local presence of reactive gliosis, but without any presence of residual necrotic tumour cells. Immunohistochemistry stains for MIB-1 and CD-45 revealed no tumour cells, but did show a lymphocytic infiltrate throughout the optic nerve (fig 2C). The dura showed no thickening or inflammation. A second uncommon histopathological finding in the optic nerve was endothelial cell proliferation and swelling, with total obliteration of some vessels as a consequence (fig 2D).

Comment

The combination of inflammation and endothelial proliferation in our patient, which are thought to be responsible for at least the residual optic nerve enhancement after neoadjuvant chemotherapy, have never been described before as a possible cause of (post-treatment) false positive MRI. However, a striking discrepancy between pretreatment radiologically detectable extensive optic nerve invasion and post-treatment histopathology, without any remaining signs of a former minimal or extensive post-laminar invasion is left unsolved. Histopathological findings in eyes after multiple courses of chemoreduction therapy for retinoblastoma are well documented and consist mainly of viable and necrotic tumour cells and gliosis, without presence of inflammation or endothelial proliferation.^{3,4} The latter occurs characteristically in brain tissue and is associated with contrast enhancement in brain tumours.⁵ Only Bellaton *et al*¹ published three cases with a comparable discrepancy of extensive optic nerve invasion on pretreatment MRI without any remaining histopathological signs of former extensive tumour invasion after two or three courses of chemotherapy, although a slight residual enhancement is reported in at least one patient. Unfortunately, they did not mention a possible histopathological substrate for (residual) enhancement. In conclusion, optic nerve enhancement on MRI is an indicator for tumour invasion, but it must be taken into consideration that other histopathological changes (inflammation, endothelial proliferation) can occur in combination with retinoblastoma and may mimic (residual) tumour invasion, also after neoadjuvant chemotherapy.

P de Graaf

Department of Radiology, VU University Medical Center, Amsterdam, Netherlands

A C Moll, S M Imhof

Department of Ophthalmology, VU University Medical Center, Amsterdam, Netherlands

P van der Valk

Department of Pathology, VU University Medical Center, Amsterdam, Netherlands

J A Castelijns

Department of Radiology, VU University Medical Center, Amsterdam, Netherlands

Correspondence to: Pim de Graaf, MD, VU University Medical Center, Department of Radiology, Postbox 7057, 1007 MB Amsterdam, Netherlands; p.degraaf@vumc.nl

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Cytokeratin subtyping to distinguish reactive and neoplastic RPE cells

Retinal pigment epithelial (RPE) hyperplasia is common in retinal disease, whereas RPE neoplasia is rare. In tissue sections it can occasionally be difficult to distinguish between the two conditions on morphological features alone. In a retrospective case series that addressed this issue, features thought to favour a reactive hyperplasia of the RPE included a history of previous ocular disease in the affected eye, conspicuous elaboration of basement membrane, rarity of mitotic figures, and histological pattern.¹ These features are not

Figure 1 (A) Preoperative fundus photograph of right eye showing foveal choroidal neovascularisation (CNV) with surrounding exudate. (B) Section through the excised CNV stained with haematoxylin and eosin. (C) The cortex of the CNV (haematoxylin and eosin). Note the tubular-vascular arrangement of the cells and their association with basement membrane-like material. Scale bar: 50 μ m. Inset: diastase periodic acid Schiff staining of the CNV cortex demonstrates copious amounts of basement membrane-type material surrounding the RPE cells (haematoxylin counterstain). (D, E) Sections through the CNV stained for cytokeratin 7 and 8/18 respectively, using the immunohistochemical method (red reaction product) and counterstained with haematoxylin. The cells in the CNV cortex demonstrate strong positivity for cytokeratin 7 but not 8/18. A few RPE cells in the surface monolayer do, however, stain for simple epithelial cytokeratins (e). Scale bars: 50 μ m. (F, G) Immunohistochemical stain of hyperplastic RPE cells in a disciform CNV (used as a cytokeratin reference specimen) for cytokeratin 7 (F) and 8/18 (G) respectively. The reactive cells have mostly lost positivity for cytokeratin 8/18 but are immunoreactive for cytokeratin 7 (arrows). Cells in a surface layer mostly express both cytokeratins (arrowheads). (H, I) Immunohistochemical stain of known low grade RPE adenocarcinoma (used as a cytokeratin reference specimen) demonstrating absence of cytokeratin 7 staining (H) but strong cytokeratin 8/18 labelling (I).

absolutely discriminatory. For example in case reports of RPE adenocarcinomas basement membrane elaboration has been detected.^{2,3} Likewise, no mitoses were observed by light microscopy in a lesion eventually determined to be neoplastic⁴ and there were no unique histological patterns that differentiated hyperplasia from neoplasia. To complicate the issue there is evidence that neoplasia can arise from sites of hyperplasia/inflammation⁵ and RPE hyperplastic lesions can assume tumorous proportions.⁶ Therefore, some tumours still have to be placed equivocally in spectrum between definite benign hyperplasia and definite neoplasia.¹

Case report

A 10 year old girl presented with idiopathic left anterior iritis, visual acuity was Snellen 20/20 bilaterally. Over the next year the condition progressed to bilateral panuveitis necessitating the use of oral corticosteroids. Bilateral submacular haemorrhages secondary to choroidal neovascular membrane developed (fig 1A) and visual acuity decreased to 20/200 bilaterally. Fundal examination at this time also showed bilateral "punched out" chorioretinal lesions in the peripheral retina but more prominent inferiorly. Right visual acuity improved to 20/80 after surgical removal of choroidal neovascular membrane in this eye.

The excised choroidal neovascular membrane had a fibrovascular core as has been reported with CNV of various aetiologies in other series.⁷ The cortex was unorthodox in structure, consisting of a thick mass of RPE cells in a tubulo-acinar pattern separated from each other by periodic acid Schiff positive extracellular material as opposed to a thin layer of RPE cells and fibrin normally expected⁷ (fig 1 B, C). By immunohistochemistry these RPE cells were cytokeratin (CK) 7 positive but CK8/18 negative (fig 1D, E). The intervening extracellular material stained for collagen IV and laminin indicating that it is essentially basement membrane (data not shown).

Comment

An unusual feature in this patient is the RPE pattern, which is akin to that usually found in RPE neoplasia⁴ or rare tumour-like hyperplasia associated with inflammatory scars⁶ rather than CNV.

Previously, we have examined cytokeratin expression in hyperplastic RPE cells in a series of subretinal lesions (where the cells may also adopt a variety of shapes ranging from spindle to oval or cuboidal). In these cells, CK7 is prominent and the simple epithelial cytokeratins 8 and 18 tend to be downregulated⁸ (fig 1F, G). True RPE neoplasia is rare. However, we were able to compare the cytokeratins in one such neoplasm with those of normal and reactive RPE cells. Consistent with neoplasia in other simple epithelia,⁹ neoplastic RPE cells retained CK8/18. Moreover, these cells did not express CK7 (fig 1H, I). Thus the pattern of CK in the present specimen, with loss of CK8/18 and gain of CK7, is consistent with that of hyperplastic rather than neoplastic RPE. Therefore, the final histological diagnosis was CNV of inflammatory aetiology with associated RPE gross hyperplasia. It can be difficult to discriminate between neoplastic and hyperplastic RPE when the latter adopt a tubulo-acinar arrangement: our findings suggest that cytokeratin subtyping may help distinguish between these two forms of growth.

E P Guerin
Unit of Ophthalmology, Department of Clinical Sciences, UCD, Duncan Building, University of Liverpool, Daulby Street, Liverpool L69 3GA, UK

D Wong
St Paul's Eye Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

G Silvestri
Centre for Vision Science, The Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, UK

P S Hiscott
Unit of Ophthalmology, Department of Clinical Sciences, UCD, Duncan Building, University of Liverpool, Daulby Street, Liverpool L69 3GA, UK

Correspondence to: Eoin P Guerin, Unit of Ophthalmology, Department of Clinical Sciences, UCD, Duncan Building, University of Liverpool, Daulby Street, Liverpool L69 3GA, UK; eoinguerin@hotmail.com

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Use of pulmonary interferon γ responses to mycobacterial antigen to distinguish sarcoid associated optic neuropathy from tuberculosis

The clinical distinction between sarcoidosis and tuberculosis (TB) can be difficult.¹ Abnormal CD4 T cell function, demonstrated as cell mediated hyporesponsiveness

(anergy), is considered to be a feature of sarcoidosis.² Here we report the use of a sensitive assessment of mycobacterial specific CD4 T cell response to assist in the diagnosis of sarcoid associated optic neuropathy in a subject at high risk of TB.

Case report

A 53 year old Asian-Indian woman was referred with a 2 month history of intermittent blurred vision in her right eye and right optic disc swelling. She developed right eye ache and her vision deteriorated over 3 days to counting fingers in this eye. She also complained of malaise and night sweats though her weight was stable. She had recently returned to the United Kingdom after living in Uganda. Examination revealed a right afferent pupillary defect, chronically swollen right optic disc, and a partial macular star with peripheral retinal vascular sheathing (fig 1).

Investigations showed a normal chest radiograph, full blood count, renal and hepatic function, erythrocyte sedimentation rate and C reactive protein; with a moderately raised serum angiotensin converting enzyme of 90 IU/l (normal range 27-82). Treponemal antibodies were not detected. *Toxocara*, *Bartonella henselae*, and *B quintana* IgM and IgG were negative; as were HIV-1 and HIV-2 antibody tests. Toxoplasma IgG was not detected. A tuberculin skin test (TST) was negative. A magnetic resonance imaging (MRI) scan of her brain and orbits showed gadolinium enhancement of her right optic nerve head. Gallium scanning demonstrated tracer uptake in the lacrimal and parotid glands, pulmonary hila and liver, as well as diffusely in the lungs. Bronchoscopy and bronchoalveolar lavage (BAL) revealed no mucosal abnormalities. TB smear, nucleic acid amplification test, and culture were negative. Absolute leucocyte and lymphocyte numbers, as well as the percentages of CD3+, CD4+, and CD8+ T cells were determined using CD45, CD4, and CD8 antibodies.³ The lymphocyte percentage was elevated at 36.3% (normal <15%) as was the CD4/CD8 lymphocyte ratio among CD3+ lymphocytes at 27.7 (normal range 1-3). The BAL was then examined for interferon γ (IFN- γ) production by lymphocytes in response to overnight stimulation with purified protein derivative of *M tuberculosis* (PPD) as previously described.⁴ Within the CD4+ T cell population the frequency of PPD specific IFN- γ lymphocytes was 0.47%. This is one tenth of the frequency observed in pulmonary and extra-pulmonary TB.⁴ Taking all data together, a

Figure 1 Colour fundus photograph of patient's right eye showing optic disc swelling with a partial macular star.