membrane,^{9 10} and lymphocyte infiltration around blood vessels.¹¹ The mechanisms in respiratory disease are also ill understood.¹² There is a dilemma about the therapeutic advantage in antibiotic treatment of non-respiratory manifestations, as these may not involve organisms.

In this case a differential diagnosis included viral causes of cranial nerve palsies,^{13 14} but the serological results and a well recognised¹⁵ clinical sequence of an emerging central nervous system lesion after a respiratory infection confirmed *M pneumoniae* infection. Often the serological response will be late, making a laboratory diagnosis difficult and of limited clinical value. A new exquisitely sensitive PCR detection method specific for *M pneumoniae* DNA² applied to this child's sera failed to detect any evidence of *Mycoplasma* DNA.

Partial third nerve palsies, particularly those which are pupil sparing, are well documented in microvascular disease especially diabetes mellitus. The lesion site in this case is likely to be the superior division of the third nerve as complete recovery eventually occurred. The inferior oblique is known to be unable to elevate the globe above the primary position in the presence of a paretic superior rectus. Other observers¹⁶ looked at seven patients with an acquired monocular elevation paresis. Their patients showed impairment of Bell's phenomenon but no ptosis and no significant recovery and they postulated that a microvascular lesion in the pretectal area close to the oculomotor nucleus was responsible.

If *M pneumoniae* organisms were associated directly with any microvascular occlusion in our case, it is very likely that the PCR system would have detected *M pneumoniae* DNA in the serum, with detection levels of one copy of DNA per sample which is at least a thousand times more sensitive than any culture or antigen detection system for *M pneumoniae*.² These findings suggest that the pathology resulted from host immune activity without organisms being directly involved. The antibiotic given to this patient may shorten the time that organisms are present in the host but would not destroy

specific DNA recognised by PCR until later degradation by host enzyme activity. A lumbar puncture was not justified in this case, but studies (Fink CG, Read SR, Butler L, Pike M. *Mycoplasma pneumoniae* and CNS lesions. PCR evidence that the pathology is immune mediated, in preparation) have shown no evidence of organisms in the cerebrospinal fluid in central nervous system lesions associated with *Mycoplasma* infection.

These findings support the observation that *Mycoplasma* associated central nervous system lesions are an exaggerated immune response.

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- 1 Wreghitt T, Sillis M. A microcapture ELISA for detecting *Mycoplasma pneumoniae* IgM: comparison with indirect immunofluorescence and direct ELISA. *J Hyg (Lond)* 1985; **94**: 217-27.
- 2 Fink CG, Read SR, Sillis M. Detection of *Mycoplasma pneumoniae* by direct sample polymerase chain reaction (PCR) - a simple system for clinical application. *J Clin Path* 1993; submitted.
- 3 Clyde WA Jr. *Mycoplasma pneumoniae* infections of man. In: *The mycoplasmas II*. New York: Academic Press, 1979: Chapter 9, 275-306.
- 4 Miller AC, Hanson GC. Respiratory failure due to *Mycoplasma pneumoniae* in young adults. *BMJ* 1938; **287**: 1028.
- 5 Koletsky RJ, Wanskin AJ. Fulminant *Mycoplasma pneumoniae* infection. Report of a fatal case and a review of the literature. *Am Rev Resp Dis* 1980; **122**: 491-6.
- 6 Murray HW, Masur M, Senterfit LB, Roberts RB. The protean manifestations of *Mycoplasma pneumoniae* infections in adults. *Am J Med* 1975; **58**: 229-42.
- 7 Lyell A, Gordon AM, Dick HM, Sommerville RG. Mycoplasmas and erythema multiforme. *Lancet* 1967; **ii**: 1116-8.
- 8 Biberfeld G. Antibodies to brain and other tissues in cases of *Mycoplasma pneumoniae* infection. *Clin Exp Immunol* 1971; **8**: 319-33.
- 9 Smith C, McGinniss M, Schmidt P. Changes in erythrocyte I-agglutinin and anti-I agglutinins during *Mycoplasma pneumoniae* infection in man. *J Immunol* 1967; **99**: 333-9.
- 10 Feizi T, Taylor Robinson D. Cold agglutinins, anti-I and *Mycoplasma pneumoniae*. *Immunology* 1967; **13**: 405-9.
- 11 Brunner H. Studies on the pathogenesis of experimental *Mycoplasma pneumoniae* infection in the guinea pig. *Inserm* 1974; **33**: 411-9.
- 12 Wreghitt T. *Mycoplasma pneumoniae*. In: Morgan-Capner P, ed. *Current topics in clinical virology*. London: Public Health Laboratory Service, 1992.
- 13 Nelhaus G. Isolated oculomotor nerve palsy in infectious mononucleosis. *Neurology* 1966; **16**: 221-3.
- 14 Hertenstein JR, Sarnat HB, O'Conner DM. Acute unilateral oculomotor palsy associated with ECHO 9 viral infection. *J Paediatr* 1976; **89**: 79-81.
- 15 Sillis M. Modern methods for diagnosis of *Mycoplasma pneumoniae*. *Rev Med Microbiol* 1993; **4**: 24-31.
- 16 Jampel RS, Fells P. Monocular elevation paresis caused by a central nervous system lesion. *Arch Ophthalmol* 1968; **80**: 45.

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Topical chemotherapy for conjunctival melanoma

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Surgical excision, cryotherapy, and radiotherapy have been used for treatment of conjunctival tumours.¹⁻³ When treating conjunctival melanoma surgical margins include areas of visible pigmentation and 2 mm pigment-free margins. Since pathological evaluations of excised specimens commonly display patches of

amelanotic melanoma extending beyond hyperpigmented areas, the visually pigmented margin offers a poor definition of the tumour's 'edge'.

Topical chemotherapy of conjunctival tumours offers a non-surgical treatment with less dependence on surgical margins, should treat tumour extension onto the corneal epithelium,

Figure 1A Before topical mitomycin C therapy we noted superficial and deep conjunctival melanosis with thickness at the inferior limbus.

Figure 1B Three weeks after onset of topical mitomycin C therapy the superficial melanosis had largely resolved leaving a deep nodular nest of melanotic tissue.

and could be easily repeated. This approach also allows for high concentrations of chemotherapy to be delivered directly to the tumour.^{4,5}

Ophthalmologists have experience using 5-fluorouracil (5-FU) and mitomycin C (MMC) to inhibit fibroblast proliferation after glaucoma and pterygium surgery.⁶⁻¹² While both inhibit DNA synthesis, 5-FU only interacts with S phase cells (those actively synthesising DNA). Dormant cells become able to proliferate when treatment has been discontinued.¹³ In contrast, MMC affects cells within all phases of the cell cycle inducing scission of tumour DNA even after treatment has been discontinued.¹⁴⁻¹⁶ Since melanomas are typically slow growing tumours (with a small subset of S phase cells), and our goal was to sterilise a cancer, we chose to investigate topical MMC chemotherapy.

Case report

A 51-year-old woman underwent primary surgical excision for a conjunctival melanoma on her left eye. Over the next 5 years she received three laser treatments to her temporal limbus to control tumour regrowth.

Upon referral to the Ocular Tumor Service of the New York Eye and Ear Infirmary, ophthalmic examination revealed a visual acuity of 20/25 in both eyes. All conjunctival surfaces were inspected by slit-lamp biomicroscopy. Three hypervascular pigmented lesions were noted to have thickness. Two were located at the corneo-scleral limbus at the 3 and 6 o'clock meridians. The third lesion was located on the supero-temporal tarsus. Areas of acquired melanosis covered most of the temporal bulbar conjunctiva and onto the edge of the temporal cornea. A metastatic survey was negative.

Informed consent involved a discussion of the risks and benefits of surgical excision with adjuvant cryotherapy versus topical application of mitomycin C (Bristol Labs, Evansville, Indiana, USA). She was aware that she would be the first patient (to our knowledge) to undergo this form of treatment.

Collagen plugs were placed in her inferior and superior punctae on a weekly basis. The MMC dose regimen was similar to that published for postoperative treatment of pterygium.^{7,8,12} One drop of MMC (0.04%) was placed in her superior fornix four times a day. During weekdays she also received an ophthalmic examination and one of her drops in the form of three 15 second applications of MMC-soaked surgical sponges onto the three nodular areas. Treatment was discontinued after 28 consecutive days.

Decreased pigmentation of the acquired melanosis and thinning of the nodular tumours were noted within 1 week of treatment. Areas of pigmentation decreased in size over the next 3 weeks (Fig 1). Residual clumps of pigmentation were noted beneath the conjunctival epithelium. A circular 2 mm corneal abrasion appeared on day 7 and was noted to resolve by day 14. Three weeks after the end of treatment our patient underwent surgical removal of the residual pigmented tissues with adjuvant cryotherapy.

Histopathology revealed no viable tumour in a limbal specimen taken from the 12 to the 9 o'clock meridians. In the tarsal lesion (which had never before been treated by any other means than MMC chemotherapy) the superficial half of this tumour was largely eradicated (Fig 2). Scattered neoplastic cells were present along the tracts of pseudoglands of Henle. These cells were confirmed to be melanomatous by HMB-45 (Dakopatts) immunoperoxidase staining. The deep portion of the tumour persisted and was noted to be associated with reactive lymphoid tissue at its base (Fig 2). The conjunctiva was largely intact, but was thinned and atrophic. There was sclerosis and inflammation (acute and chronic) in the tissues where the neoplasm was eliminated. Frankly necrotic tissue was not seen.

Comment

We present a case where topical MMC chemotherapy of conjunctival melanoma induced a partial response characterised by a significant reduction in tumour volume. Though the nodular tumours and subepithelial rests were found to be resistant to chemotherapy, it is important to note that we have investigated only one dosage and duration of treatment. Local

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Figure 2A An island of malignant melanoma persisted in the deep subepithelial tissue (arrow). Superficial tissues were noted to be inflamed and showed persistent neoplastic in the tracts of pseudoglands of Henle (haematoxylin and eosin, $\times 12$).

Figure 2B Higher magnification showed residual melanoma deep into the specimen, a transition to the overlying tissues where the tumour was largely eliminated, and the overlying atrophic and inflamed conjunctival epithelium (haematoxylin and eosin, $\times 85$).

cures in subsequent patients may require different dosages and/or durations of treatment, removal of tumour nodules before topical therapy, or a switch to another chemotherapeutic agent (for example, cis-platinum) which may be more effective against malignant melanoma.⁴ It was also significant to note that after we treated her residual tumour with excision and extensive cryotherapy no symblepharon formed. This may have been a manifestation of MMC-related long term inhibition of Tenon's capsule fibroblasts.^{16 17} Prevention of symblepharon after cryotherapy for conjunctival tumours may be an additional use for topical MMC therapy.¹⁸

- 1 Jakobić FA, Rini FJ, Fraunfelder FT, Brownstein S. Cryotherapy for conjunctival primary acquired melanosis and melanoma: experience with 62 cases. *Ophthalmology* 1988; **95**: 1058–70.
- 2 Lommatzsch PK. Beta-ray treatment of malignant epibulbar melanoma. *Graefes Arch Klin Exp Ophthalmol* 1978; **209**: 111–24.
- 3 Ridley F. Applicators for irradiation of the conjunctival sac. *Trans Ophthalmol Soc UK* 1958; **78**: 171–8.
- 4 Albert DM, Niffenegger AS, Willson JKV. Treatment of metastatic uveal melanoma: review and recommendations. *Surv Ophthalmol* 1992; **36**: 429–38.
- 5 Kawase K, Matsushita H, Yamamoto T, Kitazawa Y. Mitomycin concentration in rabbit and human ocular tissues after topical administration. *Ophthalmology* 1992; **99**: 203–7.
- 6 Palmer SS. Mitomycin as adjunct chemotherapy with trabeculectomy. *Ophthalmology* 1991; **98**: 317–21.
- 7 Hayasaka S, Noda S, Yamamoto Y, Setogawa T. Post-operative instillation of low-dose mitomycin-C in the treatment of primary pterygium. *Am J Ophthalmol* 1988; **106**: 715–8.
- 8 Singh G, Wilson RM, Foster CS. Mitomycin eye drops as treatment for pterygium. *Ophthalmology* 1988; **95**: 813–21.
- 9 Derick RJ, Pasquale L, Quigley HA, Jampel H. Potential toxicity of mitomycin-C. *Arch Ophthalmol* 1991; **109**: 1635.

- 10 Gupta S, Basti S. Corneoscleral, ciliary body, and vitreoretinal toxicity after excessive installation of mitomycin-C. *Am J Ophthalmol* 1992; **104**: 503–4.
- 11 Rubinfeld RS, Pfister RR, Stein RM, Foster CS, Martin NF, Stoleru S, *et al.* Serious complications of topical mitomycin-C after pterygium surgery. *Ophthalmology* 1992; **99**: 1647–54.
- 12 Murakami M, Mori S, Kunitomo N. Studies on pterygium. Report 5. Follow-up observations of the pterygium patients treated by mitomycin. *Jpn J Clin Ophthalmol* 1967; **21**: 580.
- 13 Jampel HD. Effect of brief exposure to mitomycin-C on viability and proliferation of cultured human Tenon's capsule fibroblasts. *Ophthalmology* 1992; **99**: 1471–6.
- 14 Crooke ST, Bradner WT. Mitomycin-C: a review. *Cancer Treat Rev* 1976; **3**: 121–39.
- 15 Lee DA, Shapourifar-Tehrani S, Kitada S. Effects of mithramycin, mitomycin, daunorubicin, and bleomycin on human subconjunctival fibroblast attachment and proliferation. *Invest Ophthalmol Vis Sci* 1990; **31**: 2136–44.
- 16 Yamamoto T, Varani J, Soong HK, Lichter PR. Effects of 5-fluorouracil and mitomycin-C on cultured rabbit subconjunctival fibroblasts. *Ophthalmology* 1990; **97**: 1204–10.
- 17 Khaw PT, Sherwood MB, MacKay SLD, Rossi MJ, Schultz G. 5-minute treatments with fluorouracil, floxuridine, and mitomycin have long term effects on human Tenon's capsule fibroblasts. *Arch Ophthalmol* 1992; **110**: 1146–50.
- 18 Finger PT, Gougelman HP. A barrier plaque designed to prevent conjunctival adhesions. *Arch Ophthalmol* 1990; **108**: 1669–70.