

Orbital MALT Lymphoma Arising out of Graves Ophthalmopathy: Update and Review of Recent Literature

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Orbital MALT lymphoma arising in a patient with pre-existing Graves' ophthalmopathy was first described by Stark et al. in 2005 [1]. Prior reports [2,3], had demonstrated orbital lymphoma in two patients with hyperthyroidism, but neither had MALT lymphoma; furthermore, in at least one of the cases the hyperthyroidism was from a thyroid adenoma, not classic Graves' disease. In the Stark case, the patient had long-standing Graves' disease and ophthalmopathy that failed to regress after the patient was rendered euthyroid pharmacologically and then ablated with radioiodine. Her lymphoma developed four years after her definitive thyroid treatment and progressed to unilateral lacrimal swelling over a two-year period. She was found to have MALT lymphoma confined to the lacrimal gland, treated with radiation only and was cured of her lymphoma.

Subsequent authors have expanded on this experience. This short review will comment on those observations and offer further guidance. Griepentrog et al. [4] reported on three patients with long-standing thyroid eye disease in whom tumors developed. The first had proptosis from a cavernous sinus meningioma; the second had metastatic breast cancer as the basis for proptosis. The third had long-standing thyroid eye disease and metastatic breast cancer, and required decompression of the orbit to preserve vision. At surgery she had B cell lymphoma, but no breast cancer metastasis the subtype of lymphoma was not mentioned. So of his three patients only one resembled, albeit with incomplete data, the initial report but cannot be called MALT lymphoma without further review.

Decaudin et al. [5] review all the underlying causes for orbital adnexal lymphoma. Certain chlamydia species are associated with this and reports of its regression with antimicrobial therapy have been reported. They discuss the association of autoimmunity with non-Hodgkin lymphoma but not specifically orbital lymphoma. They do not discuss the association of thyroid ophthalmopathy specifically and NHL. The two cases they present are not sufficiently detailed for us to draw any conclusions about a relation to thyroid disease.

Monteiro et al. [6] present an interesting case in which MALT ocular lymphoma preceded the development of clinical Graves' disease. Only a detailed thyroid workup showed any abnormality. There was no pre-existing ophthalmopathy. They also reviewed several cases published since the initial observation by Stark

et al. [1] in 2005, including two cases of orbital lymphoma without thyroid disease, a case of orbital MALT 17 years after Graves' diagnosis, a case of B-cell NHL (subtype not commented upon) with an autonomous thyroid nodule (co-incidence?) and another case of ocular large cell B cell lymphoma with hypothyroidism etiology not mentioned. Most of the patients had an excellent outcome of their cases only their case and the one they cite one with orbital lymphoma 17 years after the diagnosis of Graves' expands our concept of the natural history of the relationship between Graves' and MALT orbital lymphoma.

Hajdukoviü et al. [7] reported after the review by Neto a single case report very similar to that of Stark et al. [1]. The interval between diagnosis of Graves' and MALT was three years. The outcome was similarly excellent, although that patient also received chemotherapy.

Moslehi et al. [8] offer a comprehensive review of causes of ocular adnexal lymphoma, of which Graves' is only one cause. Chlamydia is mentioned here again, but also *H. pylori* (also a cause of gastric lymphoma), herpes virus 8, EB Virus, HIV and Hepatitis C. They offer theories, largely related to chronic antigen stimulation as to why these agents could cause ocular lymphoma, but do not offer an estimate as to the relative importance of each. They offered no new cases from their own experience.

In summary there are now several cases of orbital lymphoma arising out of Graves' ophthalmopathy, three new ones in addition to Stark's well enough documented regarding the diagnosis of underlying Graves' and MALT lymphoma. **Table 1** shows summary of their clinical features.

Table 1 Summary of clinical features.

Graves' and MALT lymphoma cases			
Citation	Interval between treatment outcomes		
	Graves and OL		
Stark	4 years	RT	Cured
Neto (his)	Preceded	RT/Chemo	Cured
Neto (other)	17 years	Chemo	Cured
Hajdukovic	3 years	RT/Chemo	Cured

What can the careful clinician glean from the above discussion? The association of Graves' disease and orbital lymphoma, usually in the setting of pre-existing Graves' ophthalmopathy but not always, is now well established. In only one case did orbital lymphoma precede the obvious diagnosis of Graves'.

References

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The presence of unilateral proptosis or other evidence of adnexal enlargement or infiltration may be from lymphoma but a variety of other causes should be considered. Various infectious agents can also cause orbital lymphoma. It behooves the prudent ophthalmologist to have an index of suspicion if someone with stable or regressing Graves' ophthalmopathy develops a new adnexal fullness or swelling, or evidence of new peri-orbital infiltration. With prompt biopsy and diagnosis the prognosis for Graves' associated MALT lymphoma is excellent. Orbital lymphoma arising out of causes other than Graves' is insufficiently documented in these papers for us to comment upon. Based on current theories of the relation of autoimmunity and the development of lymphoma, it would seem that the development of orbital lymphoma with pre-existing non-Graves' hyperthyroidism is coincidental (**Table 1**).