Squamous cell carcinoma of the eyelid masquerading as 'malignant' ophthalmopathy of Graves's disease

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SUMMARY A patient with Graves's disease is described in whom the periorbital changes of severe ophthalmopathy and iatrogenic Cushing's syndrome delayed the diagnosis of a squamous cell carcinoma of the eyelid. It is suggested that the immunosuppressive therapy which the patient received may have enhanced the growth of a pre-existing malignancy.

Progressive inflammation of the orbital tissue occurs in less than 3% of patients with Graves's disease.^{1,2} In severe cases glucocorticoid treatment is indicated,³ and immunosuppression with azathioprine⁴⁻⁷ and cyclophosphamide^{8,9} has also been used by some groups, with or without plasmapheresis.

In immunosuppressed patients the incidence of malignant neoplasms is markedly increased.¹⁰ A large proportion of these tumours are skin cancers, which may develop within 4 months of the initiation of

immunosuppressive therapy.¹¹⁻¹⁵ Basal cell carcinomas are the predominant type of skin cancer in the general population; however, in the immunosuppressed patient the majority are squamous cell.

We describe a patient with Graves's ophthalmopathy of sufficient severity to warrant treatment with azathioprine and prednisone, in whom the presence of a squamous cell carcinoma of one lower eyelid was not promptly recognised as a factor contributing to the retraction and inflammation of the lid. The diagnostic difficulties that were encountered and the possibility that the high doses of immunosuppressive drugs that the patient received accelerated tumour growth prompted us to offer the following case report.

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Fig. 1 Summary of the patient's course and treatment.

Fig. 2 The patient, May 1980. Swelling of the periorbital tissue, exophthalmos and chronic inflammatory changes of the conjunctivae are evident. The contour of the left lower lid margin is lost and the surrounding skin has a glistening, irregular appearance.

Case report

The patient, a 59-year-old male construction foreman, was first discovered to be hyperthyroid in August 1978 after 2 months of symptoms which did not include eye complaints. He was initially treated with carbimazole and propranolol, and first received ^{131}I (10 mCi) in November 1978. Because of biochemical evidence of recurrent hyperthyroidism, further treatment with radioiodine was given in April 1980 (10 mCi), October 1980 (15 mCi), and July 1981 (20 mCi). During this time thyroid function was maintained largely within normal biochemical limits with appropriate doses of carbimazole. With occasional minor exceptions the levels of thyroid stimulating hormone remained within normal limits.

He was admitted to the hospital in February 1979 with a history of progressive exophthalmos associated with a painful, gritty sensation of the eyes and photophobia (Fig. 1). There was moderate proptosis, oedema of the periorbital tissues, especially the lower lids, chemosis, and slight limitation of upward gaze bilaterally. The conjunctivae were inflamed and were very boggy and swollen near the inner canthus. No specific abnormalities of the left lower eyelid were noted. There was no change in visual acuity and no papilloedema. Prednisone (60 mg/day) was admin-

istered and was followed by a decrease in proptosis bilaterally (23–22 mm right eye and 24–21 mm left eye, measured with a Hertel ophthalmometer). Over the next several months the dose of prednisone was decreased to 30 mg/day, with little change in the eyes. In May 1980 prednisone was decreased to 20 mg daily, but this was associated with an increase in proptosis, conjunctival injection, and eye pain (Fig. 2).

In June 1980 azathioprine therapy was begun at a daily dose of 150 mg/day (1.7 mg/kg) and was increased to 200 mg/day in September 1980; prednisone (20 mg/day) was continued. Because it was considered that the eye changes were entering a more chronic stage, the prednisone treatment was gradually discontinued over the ensuing months. There was little change in the eye signs except for a diminution in periorbital fullness associated with disappearance of the Cushingoid facies. The scleral conjunctivae were thickened and were markedly inflamed and oedematous at the inner canthus bilaterally. As the Cushingoid facies regressed, asymmetry of lid retraction and irregularity of the contour of the left lid margin became more apparent.

In September 1981 azathioprine therapy was discontinued, and the left lower lid was biopsied and subsequently excised and replaced. Pathological examination showed a moderately differentiated

Fig. 3 Photomicrograph of a representative area of the eyelid biopsy. The surface epithelium (above) is replaced by disorganised bands of pleomorphic hyperchromatic squamous carcinoma cells showing intercellular 'prickles' (small arrow). Islands of carcinoma (large arrows) are seen in the adjacent connective tissue. (Haematoxylin and eosin, $\times 300$).

nonkeratinising squamous cell carcinoma of the lower lid with invasion of the adjacent connective tissue (Fig. 3).

The patient is currently receiving a replacement dose of thyroxine. There is moderate exophthalmos, but visual acuity is unchanged, and range of motion of the eyes is full (Fig. 4). There is no evidence of tumour recurrence.

Discussion

Squamous cell carcinoma of the eyelid is an unusual tumour occurring with about one-fortieth the frequency of basal cell carcinoma.^{16 17} The presence

of the tumour in our patient was not promptly recognised—in part because it was infiltrative rather than papillomatous.¹⁶ Moreover, the periorbital changes were at first attributed to acute and chronic Graves's ophthalmopathy and to Cushing's syndrome. Another case of squamous cell carcinoma of the left lower lid in an immunosuppressed patient has recently been reported.¹⁸

In retrospect there is little doubt that the carcinoma of the eyelid was present in our patient before azathioprine therapy was begun (Fig. 2). There is no convincing evidence, to our knowledge, that prolonged treatment with pharmacological doses of glucocorticoid alone increases the risk of the development of epithelial tumours in man. Whether immunosuppression with azathioprine and prednisone combined increased the chance of unhindered development of the malignant cells already present, as has been suggested,^{11 14} remains a worrying possibility.

The role of immunosuppressive treatment in severe Graves's ophthalmopathy is undergoing evaluation at present.¹ Although it cannot be decided with certainty whether our patient's skin cancer was enhanced by the therapy he received, we believe it is important to remind clinicians of the association of immunosuppressive therapy and an increased incidence of malignant neoplasms.

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Fig. 4 The patient, February 1983, 17 months after excision of the tumour and reconstruction of the left lower lid.

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