Case report

Combined therapy with IL-1 and JAK inhibitors in a patient with the *NLRP1* gene mutation and a complex inflammatory phenotype

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A patient presented with overlapping clinical and laboratory features of 2 rare autoinflammatory diseases, NLRP1-associated autoinflammation with arthritis and dyskeratosis and familial multiple self-healing palmoplantar carcinoma. Her severe inflammatory attack was treated with the IL-1 receptor-α inhibitor anakinra along with the Janus kinase inhibitor ruxolitinib. Three years into the treatment, the patient's inflammatory symptoms are completely in remission. (J Allergy Clin Immunol Global 2024;3:100251.)

Key words: *Autoinflammatory disorder, dyskeratosis, NLRP1, inborn error of immunity, IL1RA-inhibitor, anakinra, ruxolitinib*

NLRP1-associated autoinflammation with arthritis and dyskeratosis (NAIAD) is a rare autoinflammatory disease caused by gain-of-function mutations in the *NLRP1* gene and characterized by systemic inflammation, including arthritis and dyskeratosis, as well as by signs of impaired B-cell maturation.[1] Familial multiple self-healing palmoplantar carcinoma (MSPC) is a distinct, yet different disease that is also caused by *NLRP1* inflammasome activation,[2] leading to hyperkeratosis, progressive corneal opacity, and predisposition to skin cancer.[2,3]

To the best of our knowledge, this is the fifth case of NAIAD syndrome reported worldwide.[2,4]

Abbreviations used

CRP: C-reactive protein
IMV: Invasive mechanical ventilation
JAK: Janus kinase
MSPC: Multiple self-healing palmoplantar carcinoma
NAIAD: NLRP1-associated autoinflammation with arthritis and dyskeratosis

CASE PRESENTATION

Here, we describe a female patient of Slavic ethnicity who was born to nonconsanguineous parents with no known family history of autoimmune or inflammatory diseases. At birth, she presented with hyperkeratotic dermatitis, and at age 18 months, she developed bilateral keratoconjunctivitis that was thought to be caused by herpesvirus. Despite long-term antiviral and local corticosteroid treatment, the patient's keratoconjunctivitis progressed and led to bilateral corneal opacity (Fig 1, *A*) with almost complete vision loss by age 5 years.

At admission to the Dmitry Rogachev Center at age 7 years, the patient had a diffuse hyperkeratosis on her body and limbs, alopecia areata with brittle light hair, nail dystrophy, hypertrophic gingivitis, plantar hyperkeratotic lesions (Fig 1), and mild arthritis of the ankles and elbows. Ophthalmologic examination revealed bilateral vascularized complete corneal opacity and phthisis bulbi of both eyes. The results of blood biochemistry, total blood counts, and immunoserologic tests were unremarkable except for mild Coombs-negative anemia (hemoglobin level 110 g/L) and an elevated C-reactive protein (CRP) level (34.5 mg/L) (see Table E1 in the Online Repository at www.jaci-global.org). Flow cytometry showed impaired B-cell maturation with decreased numbers of class-switched B cells (see Table E1). Genetic testing identified a heterozygous mutation, c.160 G>A, p.Ala54Thr in the *NLRP1* gene, which had previously been described as pathogenic in patients with MSPC.[2] The patient's mother carried the same mutation and had hyperkeratotic lesions on her elbows and an elevated CRP level (50 mg/L [reference = 0-5 mg/L]) but was otherwise asymptomatic.

Shortly after admission, the patient developed an inflammatory attack with fever, an elevated CRP level (227 mg/L [see Table E1]), bilateral ground-glass lung opacities (Fig 1), and respiratory distress syndrome requiring invasive mechanical ventilation (IMV). As no bacterial or viral infections were proved, we presumed the attack to be autoinflammatory in nature and administered high-dose methylprednisone (20 mg/kg per day) for 5 days

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Consent for publication: Informed consent for publishing the case description was obtained from the patient's caregiver (the patient's mother, as the patient was younger than the age of consent). Ethics approval and consent to participate: This article was approved for publishing by the Dmitry Rogachev National Medical Center of Pediatric Hematology, Oncology and Immunology ethics committee.

Received for publication June 16, 2023; revised December 8, 2023; accepted for publication January 3, 2024.

Available online April 4, 2024.

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2772-8293

https://doi.org/10.1016/j.jacig.2024.100251

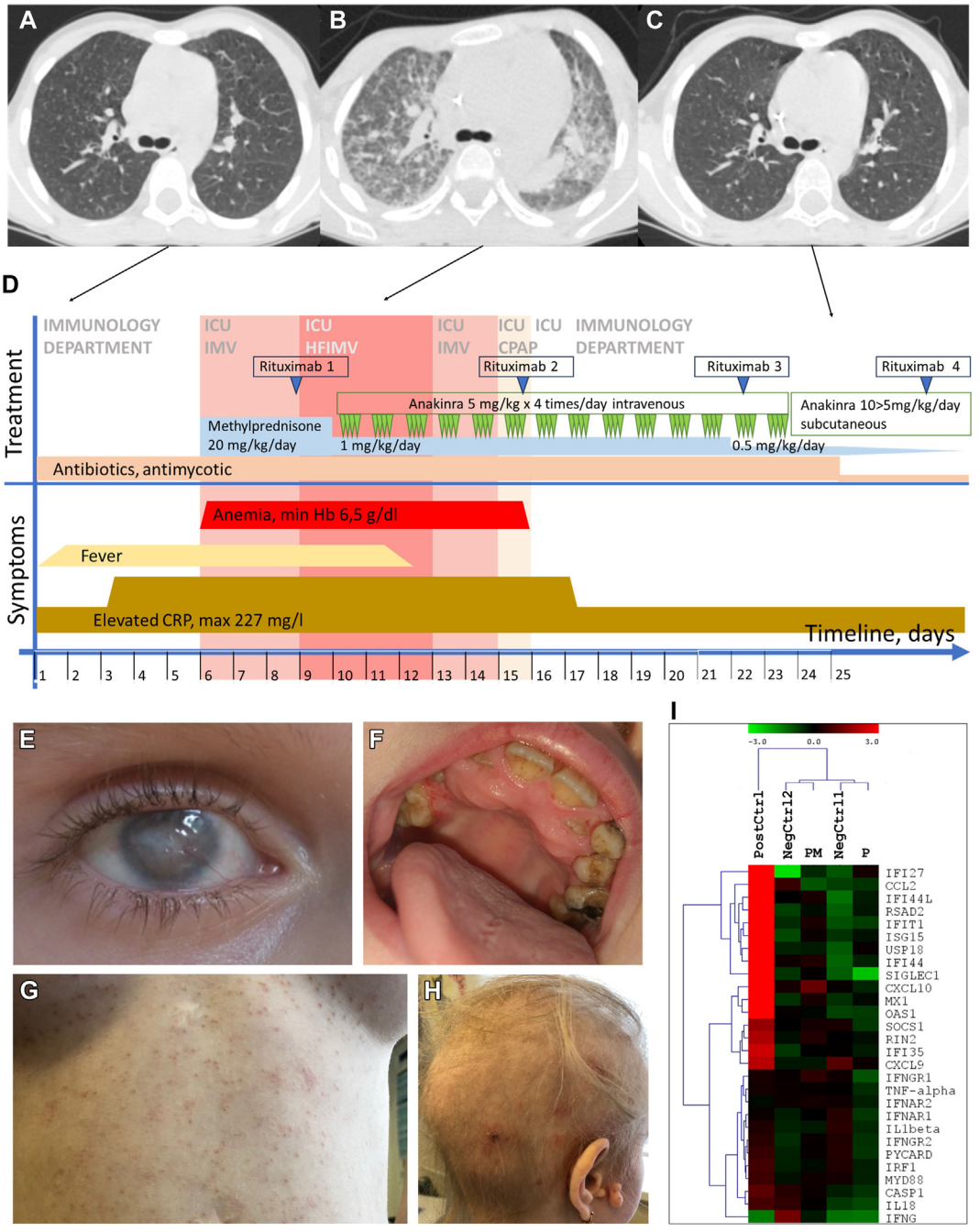

FIG 1. Clinical presentation, course of the disease, and interferon-stimulated gene (ISG) signature of the patient with *NLRP1* mutation. **A-C,** Bilateral lung interstitial involvement **(A)** with progression into opacities during the inflammatory attack **(B)** and reduction of opacities subsequent to therapy with anakinra **(C)**. **D,** Schematic representation of the course of the inflammatory attack and treatment. **E,** Vascularized corneal opacity. **F,** Hypertrophic gingivitis. **G,** Follicular hyperkeratosis. **H,** Alopecia areata and additional auricular appendages. **E** and **F**, Photos taken before the inflammatory attack (currently unchanged). **I,** Gene expression profiles of 2 carriers of the *NLRP1* mutation. The patient's sample was obtained after 60 days of treatment with a combined therapy with IL-1 inhibitor (anakinra) and JAK inhibitor (ruxolitinib). The heat map shows the transcript expression levels of interferon-induced genes and other proinflammatory cytokines in whole blood, with red representing higher expression and green representing lower expression. *CPAP*, Continuous positive airway pressure; *Hb*, hemoglobin; *HF*, high-frequency; *ICU*, intensive care unit; *P*, the patient; *PM*, the patient's mildly affected mother; *PostCtrl*, a patient with lupus who is positive for an ISG signature; *NegCtrl1* and *NegCtrl2*, 2 unrelated healthy controls who are negative for ISGs.

(with gradual tapering), which had no effect. Taking into account hyperimmunoglobulinemia and a possible antibody-mediated mechanism of lung damage, the patient was then given rituximab (375 mg/m^2 per week) for a total of 4 infusions. Despite the treatment, the patient's condition deteriorated, and she required high-frequency IMV. In consideration of the patient's *NLRP1* causal mutation, she was then given high doses of the IL-1 receptor antagonist anakinra (5 mg/kg administered intravenously, 4 times per day). An immediate and dramatic improvement was observed, with resolution of her fever and respiratory distress syndrome (Fig 1) and IMV discontinuation after she had received anakinra for only 5 days. The patient continued receiving anakinra intravenously and was subsequently transitioned to subcutaneous administration at a dosage of 10 mg/kg and later 5 mg/kg daily.

Despite the complete resolution of her clinical inflammatory features, including arthritis, after 90 days of anakinra treatment, the patient still had elevated levels of ferritin and CRP. As the activation of NLRP1 inflammasome results not only in high IL-1 but also high IL-18 production,[5] a Janus kinase (JAK) inhibitor, ruxolitinib, was added to the treatment at the dose 25 mg/m^2 per day, which within 2 weeks led to complete normalization of the patient's laboratory inflammatory activity.

Unfortunately, we could not test the inflammatory gene expression signature in the patient's peripheral blood before the therapy. To assess the efficacy of the combined therapy with IL-1 and JAK inhibitors in ameliorating the patient's inflammation, we evaluated gene expression signature by using a custom-made array. This array included a set of interferon-induced genes, as well as genes related to IL-1, IL-18, and TNF.

In the patient, the levels of expression of interferon-stimulated genes, IL-1, IL-18, and TNF cytokines were similar to those in healthy controls and her mildly symptomatic mother (Fig 1). These results, together with the evidence of the patient's normalized levels of acute-phase reactants, suggest the efficacy of this combined therapy. At the time of writing this article (3 years after initiation of the therapy), the patient is doing well, and except for hyperkeratotic skin lesions and irreversible eye damage, she shows no signs of inflammatory activity. No side effects of the combined treatment, including a propensity toward viral infections, were recorded.

DISCUSSION

Here we have described a patient with clinical overlap of MSPC and NAIAD syndromes who had mild inflammatory features for the first 7 years of her life before developing a severe, life-threating attack with multiorgan involvement. Her family history was remarkable for a reduced penetrance of the *NLRP1* defect in the mother—a phenomenon that is rarely observed in inflammasomopathies yet is a common feature of type I interferon–mediated diseases. In fact, the success of the patient's treatment with an IL-1 inhibitor in combination with a JAK inhibitor might suggest a possible contribution of both inflammasome and type I interferon pathways to the pathogenesis of NLRP1-asscoiated diseases, which adds complexity to understanding of the patient's condition.

The patient demonstrated a dramatic response to therapy with an IL-1 inhibitor, and a long-term effect was achieved by its combination with a JAK inhibitor. This combination was safe over the long term and has not been reported previously in patients with NLRP1-associated disease. It is worth noting that at the height of the patient's inflammatory attack, she received high doses of anakinra administered intravenously. Several reports of patients with sepsis or macrophage activation syndrome describe safe and effective use of anakinra in doses as high as 30 mg/kg per day or a 72-hour continuous intravenous infusion of 2.0 mg/kg per hour.[6,7] Yet there are no studies focusing on the use of high-dose anakinra in patients with monogenic autoinflammatory diseases during severe attacks. Although our case provides some insights into the potential benefits of high-dose anakinra, further investigation is necessary to evaluate its efficacy and safety in various clinical scenarios. For instance, the frequency and severity of infections and virus reactivation in a setting of combined cytokine suppression require long-term monitoring.

Finally, this case highlights the critical role of genetic information in the management of and targeted therapies for autoinflammatory conditions.

DISCLOSURE STATEMENT

Editorial assistance was provided by Bioscript Group, Macclesfield, United Kingdom, and funded by Sobi.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

We thank Helen Bristow of Bioscript Group, Macclesfield, United Kingdom, for editorial assistance.

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