Reply re: “Drug-Induced Graves Disease From Cytotoxic T-Lymphocyte Antigen-4 Receptor Suppression”

To the Editor:

Dr. Sohrab et al. provide still another interesting case of ipilimumab-associated orbital disease, induced by use of this agent for metastatic melanoma. This case demonstrated findings similar to those we previously described with respect to proptosis, chemosis, and diffuse fusiform thickening of extraocular muscles and response to systemic corticosteroids. Ipilimumab targets cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) protein receptors, a cell determinant critical in suppressing T-cell activation. Mutations in the gene generating this surface protein have been associated not only with thyroid eye disease but also with insulin-dependent diabetes mellitus, primary biliary cirrhosis, and other autoimmune diseases. Based on population studies, certain polymorphisms within the CTLA-4 gene are associated with autoimmune thyroid disease. Given both its genetic associations and syndrome inducement by the suppressive interaction with biologically active monoclonal antibody, this lymphocyte receptor seems to play a role in generation of inflammatory orbital disease.

Although the images presented by Sohrab and our original report bear resemblance orbital Graves myopathy, it is possible that the ipilimumab-associated inflammatory orbitopathy is distinct as a clinical syndrome. The natural history and long-term chronic changes of the drug-induced inflammatory effect still remains to be characterized. Notwithstanding this comment, the orbital imaging resemblance to Graves disease is remarkable. At the very least, impairment of the CTLA-4 T-cell receptor seems to play a role in generation of inflammatory orbital disease.

Other genes governing the immune response have been linked to Graves disease and Hashimoto thyroiditis (collectively referred to as autoimmune thyroid disease). These include HLA-DR3 allele (major histocompatibility loci), present in about 50% of patients with Graves disease, C/T polymorphism increasing expression CD40 surface protein enhancing T-cell activation, PTPN22 (Arg polymorphism) functioning to surpass T-cell activity, polymorphism of thyroglobulin gene, and certain polymorphisms of the thyroid hormone receptors. It is possible that environmental interplay with specific genetic polymorphisms may play a role in the pathogenesis of Graves orbitopathy or perhaps forms of inflammatory orbital pseudotumor.

Understanding the significance of genetic determinants and gene products involved in disease pathogenesis will not only provide understanding but also, no doubt, an important approach to therapeutic medicinal development and application.

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