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The significance of cicatricial conjunctivitis in Wegener's granulomatosis

Sir,
Wegener's granulomatosis exhibits large heterogeneity in clinical expression. The spectrum of ocular disease can occur at any stage in its natural history. Cicatricial conjunctivitis, a fibrotic conjunctival scarring response is rare and associated with subglottic stenosis.

Case

A 70-year-old man was referred to the ophthalmology department with symptoms of ocular discomfort and abnormal conjunctival appearances. He had no previous ophthalmic history. He was recently clinically diagnosed with Wegener's granulomatosis (WG) with inflammation involving his kidneys, nose and lungs with positive c-ANCA (EIA) levels of 7.6 units (<2.0). Nasal mucosa biopsy revealed mixed inflammatory infiltrate. He was too ill to undergo a renal biopsy.

Ocular examination revealed bilateral sub-tarsal conjunctival fibrosis with symblephara appearing as vertical folds between bulbar and palpebral conjunctiva (Figure 1) representative of conjunctival cicatrization. Conjunctival biopsy demonstrated minimal inflammation with no specific C3, IgA or IgG distribution as occurs with mucous membrane pemphigoid (MMP), an important differential. Serum indirect immunofluorescence for both IgG and IgA were also negative, excluding MMP.

Discussion

Our case demonstrates the heterogeneity in clinical expression of WG. Conjunctival disease has been reported in 4–16% of patients with ocular manifestations [1–4]. This can vary from conjunctival hyperaemia to granulomatous lesions, tarsal conjunctival necrosis, active fibrovascular proliferation or inactive scar tissue. Cicatricial conjunctivitis in WG is extremely rare [4]. An important differential diagnosis is MMP, an autoimmune disease whose target antigen is the β_4 peptide of the $\alpha_6\beta_4$-integrin of the basement membrane zone of conjunctiva and epidermis [5]. The conjunctival autoantigen in WG is currently unknown.

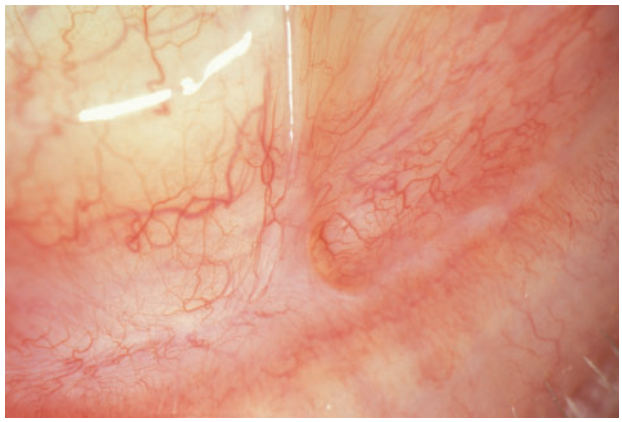

Fig. 1. Cicatricial conjunctivitis with subepithelial fibrosis and symblepharon formation. Note subepithelial fibrotic stria.

Chronic inflammation and fibrosis of the conjunctiva can induce dry eyes via occlusion of the ducts of the lacrimal and accessory glands, eyelid and eye lash abnormalities (entropion, lagophthalmos, trichiasis and dystrichiasis). The aetiology of fibrosis is unknown but these changes can lead to corneal scarring, infection, perforation and loss of vision.

The location of conjunctival disease predominantly at the eyelid borders may further the understanding of the pathogenesis of WG. The eyelids are supplied by terminal branches of the marginal and peripheral arcade vessels [6]. An occlusive vasculitis of these peripheral vessels, branches or both may lead to ischaemia or infarction [4].

Physicians should be aware that 'conjunctivitis' may represent serious eye involvement from WG and liaison with an ophthalmologist is desirable. Mucous membrane pemphigoid is an important differential diagnosis and should be excluded in all cases. A significant association exists between conjunctival disease and subglottic stenosis [4]. Subglottic stenosis can rapidly progress, leading to laryngeal obstruction and respiratory failure [7]. Our patient continues to be closely monitored and is currently stable.

Conflict of interest statement. None declared.

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MR blockade in patients with chronic renal disease—not the more the merrier, but the earlier the better

Sir,

We read with interest the recent review by Covic and coworkers [1], which highlights the possible role of spironolactone therapy in dialysis patients and summarizes the current literature. One of the major goals of spironolactone treatment in dialysis patients is the reduction of cardiomyopathy and cardiovascular morbidity and mortality. One of the major risks of spironolactone treatment is hyperkalaemia, as pointed out by the authors. The risk of hyperkalaemia correlates with the increase of the spironolactone dose. This pattern resembles the anti-androgenic effect of spironolactone (gynaecomastia, decreased libido and erectile dysfunction in men, and menstrual disturbances and mastodynia in women), which is weak at low doses and increases with higher doses (incidence of gynaecomastia with 50 mg spironolactone 6.9 and 52% at 150 mg daily) [2].

The doses of spironolactone in the treatment of primary hyperaldosteronism decreased from 200–400 mg in the 1970s and 80s to 12.5–50 mg daily in recent years. It has been shown that doses of 12.5–50 mg are often as effective as higher doses and in the treatment of therapy-resistent hypertension [3,4]. The new mineralocorticoid eplerenone requires higher doses than spironolactone, due to its lower potency, but it lacks the anti-androgenic side effects.

We share the opinion with the authors that spironolactone treatment in low doses and under tight supervision and control is possible in dialysis patients and might reduce their cardiac morbidity and mortality. Therefore, large numbers of trials are urgently needed.

However, we would like to emphasize the possible benefit of an anti-mineralocorticoid treatment at an earlier stage of renal disease, when the kidneys could profit from this treatment as well as the heart. Apart from deleterious effects on the heart, it is known that activation of the mineralocorticoid receptor (MR) also contributes to kidney damage in experimental models of hypertension. In hypertensive rats, aldosterone treatment induces severe vascular and glomerular sclerosis, fibrinoid necrosis and thrombosis. In addition, it causes interstitial leucocyte infiltration, tubular damage and results in an increase in albuminuria and pro-inflammatory molecules [5]. Administration of MR blockers or aldosterone ablation by adrenalectomy attenuates renal injury, reduces albuminuria and renal expression of proinflammatory molecules in rats independent of blood pressure reduction [5–7]. These observations support the renoprotective effects of MR antagonism in nephropathy. In humans, preliminary data suggest that spironolactone decreases proteinuria in patients with chronic renal disease and those with type 2 diabetes mellitus and early nephropathy [8–11].

We analysed renal biopsies of a large cohort of nearly 100 patients with chronic renal disease [12]. Patients with heavy albuminuria presented with high macrophage chemoattractant protein-1 expression and urinary excretion, with high macrophage invasion, with a high index of chronic damage and the worst renal survival. This group showed a significant 5-fold increase in mineralocorticoid receptor expression and a significant increase in inflammatory mediators such as transforming growth factor-β1 and interleukin-6 [12]. Our data strongly support animal data linking aldosterone–MR activation to renal inflammation and proteinuria. Further studies are urgently required to assess the potential beneficial effects of MR antagonism in patients with renal disease. However, hyperkalaemia has been raised as a potential deleterious side effect, particularly in patients with reduced renal function, heart failure or diabetes [13,14], but careful titration [15] and the use of lower doses of MR antagonists minimizes this risk. Therefore, there is now an obvious need for larger trials with anti-mineralocorticoid treatment in patients with chronic renal disease as well as end-stage renal failure.

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