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REVIEW

Thyroid orbitopathy possibly predisposes to late-onset of periocular lymphoma

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Abstract

Aim **The prevalence of thyroid orbitopathy, compared with an estimate for the United Kingdom population, is examined in a large cohort of patients treated for periocular lymphoma.**

Patients and methods **Clinical details were reviewed for patients presenting to the Orbital Clinic at Moorfields Eye Hospital with biopsy-proven periocular lymphoma. Recorded evidence of prior thyroid gland abnormality or thyroid eye disease was sought and treatment details recorded, together with that of the subsequent periocular lymphoma. The calculated prevalence of thyroid orbitopathy in our patients with periocular lymphoma was compared with an estimate based upon published figures for a United Kingdom population.**

Results **Of 369 patients with periocular lymphoma, 20 (5%) had a history of thyroid disease and adequate notes were available in 10 cases: All had autoimmune thyrotoxicosis between 11 and 27 years (median 17.5) before diagnosis of periocular lymphoma and 6/10 had thyroid orbitopathy—none receiving orbital radiotherapy for treatment of their thyroid eye disease. Using a calculated estimate for the UK prevalence of thyroid orbitopathy, the probability of even these six cases of ophthalmopathy among 369 patients with periocular lymphoma is very low ($P = 0.007$).**

Conclusion **Compared with a population estimate, patients with periocular lymphoma had a significantly greater prevalence of preceding thyroid orbitopathy, with a median latency of 17 years. Thyroid orbitopathy possibly predisposes to later local lymphoma in a manner similar to the late emergence of lymphoma with other chronic inflammatory diseases—such as Sjögren's syndrome, Hashimoto's thyroiditis, coeliac disease, or *Helicobacter* gastritis.**

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Introduction

Chronic inflammation of extra-ocular muscles and periocular fat in thyroid orbitopathy (ophthalmopathy) is due to cell-mediated and humoral immunity, with frequent serum antibodies against thyroglobulin, thyroid microsomes, and thyroid stimulating hormone (TSH) receptors. The strong association of autoimmune thyroid orbitopathy and autoimmune thyrotoxicosis suggests a shared antigen for both conditions—the favoured one being TSH receptors on the preadipocyte sub-population of periocular fibroblasts.[1,2]

Several autoimmune diseases predispose to lymphoma, with a typical latency of 10–20 years—such as Hashimoto's thyroiditis,[3–5] Sjögren's syndrome,[6,7] and coeliac disease.[8,9] Inflammatory glandular destruction and MALT acquisition in Sjögren's syndrome renders such patients about 44 times more likely to develop late-onset marginal zone lymphoma (MZL) in affected tissues.[7] Lymphocyte accrual during the chronic inflammation of Hashimoto's thyroiditis predisposes to later lymphoma (most commonly follicle centre cell variant[4]) and intestinal lymphomas arising with coeliac disease (typically 7 years after onset[8]) are predominantly of high-grade T-cell histology.[9] The chronic inflammation of gastric MALT due to *Helicobacter pylori* infection, although not autoimmune, also predisposes to the emergence

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of gastric marginal zone lymphoma,[10,11] and eradication of the infection can lead to disease regression.[12]

We report a series of patients with autoimmune thyrotoxicosis and thyroid orbitopathy, who later developed periocular lymphoma.

Patients and methods

Database records for patients with biopsy-proven lymphoma of the orbit or lids (hereafter termed 'periocular' lymphoma), treated at the Orbital Clinic at Moorfields Eye Hospital, were reviewed for a history of thyroid gland disease or thyroid orbitopathy. For those patients with a database history of thyrotoxicosis or thyroid orbitopathy, the clinical case notes were reviewed with special regard to the nature and chronology of the various conditions. Ethical review was not required for a retrospective investigation.

Results

A total of 369 patients were recorded, between 1979 and 1999, as presenting with periocular lymphoma, and 20 (5.4%) had evidence of a thyroid abnormality. Adequate clinical case notes were available for only 10 patients with autoimmune thyroid disease.

Six of the 10 patients had thyroid orbitopathy (Figure 1), four bilateral, with a median age of 36.5 years at diagnosis (range 23–64 years): 3/6 had medical treatment for thyrotoxicosis and 2/6 had systemic steroids and orbital decompression for ophthalmopathy; none underwent orbital radiotherapy or radio-iodine therapy. The median latency between diagnosis of thyroid orbitopathy and development of periocular lymphoma in the six patients was 17.5 years (range 15–27 years). In 4/10 patients *without* prior ophthalmopathy, the diagnosis of lymphoma and thyrotoxicosis was simultaneous in two patients, but with a latency of 17 and 51 years in the two others (the lymphoma being of later onset in each case).

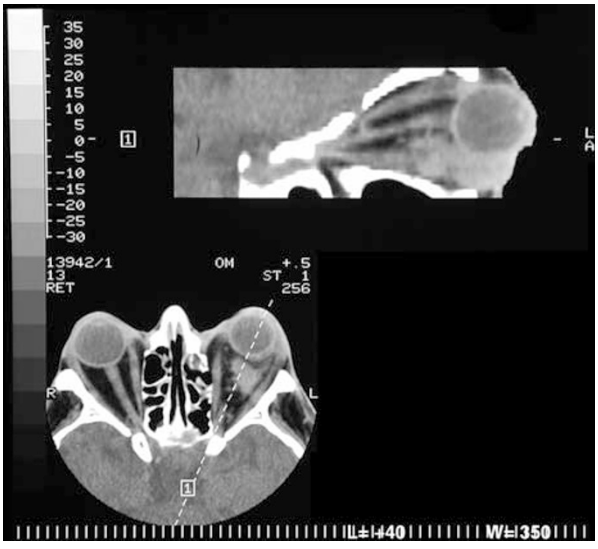

Figure 1 MR images demonstrating biopsy-proven lymphomatous infiltration of the left eyelid and anterior orbit, in the presence of bilateral diffuse extraocular muscle enlargement due to longstanding thyroid ophthalmopathy.

All lymphomas were solely periocular (unilateral Stage IE) at presentation, being marginal zone variant in 9/10 and diffuse large B-cell lymphoma in one patient; the tumour affected mainly the retrobulbar tissues in three cases, the lacrimal gland (two cases) or the conjunctiva (five patients). The periocular disease was treated with external beam radiotherapy (30–32 Gy, in 2 Gy fractions) and the patient with diffuse large B-cell lymphoma received 3 cycles of CHOP adjunctive chemotherapy. All patients were alive at more than 5 years after the diagnosis of lymphoma, with a 5-year disease-free survival of 89% (Table 1).

Discussion

Owing to problems in case-note retrieval after more than two decades (only 10/20 notes being adequate for analysis), it is probable that this investigation's estimate for the prevalence of thyroid orbitopathy or autoimmune thyrotoxicosis after periocular lymphoma is too low. On this basis, among our patients with lymphoma the prevalence estimates for thyroid ophthalmopathy would appear to be at least 6/369 (1.6%), and at least 10/369 (2.7%) for autoimmune thyroid gland disease.

Although the annual incidence of thyroid ophthalmopathy in Olmsted County, Minnesota, was estimated as 16/100 000 for women and 2.9/100 000 for men,[13] such data cannot readily be used for prevalence calculations. A reported UK prevalence of thyrotoxicosis is 2.2%,[14] of which nearly two-thirds is autoimmune—that is, 1.4% prevalence. There have been various and changing reported incidences for overt ophthalmopathy in patients with autoimmune thyroid disease,[15] but a recent UK estimate is about 30%[16]—giving a UK population estimated prevalence of about 0.4% (30% of 1.4%); at this prevalence, there should have been no more than two cases of orbitopathy among our 369 lymphoma patients. The observed prevalence of at least 6/369 (1.63%) patients with thyroid ophthalmopathy in our series is, therefore, highly unlikely to have occurred by chance ($P = 0.007$).

Primary periocular lymphomas are uncommon, about 85% are low-grade (such as marginal zone, diffuse lymphoplasmacytoid, or follicle cell lymphoma[17]), and

Table 1 Patients with periocular lymphoma who had prior autoimmune thyroid gland disease

Patient sex	*Details of prior thyroid orbitopathy*			*Age at onset of thyroid gland disease*	*Age at lymphoma*	*Latency (years)*	*Lymphoma histology*	*Site of lymphoma*	*Treatment of lymphoma*	*Thyroid status at diagnosis of ophthalmopathy*
	Affected sides	*Age at diagnosis*	*Treatment*							
Lymphoma patients with autoimmune thyroid anomalies and prior orbitopathy										
Male	Unilateral	31	Steroids and decompression	Uncertain	50	19	MZL	Retrobulbar	RT	Euthyroid[a]
Female	Bilateral	23	—	23	39	16	MZL	Lid/Anterior	RT	Hyperthyroid
Female	Bilateral	29	—	19	49	20	MZL	Retrobulbar	RT	Hyperthyroid
Female	Unilateral	42	—	Uncertain	53	11	MZL	Retrobulbar	RT	Euthyroid[a]
Female	Bilateral	50	Steroids and decompression	Uncertain	77	27	DLCL	Lid/Anterior	CT and RT	Euthyroid[a]
Female	Bilateral	64	—	64	79	15	MZL	Lid/ Conjunctiva	RT	Hyperthyroid
Lymphoma patients with autoimmune thyrotoxicosis, but without orbitopathy										
Female	(None)	NA	NA	40	57	17	MZL	Lacrimal gland	RT	Hyperthyroid
Male	(None)	NA	NA	21	72	51	MZL	Lid/Anterior	RT	Hyperthyroid
Female	(None)	NA	NA	59	59	0	MZL	Lacrimal gland	RT	Hyperthyroid
Female	(None)	NA	NA	68	68	0	MZL	Lid/Anterior	RT	Hyperthyroid

[a]All Euthyroid patients had typical signs of orbitopathy and abnormal levels of thyroid-related autoantibodies.MZL denotes marginal zone lymphoma, DLCL denotes diffuse large cell lymphoma, RT denotes orbital radiotherapy, CT denotes chemotherapy,and NA denotes nonsignificance.

most involve the deep orbit (44%) or lacrimal gland (26%).[18] Nine of the 10 cases in this investigation were MZL, the variant commonly arising in Sjogren's syndrome, Hashimoto's thyroiditis, or *H. pylori* infection; the 90% proportion of MZL after autoimmune thyroid disease is, however, much greater than the 37% found in a large, unselected cohort.[16] It is also of interest that 8/10 lymphomas arose anteriorly, this predilection for conjunctival and lacrimal gland (as with all periocular MZL[18]) possibly reflecting the normal presence of MALT in these two tissues.

As lymphoma may emerge from a background of chronic lymphocytic stimulation—often autoimmune—the unexpectedly high prevalence (at least 1.6%) of preceding thyroid orbitopathy in patients with periocular lymphoma (median latency 17.5 years; range 11–27) suggests a causal relationship between the two conditions. The statistical association is supported by examples of other lymphomas arising in other chronic inflammatory conditions—such as Sjogren's syndrome, Hashimoto's thyroiditis, coeliac disease, and gastric lymphoma.

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