are readily available. Our aim in this report is to raise awareness of the diagnosis of DIRA and adequate treatment choices for achieving remission and preventing permanent damage and early mortality, leading to improved quality of life in these patients.

Consent
Written informed consent was obtained from the patient’s parents for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations
AID: autoinflammatory disease; CNS: central nervous system; CRP: C-reactive protein; DIRA: deficiency of interleukin-1 receptor antagonist; ESR: erythrocyte sedimentation rate; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; IL: interleukin; IL-1Ra: interleukin-1 receptor antagonist; NOMID: Neonatal onset multi-system inflammatory disease; SAA: serum amyloid A.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
NK, NEX, GA, EU and EK were involved in the diagnosis, findings, and interpretation of the case. HE performed the genetic analysis. EU and NEX wrote the manuscript. EU and NEX contributed equally. All authors read and approved the final manuscript.

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