CASE REPORT

Generalized pustular psoriasis with a novel mutation of interleukin-36 receptor antagonist, responding to methotrexate

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INTRODUCTION

Generalized pustular psoriasis (GPP) is a rare but serious inflammatory skin disease that may be caused by deficiency of interleukin-36 receptor antagonist in which there is presence of homozygous or compound heterozygous mutations of the IL-36RN gene. Most GPP cases are sporadic, although some may be autosomal recessive. A significant proportion of GPP without psoriasis vulgaris (PV) had homozygous or compound heterozygous mutations in IL-36RN. GPP alone is a distinct subtype and is etiologically distinguished from GPP with PV. Most GPP alone is caused by deficiency of the IL-36RN caused by IL-36RN mutations, in contrast to GPP associated with PV, in which this mutation is usually absent.

CASE REPORT

A 20-year-old Chinese Indonesian woman presented to our clinic in February 2014 with erythroderma and pustules on the trunk, limbs, and nails. The generalized erythema with crusting and pustules started from the age of 17 months and comes in waves with periods of exacerbation and quiescence. There was no family history of psoriasis. There was limited response to topical steroids, acitretin, and ustekinumab. She was administered pulsed methylprednisolone for many years by her previous doctors, which led to secondary adrenal insufficiency. She is taking regular hydrocortisone tablets, 10 mg in the morning and 5 mg in the afternoon. Skin biopsy results from the shin were consistent with pustular psoriasis (Fig 2).

Blood samples were taken from the patient and her parents and sent for genetic analysis for mutations of IL-36RN. Our patient carries a homozygous pathogenic splice mutation of the IL-36 gene with IVS3C>T (Fig 3). Her parents did not carry any mutations of the IL-36 gene.

We initially planned to treat the psoriasis with the recombinant interleukin-1 receptor antagonist, anakinra. In view of the high treatment cost, she declined anakinra treatment.

She has responded well to methotrexate, 7.5 mg/week; calcitriol ointment twice daily to the face, shin, and neck plaques; and betamethasone valerate, 0.05% cream twice daily, to the rest of the shins and trunk.

DISCUSSION

Our patient has a de novo mutation of the IL-36RN, as neither of her parents was heterozygous for the mutation. To the best of our knowledge, this is the first reported case of homozygous splice mutation of the IL-36 gene with IVS3C>T causing GPP clinically. She had a change of nucleotide in which cytosine pyrimidine was substituted with thymine pyrimidine at intron 3. The mutation impairs the splicing of introns from the mRNA of the IL-36RN gene and results either in an aberrant or absence of the IL-36RA protein. It did not lead to a change of amino acids.
Fig 1. A, Scattered discrete pustules on erythematous skin on the shins. B, Dystrophic toenails with pustules on both feet.

Fig 2. Skin biopsy results showed acanthosis, elongated rete processes, spongiosis, and focal parakeratosis. Neutrophils migrate through the epidermis and concentrate in the parakeratotic layer. It has perivascular inflammation and includes neutrophils, lymphocytes, plasma cells, and some eosinophils. Extravasation of red blood cells is noted in the papillary dermis. (Hematoxylin-eosin stain; original magnification: ×40.)

Fig 3. Homozygous point mutation in which the cytosine pyrimidine was substituted with the thymine pyrimidine in the splicing donor site on the region of exon 3.
acids, as it is not located in an exon region, but the effect is more drastic than a change in amino acid.

The IL-36RN antagonist and the additional 3 agonists, interleukin-36α, interleukin-36β, and interleukin-36γ, are expressed in epithelial tissues such as the skin. Interleukin-36RN inhibits downstream inflammatory signaling (nuclear factor κ-light-chain-enhancer of activated B cells and mitogen-activated protein kinases), avoiding excessive inflammatory responses. Dysregulation of the interleukin-36–interleukin-36RN signaling pathway is a predisposing factor GPP development.

The interleukin-1 family consists of 11 members of which IL-36RN shares 44% homology with interleukin-1 receptor antagonist (IL-1RA). IL-36RA (interleukin-36 receptor antagonist) is a product of IL-36RN, which downregulates both interleukin-1α and interleukin-1β.

Some of the reported homozygous IL-36RN mutations include p.His32Arg, p.Pro76Leu, or p.Ser113Leu, and compound heterozygous mutations include p.Ser113Leu and p.Arg48Trp, p.Glu94X, or p.Pro76Leu. These stop and missense mutations can destabilize the IL-36RA protein through changes to the protein structures and their ability to bind to receptors.

Previous case reports have shown successful treatment of GPP with anakinra, although the high cost for long-term anakinra is likely to be prohibitory to many patients, especially in developing countries. Although some case reports show poor response to methotrexate, our patient has improved significantly with low doses of methotrexate.

**CONCLUSION**

We present a new de novo homozygous splice mutation of IL-36RN that has not been described in the literature. The patient’s condition is currently well controlled with methotrexate. We highlight that methotrexate can be considered an alternative in patients who are unsuitable or unable to afford the cost of anakinra.

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