Retinal vasoproliferative tumours

IG Rennie

Abstract

Vasoproliferative tumours are uncommon retinal lesions that may occur in isolation (primary) or in association with another ocular condition (secondary). They may be unilateral or bilateral and have a predilection for the peripheral inferior temporal quadrant of the retina. Vasoproliferative tumours can be associated with abnormalities of the macular, including epiretinal membrane formation and cystoid macular edema. A number of modalities have been used to treat these tumours including cryotherapy and radiotherapy.

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Introduction

Vasoproliferative tumours of the retina are uncommon and have only recently been recognized as a distinct clinical entity. In 1982 Baines *et al*¹ reported peripheral telangiectatic nodules in eight eyes of five patients. All the peripheral retinal lesions were located in the inferio-temporal quadrant and in seven cases were associated with subretinal fluid, yellow exudate surrounding the lesion, and an epiretinal membrane at the posterior pole. Two patients with bilateral involvement were also noted to have bilateral uveitis. Although this report probably represents the first documented clinical series of vasoproliferative tumours of the retina, a number of case reports appeared in the literature before this, which described similar lesions either in isolation or associated with another ocular or medical condition.

In 1966 Henkind and Morgan² reported a histopathological series of four adult patients who had undergone enucleation because of severe ocular disease and were subsequently found to have features associated with Coat's disease namely, deep retinal exudation, lipoidal

macrophages or 'ghost cells', and cholesterol clefts in the subretinal exudate. In each case a small, but pronounced, vascular malformation was noted in the retinal periphery. They concluded that the pathological appearances arose as a result of exudation and leakage of blood from the peripheral vascular abnormalities resulting in a 'Coat's-like' appearance. They also concluded that the vascular anomalies in all four cases were probably present from birth and became active as a result of local stasis and hypoxia.

Further sporadic reports of either 'angioma like' or localised peripheral adult Coat's disease appeared in the literature,^{3–5} until in 1983 two major series were published consecutively in the same issue of Ophthalmology. Laqua and Wessing⁶ reported a localised peripheral vascular lesion in 10 adult patients whose ages range from 35 to 69 years. In all cases in the disease process was unilateral and involved the temporal peripheral retina. It is interesting to note that the maculae were noted to be abnormal (macula pucker or cystoid macular oedema) in 60% of the patients. Shields *et al*⁷ reported 12 patients who had a unilateral, solitary, and vascular mass arising from this sensory retina. All the patients were adult with an age range from 34 to 85 years at the time of diagnosis. The inferior temporal retina was involved in nine cases and again an abnormality of the macular was noted in 50% of the cases that were described as presumed acquired retinal haemangiomas (PARH).

In 1995 Shields *et al*⁸ reported the clinical manifestations of 103 patients with an acquired retinal vascular tumour. They described the lesions as vasoproliferative retinal tumours, a term which has now gained acceptance in the medical literature.

Epidemiology

Retinal vasoproliferative tumours may be idiopathic (74%) or secondary to a pre-existing

Academic Unit of Ophthalmology and Orthoptics, University of Sheffield, Royal Hallamshire Hospital, Sheffield, UK

Correspondence: I Rennie, Academic Unit of Ophthalmology, Royal Hallamshire Hospital, University of Sheffield, Glossop Road, Sheffield S10 2JF, UK
Tel: +0114 271 2902.
E-mail: i.g.rennie@btinternet.com

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ocular disease (26%).⁸ Idiopathic (primary) are usually solitary lesions (87%) in contrast to secondary tumours that are often multiple in nature (42%).⁸ Both eyes appear to be affected equally. Although most cases are unilateral, bilateral involvement may occur, particularly in patients with secondary lesions. Retinal vasoproliferative tumours may be present at any age, although the majority are present in the third and fourth decades of life.⁸ These tumours, in contrast to those observed in von Hippel Lindau disease, are sporadic in nature. Recently, however, Wachtlin *et al*⁹ reported the occurrence of multiple, bilateral retinal vasoproliferative tumours in a pair of a 58-year-old monozygotic female twins.

Secondary retinal vasoproliferative tumours have been described in association with a number of ocular conditions including intermediate uveitis,⁸ retinitis pigmentosa^{3,8,10,11} toxoplasmosis,^{8,12,13} toxocariasis,⁸ retinal detachment surgery,^{8,14} sickle cell disease,⁴ retinochoroidal coloboma,⁸ Coat's disease,¹⁵ retinopathy of prematurity,⁵ and Waardenburg's syndrome.¹⁶

Clinical features

Vasoproliferative tumours typically appear as a globular- or dome-shaped lesion arising in the peripheral retina (Figure 1). Their colour is somewhat variable, most are described as yellow or pink in colour, whereas occasionally they may appear white, grey, or reddish in appearance. The vascular nature of the lesion is usually evident and may manifest as a network of fine, telangiectatic vessels over the surface of the lesion. Clusters of small aneurysms of varying size are present within the telangiectatic plexus and may also appear embedded into deeper matrix of the tumours. In most

Figure 1 A vasoproliferative tumour of the retina. Note the peripheral location, extensive subretinal exudate, and associated retinal pigment epithelial changes.

cases, retinal 'feeder' vessels, which have a normal or slightly enlarged caliber enter the posterior aspect of the tumour. However, these vessels lack the markedly dilated and tortuous appearances of those that are found in association with the retinal angiomas of von Hippel Lindau disease. The appearance of the tumours may be obscured, at least in part, by haemorrhage either upon the surface of the lesion or within the adjacent vitreous. Sub and intraretinal exudation, which can be extensive, occurs in more than 80% of the cases.⁸ Exudative retinal detachment is present in approximately 50% of lesions.⁸ Retinal pigment epithelial hyperplasia may be observed at the edge of the tumours and is present in over half of the secondary tumours.⁸

The majority of vasoproliferative tumours arise in the peripheral retina and can involve the ora serrata, particularly in secondary lesions associated with intermediate uveitis. Vasoproliferative tumours have a curious predilection for the inferior temporal retina, with approximately half of the cases arising in this location.⁸ Secondary tumours occur in the section of abnormal retina or at the edge of a chorioretinal scar.

Associated macular lesions including epiretinal membranes or fibrosis (31%) or cystoid macular oedema (18%) may give rise to visual loss.^{1,8,17,18} Indeed, careful examination of the peripheral retina should always be undertaken in cases of apparent idiopathic macular epiretinal membranes or oedema to exclude the presence of an occult vasoproliferative tumour. Visual loss may also rise as a result of the posterior extension of an associated exudative retinal detachment or subretinal exudate.

Ancillary investigations, in general, are of limited value in establishing the diagnosis of this condition. Fluorescein angiography is often technically difficult or even impossible, given the peripheral nature of most lesions. In cases where angiography is possible the lesions usually fill rapidly in the early phase and become increasingly hyperfluorescent, with diffuse and leakage in the late phases. The aneurysms and dilated telangiectatic vessels on the surface and within the body of the lesion may become more apparent during angiography. Ultrasonography confirms the presence of a solid lesion without choroidal excavation on the B scan and with medium to high internal reflectivity on the A scan.⁸

Differential diagnosis

The presence of a typical lesion located in the inferior temporal periphery, surrounded by exudate and associated with an epiretinal membrane at the posterior pole will not be a diagnostic problem for the experienced observer. Atypical lesions may present a diagnostic

challenge and simulate a variety of conditions, including angiomas (capillary haemangiomas), eccentric choroidal neovascularisation (eccentric disciforms), and amelanotic melanomas.

Vasoproliferative tumours can normally be differentiated from capillary haemangiomas associated with von Hippel Lindau disease because of the absence of markedly dilated and tortuous feeder vessels, which are characteristic of the latter condition. Furthermore, patients harbouring vasoproliferative tumours do not have a positive family history or possess any of the systemic conditions normally associated with von Hippel Lindau disease.

Eccentric choroidal neovascularisation may, on occasion present a real diagnostic dilemma particularly, when associated with a retinal detachment, subretinal exudate or haemorrhage. In general, such lesions are present in the elderly age group. The lack of feeder vessels or significant telangiectatic vessels usually serve to distinguish these lesions from vasoproliferative tumours.

Occasionally peripherally located amelanotic melanomas may be confused with vasoproliferative tumours, especially if they are associated with surrounding exudation or haemorrhage. Meticulous clinical examination can usually establish that such tumours are choroidal rather than retinal in origin. Fluorescein angiography and ultrasonography may occasionally be of value in establishing the diagnosis in difficult cases. The use of intraocular biopsy has been advocated in cases wherein the diagnosis cannot be established on clinical grounds.¹⁹

Pathology

Histopathologically, vasoproliferative tumours are composed of both glial and vascular elements.^{1,2,20–24} The glial element appears as a proliferation of slender spindle-shaped cells with eosinophilic cytoplasm and small uniform nuclei which lack pleomorphism. These cells stain positively for glial fibrillary acid protein (GFAP) supporting their glial origin. Mitotic figures are usually absent and the growth fraction, as determined by using MIB-1 antibody, is low.²² Dilated blood vessels, lined with plump endothelial cells and marked hyalinisation of their walls are enmeshed within the spindle-cell matrix. Some of these vessels appear occluded, whereas others remain patent.

Recently, histopathology of an associated macular epiretinal membrane has been reported.²⁵ The membrane was vascularised and had positive immunostaining for both type IV collagen and GFAP (laminocytes). The authors noted that vascularised epiretinal membranes are typically a feature of proliferative diabetic

retinopathy and that neovascularisation may be an initiation in the development of this condition.

The histological appearances of vasoproliferative tumours have led to the speculation that these lesions are not true tumours, but rather reactive proliferations.^{20–23} Indeed, in a recent study Hiscott and Mudhar demonstrated using immunohistochemistry, the presence of retinal pigment epithelial cells in seven out of eight vasoproliferative tumours and associated periretinal membranes. They speculated that vasoproliferative tumours represent part of the spectrum of proliferative vitreoretinopathy.²³ Although the development of secondary tumours in association with intraocular inflammation or adjacent to chorioretinal scars would support this notion, it remains unclear what could initiate such a reaction in individuals with primary lesions where there is no concomitant intraocular disease.

Treatment

The relative rarity of retinal vasoproliferative tumours has resulted in a lack of an evidence-based consensus agreement on how best to treat these lesions. Small, asymptomatic peripheral lesions lacking significant exudate or macular involvement can be managed by periodic observation. If the lesion has a significant amount of exudate or detachment and treatment is warranted. Many lesions can be effectively managed using triple freeze thaw transconjunctival cryotherapy.⁸

Recent studies have also demonstrated that larger lesions can be treated with either ruthenium 106²⁶ or iodine²⁷-plaque brachytherapy. A number of case reports have also appeared in the literature advocating the use of a photodynamic therapy to treat both primary^{28,29} and secondary¹⁰ vasoproliferative tumours. Bevacizumab (Avastin)³⁰ has also been used in the treatment of vasoproliferative tumour, although it is unclear, as yet, whether the initially promising result will be maintained in the long term. Japiassu *et al*³¹ recently reported a regression of a vasoproliferative tumour following the use of systemic infliximab to treat a patient suffering from mixed connective tissue disease.

Conflict of interest

The author declares no conflict of interest.

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