Pathogenesis of Graves' Ophthalmopathy

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Fig. 1.

This figure highlights two different clinical presentations of Graves' ophthalmopathy (GO). Both patients presented with active Graves' disease (GD) and developed moderately severe, active GO shortly thereafter. Anti-thyroid drug treatment was initiated for control of their hyperthyroidism, followed by near-total thyroidectomy and early supplementation with levothyroxine. Despite these efforts, marked progression of their ophthalmopathy was noted, and severe complications (exposure keratitis in fig. 1, optic neuropathy in fig. 2) were imminent. High-dose glucocorticoid therapy, followed by orbital radiotherapy, was administered and resulted in satisfactory improvement. Figure 1 demonstrates a 54-year-old male with marked proptosis, severe

extraocular muscle dysfunction and moderate periorbital edema. In contrast, figure 2 depicts a 56-year-old female with profound bilateral periorbital edema and severe optic neuropathy in the absence of extraocular muscle dysfunction. Both individuals used to smoke heavily, but quit smoking as part of their therapeutic intervention.

GO represents a chronic inflammatory process of the orbital tissue that is closely associated with autoimmune thyroid disease, mainly GD [1]. T cells infiltrating the orbital space early in the course of the disease have recently been demonstrated to express a restricted repertoire of T cell antigen receptor variable region genes that reveal striking similarities with T cells infiltrating the thyroid gland and the involved extrathyroidal tissues [2]. T cells gain access to the orbital space via certain adhesion molecules including ICAM-1, ELAM-1, VCAM-1 and CD44. Within the orbital connective tissue and extraocular muscle, infiltrating immunological effector cells release various cytokines such as IL-1, IFN γ , TNF α , PDGF, IGF-1 and TGF β , many of which are capable of stimulating numerous important cellular functions

Fig. 2.

in orbital fibroblasts, including cell proliferation, expression of immunomodulatory proteins and metalloproteases, and accumulation of hydrophilic glycosaminoglycans [3]. As a result, mechanical problems soon arise with-

in the bony orbits due to expansion of the orbital connective tissue and extraocular muscles, giving rise to the clinical expression of GO, namely proptosis, extraocular muscle dysfunction, periorbital edema and chemosis.

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Standard therapy for severe, active GO has remained nonspecific and includes oral or intravenous glucocorticosteroids, orbital radiotherapy, and surgical decompression of the orbits.

Novel, yet unproven, strategies designed to modulate orbital lymphocyte and fibroblast activities include the usage of long-acting somatostatin analogues and certain cytokine antagonists.

The primary antigen responsible for the orbital inflammatory process in patients with GD has remained enigmatic. The close clinical and temporal association of GD and GO favors the concept of B and T cell activities directed against a common antigen that is shared by the thyroid gland and orbital tissue. In view of the central role of the TSH receptor (TSHR) and TSHR antibodies in causing the

hyperthyroidism of GD, the TSHR represents a logical candidate antigen in GO. In support of this concept, the presence of both RNA encoding the TSHR and TSHR-like immuno-reactivity in orbital tissues have recently been demonstrated both in situ and in vitro [4, 5]. Further studies are required to determine whether the TSHR is justifiably implicated in the pathogenesis of GO.

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