



Treatment of Orbital IgG₄-Related Disease

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Abstract

IgG₄-related disease (IRD) is a distinct group of disorders with specific pathological and clinical features that can manifest in various organs. It is characterised by intense lymphoplasmacytic inflammation with IgG₄⁺ cells of the involved organ, subsequently leading to fibrosis and formation of tumefactive masses. Its pathophysiology is unclear but the involvement of a T Helper2-dominant immune response and significant numbers of CD4⁺, CD25⁺ and Foxp3⁺ regulatory T cells have been implicated. Corticosteroids are currently the mainstay treatment for IRD but are associated with adverse side effects, recurrence on discontinuation of medication, and limited response if significant fibrosis is already present. Pentoxyphylline (POF) and α-tocopherol (AT) are anti-inflammatory and anti-fibrosing agents that can be effective in treating both the acute inflammatory and chronic fibrosclerosing components of IRD. This article reviews IRD and its treatment including the emerging role of POF and AT for this inflammatory fibrosclerosing condition.

Keywords

IgG₄-related disease, Orbital, Pentoxyphylline, α-Tocopherol, Inflammatory, Fibro-sclerotic, Steroids, Treatment, Autoimmune

Introduction

IgG₄-related disease (IRD) is a newly recognised, distinct group of disorders with a common pathophysiology but variable manifestations [1]. It was first described in the Japanese literature in 2003, in a case series that identified extra-pancreatic manifestations of patients with auto-immune pancreatitis [2]. It has since been widely reported by other Japanese, other Asian, and North American groups who propose useful diagnostic guidelines and criteria for different subsets of the disease [3,4]. However, there remains a paucity of literature about this condition and its treatment outside Japan, mainly due to the lack of awareness of this new entity and its variable manifestations.

Disease Characteristics

IRD is characterised by intense IgG₄⁺ plasma cell infiltration of the involved organ(s), storiform fibrosis, formation of tumour-like masses, 5 - 50 folds elevated serum levels of IgG₄ and high

sensitivity to corticosteroids [1,5]. Symptoms depend on the organ(s) affected, most commonly the pancreas (autoimmune pancreatitis) [6], biliary system (sclerosing cholangitis) [7], lacrimal and salivary glands (Mikulicz's disease) [8]. Involvement of the orbit [9], thyroid (Riedel's thyroiditis) [10], kidneys (tubulointerstitial nephritis) [11], retroperitoneum (retroperitoneal fibrosis) [12], aorta (aortitis) [13], bowel (mesenteritis) [14], prostate [15], breast [16], lungs [17], pericardium [18], meninges [19], hypophysis [20], lymph nodes [9] and skin [21] have also been described. Any number of organs can be affected simultaneously or metachronously [5].

In IRD, the extensive infiltration of IgG₄⁺ plasma cells and T lymphocytes in the affected organ(s) disrupts tissue form and function, and also initiates an intense inflammatory response [5,22]. These processes lead to fibrosis, obliterative phlebitis and formation of masses within the affected organ [5,22], which are often mistaken for tumors. As the disease progresses slowly and insidiously, the patient may present with mild and non-specific symptoms relating to organ swelling and disruption of function [5].

Orbital IRD

IRD can affect the orbit and ocular structures, causing swelling of the lacrimal glands (dacyroadenitis) [9,23], orbital septum [24], extra-ocular muscles (myositis) [25], optic nerve sheath [9], and xanthogranulomatous changes of the orbit [26], all of which can be unilateral or bilateral. In the retrobulbar region, the disease is associated with the formation of pseudotumors [25], which can cause proptosis, pain, restriction in ocular movement with subsequent diplopia, and reduced visual acuity. It has also been reported to extend beyond the orbit to infiltrate the infra-orbital nerve [25], and intracranially to involve the cavernous sinus [27]. Interestingly, the conjunctiva is not affected [9,23]. It is important to consider this diagnosis in the work-up of orbital inflammatory disease, and to distinguish it from other conditions with similar presentations, such as idiopathic orbital disease, ocular adnexal marginal zone B-cell lymphoma, systemic vasculitic conditions such as Wegener's granulomatosis, and ocular myositis. In IRD, in addition to the heavily increased presence of IgG₄⁺ cells in biopsy specimens or serum, there may also be accompanying systemic symptoms if there is concurrent involvement of other organs such as the pancreas or peripheral lymph

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nodes [9], which may help in the diagnosis of the disease.

Pathogenesis and Pathophysiology

The pathogenesis and pathophysiology of IgG₄ activation and infiltration in IRD is not well understood. There are two main immunological characteristics that have been observed both locally in the affected tissues and peripherally. The first is that of a T helper2 (Th2)-dominant immune response, which favors the production of Th2 cytokines including IL-4, IL-5, IL-10 and IL-13 [28,29]. These cytokines also trigger antibody class switch to IgE and eosinophilic migration and infiltration [29], which together with the high incidence of allergic manifestations observed in patients with IRD [30], suggest the involvement of an allergic mechanism in the pathogenesis of the disease [30].

The second is that of significantly higher numbers of regulatory T cells expressing CD4, CD25, and transcription factor Foxhead Box P3 (Foxp3) [28], along with over-expression of regulatory cytokines IL-10 and transforming growth factor- β_1 (TGF- β_1) [28]. IL-10 directs B cells to produce IgG₄ [31], while TGF- β_1 , a key pro-fibrotic cytokine, induces the deposition of extracellular matrix proteins and Type-1 collagen, leading to fibroplasia [32]. The intense inflammatory process generated by the intense infiltration of IgG₄ antibodies leads to the pathological production of oxidative stress and free oxygen radicals, which may overwhelm the cellular response mechanism, resulting in tissue injury [27].

Serological Findings

The hallmark of IRD is an elevation in serum levels of IgG₄ [5]. While useful in confirming the diagnosis of IRD, it is not a specific diagnostic marker [33], and has to be correlated with histopathological analysis [3]. In addition, it is difficult to correlate serum levels to the disease severity of a specific organ [34], as it depends on an estimate of the amount of plasma cells within a particular organ [34]. Similarly, serum levels of IgG₄ may remain elevated following treatment despite regression of the lesion [33], due to residual IgG₄ secreting cells located sub-clinically elsewhere. Clinical improvement remains the best indicator for monitoring therapeutic efficacy.

Treatment

Corticosteroids are the mainstay treatment for IRD [35] based on their immunomodulating and anti-inflammatory properties [36], specifically, inhibition of B and T cell activity, cytokine production, and inflammatory cascades [36]. However, their effects are often short-lived with recurrence upon discontinuation or early tapering of the medication [35]. In addition, they are associated with significant adverse effects including immunosuppression, osteoporosis, Cushingoid facies, glucose intolerance and hypertension [36]. Immuno-modulators, such as methotrexate, azathioprine, mycophenolate, rituximab and bortezomib have been used in recurrent or refractory cases [35]. While prolonged remission and successful treatment of the disease has been reported, it is confined to a few case studies and small retrospective series with short follow-up [35]. Hence their long term efficacy remains unknown.

Pentoxyphylline and α -Tocopherol as A Novel Treatment for IRD

Pentoxyphylline (POF) is a methylxanthine derivative which acts as a non-specific phosphodiesterase inhibitor with anti-inflammatory [37], anti-fibrotic [38] and anti-oxidant properties [39]. Specifically, it inhibits TNF- α production [37], fibroblast proliferation and collagen deposition, while stimulating collagenase activity [38]. It has been used for the treatment of a variety of inflammatory and fibrotic conditions, including peripheral vascular disease, steatohepatitis, sarcoidosis, radiation-induced fibrosis and osteoradionecrosis (ORN) [27,40,41].

α -Tocopherol (AT), more commonly known as vitamin E, is a lipid-soluble vitamin with anti-oxidant properties [42]. It scavenges free oxygen radicals produced during oxidative stress [42], and protects cell membranes against lipid peroxidation [42]. AT may also

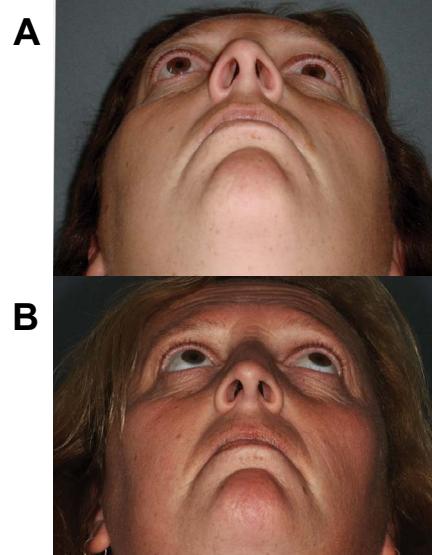


Figure 1: (A) Worm's eye view of a 32-year old female referred with on-going symptoms of right-sided diplopia, proptosis, retrobulbar pain and headaches. Full ophthalmological assessment showed 6/18 vision on right compared to 6/9 on left (aided), 5mm of proptosis and markedly reduced elevation of the right eye. (B) Complete resolution of symptoms and proptosis with normal extraocular movements without diplopia, and return of visual acuity to the pretreatment state, one month after a 22-month course of pentoxyphylline and α -tocopherol. *Reproduced with permission from BJOMFS [44].*



Figure 2: Axial T1 post-contrast MRI sequence showing a large ill-defined intra-orbital mass that occupied most of the intra-conal space extending from the globe to the orbital apex displacing the optic nerve supero-medially and 5mm of proptosis. *Reproduced with permission from BJOMFS [44].*

act as an anti-fibrotic agent [43], as it has been shown to inhibit the transcription of procollagen type 1 and over-expression of TGF- β_1 , both of which induce fibrosis [43]. It has been used in a variety of conditions where there is sensitivity to oxidative reactions, including delaying age-related macular degeneration, atherosclerosis, functional impairment or decline in patients with Alzheimer's disease, and non-alcoholic fatty liver disease [42].

A recent case report demonstrates the novel use of these two agents in the treatment of orbital IRD in a 32 year-old woman who presented with an 18-month history of diplopia, proptosis and headaches (Figure 1A, *Supplemental Figure 1A*) [44]. An MRI scan showed an ill-defined, intra-conal lesion causing 5mm of proptosis and displacement of the optic nerve supero-medially (Figure 2). The lesion initially responded to steroid therapy which was discontinued because it interfered with her diabetic control. An open biopsy showed a fibro-sclerotic lesion with B and T cell infiltration, increased IgG⁺ plasma cells, up to 135/high power field, and IgG₄⁺/IgG⁺ cell ratio of 41.8%, which confirmed the diagnosis of orbital IRD. The levels



Supplemental Figure 1: (A) Frontal view of a 32-year old female referred with on-going symptoms of diplopia, right-sided proptosis, retrobulbar pain and headaches. Full ophthalmological assessment showed 6/18 vision on right compared to 6/9 on left (aided), 5mm of proptosis and markedly reduced elevation of the right eye. (B) Complete resolution of symptoms and proptosis with normal extraocular movements without diplopia, and return of visual acuity to the pre-treatment state, one month after a 22-month course of pentoxifylline and α -tocopherol. *Reproduced with permission from BJOMFS [44].*

of serum IgG4 were not measured. Following a 22-month course of POF 800mg and AT 1,000IU orally twice daily, there was complete resolution of the symptoms and proptosis clinically (Figure 1B, Supplemental Figure 1B), as well as marked reduction of the lesion with minimal enhancement on repeat MRI scanning (Supplemental Figure 2).

The proposed mechanism of action of these two agents is that being anti-oxidant and anti-inflammatory, POF and AT trap free oxygen radicals to mitigate the inflammatory cascade in IRD [27]. They also block the expression of TGF- β_1 , as well as other cytokines and growth factors secreted by fibroblasts involved in inflammation, thus preventing the deposition of Type-1 collagen responsible for tissue fibrosis [45]. Therefore, by inhibiting both the inflammatory and fibrotic processes in IRD, they can effectively abrogate the acute as well as ongoing inflammatory response [27]. In contrast, corticosteroids and immunomodulators only target the lymphoid component but not the fibrous component of IRD. This may account for the limited response of IRD lesions to these agents, especially if there is already significant sclerosis within the lesion, as in the case reported [44].

An excellent example in the literature where this combination of POF and AT has also been shown to be effective is in the treatment of osteoradionecrosis (ORN), a condition in which there is a delayed irradiation-induced failure of bone and soft tissue healing [41]. The affected tissues in ORN show hypovascular-hypoxic effects and bony fibroatrophy [41]. Delmanian et al. [41] demonstrate that when used in combination, POF and AT result in significant reduction of exposed bone, improvement in mucosal healing, and improvement of local symptoms. They have also shown that POF or AT is ineffective when used alone [46], suggesting a synergistic effect of the two agents. Interestingly, the authors find that two years is the duration needed to



Supplemental Figure 2: Axial T1 post-contrast MRI sequence 22 months following treatment with pentoxifylline and α -tocopherol, showing reduction in the volume of the lesion that enhanced minimally and complete resolution of proptosis. *Reproduced with permission from BJOMFS [44].*

achieve two-thirds of the maximum response to the treatment [47]. A similar period of treatment with POF and AT was required for the patient with orbital IRD, resulting in complete resolution of proptosis was observed clinically and marked reduction in the volume of the lesion that enhanced minimally on repeat MRI scanning [44].

POF and AT have both been demonstrated to be safe and well tolerated by patients in the short and long term [46,47]. There is conflicting data on the safety of high dose AT with regards to mortality [48,49], although the general consensus is that it has neither significant beneficial nor adverse effects on survival regardless of dosage [48]. The main side effects of POF experienced by a small number of patients in the series reported by Delanian et al. [46,47] include epigastralgia, headaches, asthenia, vertigo, insomnia, and hypotension. However, these were easily controlled with reduction in POF dosage and symptomatic treatment, and no participant discontinued the treatment because of these side effects [47]. The dosage of POF and AT used in these trials was similar to the dosage we used for the patient with orbital IRD [44].

It will be useful to conduct clinical trials using POF and AT on IRD affecting the orbit and/or other organs.

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