LETTERS TO THE EDITOR

Paraneoplastic non-caseating granulomatous inflammation of the eyelid

EDITOR,—Periocular granulomatous inflammation is most commonly due to a chalazion or sarcoidosis, and more rarely to allergic granulomatosis (Churg-Strauss), Erdheim-Chester disease, Wegener's granulomatosis, and necrobiotic xanthogranuloma. When no cause for this inflammation can be found, it may be called idiopathic non-infectious granulomatous inflammation¹ or orbital sarcoid.² We report a case in which this idiopathic inflammation appeared to be associated with squamous cell carcinoma of the lung.

CASE REPORT

A 77-year-old man presented with a 2½ year history of non-tender inflammation of the left upper eyelid (Fig 1). There was no history of injury to the eyelid. A chest x ray showed an abnormality that was thought to be due to overprojection. Systemic steroids reduced the inflammation temporarily. After referral to our hospital, extensive clinical and laboratory investigations were performed. Computed tomography scanning showed the lacrimal gland to be of normal size. Tests for tuberculosis, other infectious diseases, and systemic inflammatory disease were negative. An incisional biopsy of the eyelid revealed a non-caseating, granulomatous inflammation without foreign body material or acid fast bacilli. In a few granulomas some B cells could be demonstrated immunohistochemically (Fig 2). A new chest x ray revealed a coin lesion of the right upper lobe and a lobectomy was performed. Histopathological examination of the specimen showed a poorly differentiated squamous cell carcinoma of the lung without signs of lymph node metastasis or sarcoidosis. Systemic corticosteroids and non-steroidal anti-inflammatory drugs had no significant effect on the inflammation in the

Figure 1 Frontal view of the patient. Note left upper lid swelling.

Figure 2 Immunohistochemical stain (L26) showing admixture of B cells in granulomas (×200).

eyelid. Some more tissue was removed for cosmetic reasons, and the histopathology was similar to the first specimen.

COMMENT

The association of granulomatous inflammation (especially in lymph nodes) and malignancy has been noted before.²⁻⁶ The pathogenesis of this malignancy associated inflammation may be diverse (sarcoid-like reaction to tumour derived components, sarcoidosis, infection, granulomatous lesions of unknown significance or GLUS.³ Sarcoid-like reactions to pulmonary neoplasms were described to occur in regional lymph nodes in the form of non-caseating granulomas.⁴ Granulomas in lymph nodes may be divided into two categories on the basis of the presence or absence of B cells in these lesions (B cell positive: toxoplasmosis, tumour related sarcoid reactions, and GLUS; B cell negative: sarcoidosis, mycobacterial infections).⁵ In our case, a few granulomas showed some admixture with B cells.

To our knowledge, the association of a non-caseating granulomatous inflammation of the eyelid and a squamous cell carcinoma of the lung has not been described before. This case suggests that screening for malignancy might be useful in patients with non-caseating granulomatous inflammation of unknown origin.

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- 1 Rootman J. *Diseases of the orbit*. Philadelphia: J B Lippincott, 1988: 178.
- 2 Henderson JW. *Orbital tumours*. 3rd ed. New York: Raven Press 1994: 317-20.
- 3 Brincker H. Interpretation of granulomatous lesions in malignancy. *Rev Oncol* 1992; 5: 85-9.
- 4 Laurberg P. Sarcoid reactions in pulmonary neoplasms. *Scand J Resp Dis* 1975; 56: 20-7.
- 5 Brincker H, Pedersen NT. Immunohistologic separation of B-cell-positive granulomas from B-cell-negative granulomas in paraffin-embedded tissues with special reference to tumor-related sarcoid reactions. *APMIS* 1991; 99: 282-90.
- 6 Römer FK. Sarcoidosis and cancer. *Lung biology in health and disease*. 1994; 73: 401-15.

Paraneoplastic retinopathy in association with large cell neuroendocrine bronchial carcinoma

EDITOR,—Cancer associated retinopathy is a rare paraneoplastic manifestation of a variety of tumours, most commonly small cell carcinoma of the lung (SCCL).¹⁻⁴ Characteristically the syndrome presents with reduced vision, photopsia, progressive ring scotomas in the visual field, and nightblindness. Ocular symptoms may precede the diagnosis of malignancy for several months, especially as the ocular signs (attenuation of retinal arteries, mild optic disc atrophy) are easily missed. Pathologically, there is a severe photoreceptor degeneration,³ and it is thought that the disease is mediated by antibodies that cross react between the tumour and photoreceptor antigens.^{1 4} We present a 60-year-old ex-smoker with the typical features of the syndrome whose investigations revealed a large cell neuroendocrine carcinoma.

CASE REPORT

A 60-year-old woman presented with a 1 year history of dimming of vision associated with severe nightblindness. A left cataract had been removed 1 year earlier. There was no relevant family or dietary history and she had taken no potentially retinotoxic drugs. More recently she noticed increasing malaise and weight loss. General examination was normal except for an enlarged right supraclavicular node. Ocular examination showed a vision of 6/24 right, 6/6 left with normal colour vision. Pupils reacted poorly and visual fields (Fig 1) showed gross constriction, the right eye being worse than the left. Fundus examination showed minimal arteriolar constriction and

Fig 1A

Fig 1B

Figure 1 Goldmann visual fields showing marked constriction in the right eye (A) and a dense ring scotoma in the left eye (B).

Figure 2A Large cell carcinoma with large nuclei. Note positive granular staining in the extensive cytoplasm of tumour cells for chromogranin A. Avidin-biotin method of immunostaining ($\times 200$).

fluorescein angiography patchy leakage at the level of the retinal pigment epithelium.

The electroretinogram (ERG) was abolished and the electro-oculogram (EOG) light rise was flat, with subnormal pattern and flash visual evoked responses. A chest x ray showed a right paratracheal mass, which was confirmed on thoracic computed tomography scanning. A biopsy of the mass was taken at mediastinoscopy which showed a large cell anaplastic carcinoma with large nuclei containing prominent nucleoli and large amounts of cytoplasm. Immunostaining for neuron specific enolase, chromogranin (Fig 2A), and synaptophysin was positive in the cytoplasm of tumour cells and transmission electron microscopy showed dense core granules (Fig 2B) indicating that the tumour was a large cell neuroendocrine bronchial carcinoma. Indirect immunofluorescence using the patient's sera (1:40 dilution) against cryostat sections of human retina revealed positive staining of ganglion cell nuclei, some cells of the inner nuclear layer, and around photoreceptor nuclei. The patient's serum (1:100) was immunoblotted against saline and detergent soluble extracts of human retina and showed a number of bands, all of which appeared in control sera from healthy subjects. The patient developed cerebral metastases soon after presentation and died. A postmortem examination was not performed.

COMMENT

This is the first reported case of paraneoplastic retinopathy found in association with large

Figure 2B Tumour cell containing large dense core granules within the cytoplasm. Uranyl acetate and lead citrate staining ($\times 18\,000$).

cell neuroendocrine carcinoma. Previous reports have demonstrated SCCL to be the commonest tumour association,¹⁻⁴ others being related to carcinoma of the breast,⁵ cervix,⁶ and uterus.⁷ There is one previous report of a large cell anaplastic lung tumour¹ but neuroendocrine features⁸ were not detected. The characteristic clinical picture of progressive nightblindness, ring scotomas, and eventual visual loss point to a process of photoreceptor degeneration which has been confirmed pathologically.^{3,7} The underlying pathogenesis for the association is thought to be due to the production of antibodies that cross react between tumour and retinal tissue. Grunwald *et al*⁴ have shown that such antibodies are only found in the sera of patients with both the relevant tumour and visual loss. The antibody is not found in those with visual loss and no tumour, nor in those with tumours but no visual loss. The retinal protein with which the sera of these patients react remains controversial. The immunofluorescent staining pattern in our patient is similar to that found by Kornuth² and Grunwald⁹ with antibody largely directed against the ganglion cell and inner nuclear layers, whereas Keltner found antibody predominantly staining photoreceptor inner segments.¹⁰ The 23 kDa protein, recently acknowledged to be the photoreceptor protein recoverin¹¹ and which has been postulated to be specific for the syndrome associated with SCCL¹ was not revealed by immunoblotting in our patient. This finding agrees with a recent study which found only one in 10 patients with cancer associated retinopathy demonstrating antibodies to this protein.¹² The most important clinical feature of this syndrome is to consider and then recognise the diagnosis and to realise that symptoms may precede detection of the underlying tumour for many months or years. Electrodiagnostic studies are important and immunological studies in future patients may clarify the relation between the retina and the tumour.

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- 1 Thirkill CE, Roth AM, Keltner JL. Cancer-associated retinopathy. *Arch Ophthalmol* 1987; 105: 372-5.
- 2 Kornuth SE, Klein R, Appen R, Choate J. Occurrence of anti-retinal ganglion cell antibodies in patients with small cell carcinoma of the lung. *Cancer* 1982; 50: 1289-93.
- 3 Buchanan TA, Gardiner TA, Archer DB. An ultrastructural study of retinal photoreceptor degeneration associated with bronchial carcinoma. *Am J Ophthalmol* 1984; 97: 277-87.
- 4 Grunwald GB, Klein R, Simmonds MA, Kornuth SE. Autoimmune basis for visual paraneoplastic syndrome in patients with small cell lung carcinoma. *Lancet* 1985; i: 658-61.
- 5 Klingele TG, Burde RM, Rappazzo JA, Isserman MJ, Burgess D, Kantar O.

Paraneoplastic retinopathy. *J Clin Neuro-ophthalmol* 1984; 4: 236-45.

- 6 Keltner JL, Roth AM, Chang RS. Photoreceptor degeneration - possible autoimmune disorder. *Arch Ophthalmol* 1983; 101: 564-9.
- 7 Sawyer RA, Selhorst JB, Zimmerman LE, Hoyt WF. Blindness caused by photoreceptor degeneration as a remote effect of cancer. *Am J Ophthalmol* 1976; 81: 606-13.
- 8 Travis WD, Linnoila RI, Toskos MG, Hitchcock CL, Cutler GB, Nieman LG, *et al*. Neuroendocrine tumours of the lung with proposed criteria for large cell neuroendocrine carcinoma. *Am J Surg Pathol* 1991; 15: 529-53.
- 9 Grunwald GB, Kornuth SE, Tow Fighi J, Sassari J, Simmonds MA, Housman CM, *et al*. Autoimmune basis for visual paraneoplastic syndrome in patients with small cell lung carcinoma. *Cancer* 1987; 60: 780-6.
- 10 Keltner JL, Thirkill CE, Tyler NK, Roth AM. Management and monitoring cancer-associated retinopathy. *Arch Ophthalmol* 1992; 110: 48-53.
- 11 Thirkill CE, Tait RC, Tyler NK, Roth AM, Keltner JL. The cancer-associated retinopathy is a recoverin-like protein. *Invest Ophthalmol Vis Sci* 1992; 33: 2766-72.
- 12 Hargrave PA, Schmied JL, Guy J, Adams G. Autoantibodies against retinal proteins in cancer-associated retinopathy. *Invest Ophthalmol Vis Sci* (ARVO abstracts) 1992; 33: 774.

Cryptococcus presenting as cloudy choroiditis in an AIDS patient

EDITOR.—*Cryptococcus neoformans* is a well known organism which causes opportunistic infection in patients with AIDS. Patients commonly present with meningitis and are referred to the ophthalmologist with extraocular muscle paresis and papilloedema.^{1,2} However, although rare, cryptococcal choroiditis has also been described: the clinical features are cells in the vitreous with focal choroidal lesions; the presence of the fungus in the choroid implies haematogenous spread and, consequently, is associated with a terrible prognosis.³ This paper describes a patient whose cryptococcal infection initially manifested with eye symptoms due to a hitherto unrecognised pattern of choroidal disease.

CASE REPORT

A 39-year-old white homosexual man with AIDS presented in May 1992 with a 1 week history of blurred vision in both eyes. He complained, in particular, that everything appeared wavy. He had been HIV positive since 1988 and had developed Kaposi's sarcoma in April 1992 when his CD4 count was $0.02 \times 10^6/\text{ml}$. Ophthalmic examination revealed visual acuities of 6/5 in each eye, full colour vision, and mild constriction to the I2e and I4e targets in both eyes on Goldmann perimetry. The pupillary reactions were normal. The eyes were white and slit-lamp examination was unremarkable with no

Fig 1A