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Ocular Manifestations of Inherited Phospholipase-C γ 2–Associated Antibody Deficiency and Immune Dysregulation

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Abstract

Purpose—To report the ocular manifestations of Phospholipase-C γ 2 (PLC γ 2)–Associated Antibody Deficiency and Immune Dysregulation (PLAID).

Methods—Case report and literature review.

Results—A 21-year-old woman with diagnosed PLAID was referred for evaluation of repeated episodes of ocular inflammation resulting in bilateral peripheral corneal pannus with episcleritis and corneal scarring accompanied by systemic manifestations including epidermolysis bullosa and interstitial lung disease. Systemic immunosuppression with corticosteroids and interleukin-1 receptor antagonist (IL-1Ra; anakinra) was supplemented with topical anakinra to avoid systemic side effects, which resulted in partial improvement of the ocular symptoms. Oral prednisone was restarted to treat active lesions during bouts of inflammation.

Conclusion—Ocular PLAID is a bilateral chronic or recurrent inflammatory disease of the ocular surface leading to severe and early cicatricial ocular surface and corneal involvement due to high IL-1 production. Management of PLAID may require both topical and systemic immunomodulatory treatment, potentially including targeted local anti-IL-1 therapy.

Keywords

PLAID; IL-1 β ; cornea; inflammation

Introduction

Phospholipase-C γ 2 (PLC γ 2)–Associated Antibody Deficiency and Immune Dysregulation (PLAID) is a rare inherited disease with a presentation that includes both auto-inflammation and immunodeficiency. The few familial identified cases of PLAID show mutations in the PLC γ 2 gene leading to aberrant function of immune cells and overproduction of IL-1 β . Clinical manifestations encompass inflammation at multiple tissues, including recurrent skin

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eruptions, nonspecific interstitial pneumonitis and bronchiolitis, sinopulmonary infections and arthralgia.¹ In this case report, we are describing a unique presentation, for the first time, of corneal manifestations in PLAID.

Case Report

A 21-year-old woman with a diagnosis of PLAID was referred to the Cornea Clinic for evaluation of her longstanding ocular symptoms. Since a few months after birth the patient had experienced repeated episodes of ocular inflammation resulting in bilateral peripheral corneal pannus inferotemporally with sectoral conjunctivitis, episcleritis and elevated limbal ridges. These episodes were accompanied by systemic manifestations, most prominently epidermolysis bullosa and interstitial lung disease.

To treat both systemic and ocular manifestations of the disease and to avoid side effects of chronic use of steroids, systemic IL-1 β receptor antagonist (IL-1Ra; anakinra) treatment had been started at 14 years of age with considerable improvement; however, it was discontinued four years later due to systemic infection.

Upon presentation to us, the patient was complaining of symptoms of ocular discomfort including photophobia, redness, foreign body sensation and tearing in both eyes. Eye examination revealed conjunctival injection and fibrosis with 360 degrees of corneal scarring and superficial neovascularization. There was >50% thinning in the peripheral cornea bilaterally with the central corneas appearing clear and healthy bilaterally. Furthermore, anterior scleritis and small corneal infiltrates devoid of overlying epithelium suggested active disease.

To prevent disease progression and considering the side effects of systemic IL-1Ra, including further immune suppression, treatment with topical 2.5% IL-1Ra (Anakinra) was started resulting in partial symptomatic improvement within 2 months. Eight months later, the patient came to us during a systemic exacerbation of the disease complaining of severe eye pain and redness; ocular examination revealed progression of corneal scarring with multiple curvilinear infiltrates and overlying epithelial defects, indicating active ocular disease (Figure 1). Oral prednisone 40 mg/day was administered to treat the active disease, leading to systemic and ocular disease abatement.

Discussion

Ocular PLAID is a bilateral chronic recurrent autoinflammatory disease of the ocular surface leading to severe and early cicatricial corneal involvement. This complex systemic immune condition links a persistent state of inflammation to a severe systemic immunodeficiency state. It is characterized by unprovoked episodes of inflammation in the absence of high-titer autoantibodies or antigen-specific T cells, distinguishing it from the classical autoimmune diseases. Therefore this dysregulation of the innate immune system, mainly associated to high IL-1 β secretion, represents a significant therapeutic challenge.

IL-1 β overexpression has been associated with several other ocular inflammatory disorders such as uveitis, dry eye, allergy, and chemical burns.²⁻⁵ Overexpression of IL-1 β induces

activation and migration of inflammatory cells to the ocular surface, where they contribute to tissue damage and neovascularization. It also promotes apoptosis in corneal fibroblasts and keratocytes resulting in corneal thinning and alteration in wound healing.² IL-1 β induce increased expression of neuronal growth factors leading to hyperalgesia and chronic pain, which is responsible for a positive neuro-inflammatory feedback facilitating further tissue injury.⁶

In addition to the persistent inflammation PLAID patients have an increased risk of infection; more than half of the patients have a history of recurrent sinopulmonary infections due to a hypogammaglobulinemia, with decreased B and NK cell numbers in the peripheral blood.⁷ Thus, the main challenge in treating these patients is to control inflammation while sustaining adequate immune response to microbial pathogens. Although systemic immunosuppressive agents such as corticosteroids as well as subcutaneous IL-1Ra remain the mainstay in the treatment of PLAID, their side effects, most prominently secondary infection, limit their prolonged use. Topical IL-1 antagonism may serve as an alternative to manage ocular exacerbations of PLAID in between the systemic flares.² In addition, more selective agents such as PLC γ 2 inhibitors may serve as novel approaches in the future.⁸

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Figure 1. Ocular surface findings in a 21-year-old woman with PLAID

Slit lamp examination showing images of the right (A) and left eye (B) with 360 degrees corneal scarring and superficial neovascularization and a central island of normal cornea. There is >50% thinning of the peripheral cornea in the right (C) and the left (D) eye. (E) Magnified image showing thinning of the peripheral cornea (arrow). (F) Subepithelial fibrosis in the lower tarsal conjunctiva of the right eye. All images were taken at the last follow up visit, 8 months after the initial presentation.