The eye in haematological disease

The eye allows living functioning blood vessels to be observed and is thus ideal for the study of haematological disease. Disorders of the blood have significant ocular manifestations and pose a real threat to vision, making knowledge of the subject essential to ophthalmologists, haematologists, oncologists and general physicians.

The ocular tissues interact intimately with the cells of the blood to sustain vision. The eye can be dramatically affected in disorders of erythrocytes, leucocytes or platelets, and provides a unique window for observing haematological disease.

Disorders of erythrocytes

The eye in sickle cell disease

Sickle cell disease affects many ocular vascular structures. In the conjunctiva, comma-shaped vascular dilatations occur as a result of vaso-occlusion. Hyphaema in sickle cell disease is a medical emergency as sickled erythrocytes fail to pass through the trabecular meshwork, leading to dramatically raised intraocular pressure. Anterior segment ischaemia was frequently a result of posterior segment surgery to treat proliferative sickle retinopathy in the 1970s, but is rare with modern surgical techniques.

Posterior segment complications in sickle cell disease lead to visual loss in up to 10% of untreated eyes and may be proliferative or non-proliferative, although the former is a much bigger threat to vision. Proliferative sickle retinopathy is more common in SC and S-β thalassaemia patients than in those with SS disease (Downes et al, 2005). The former subtypes typically have milder systemic disease, and the reasons for their more aggressive ocular complications are not fully understood.

Proliferative sickle retinopathy is characterized by the development of new retinal vessels secondary to ischaemia. *Table 1* highlights the stages of proliferative sickle retinopathy. Stages I, II and III are asymptomatic, but are a pathological attempt to perfuse ischaemic retina (*Figure 1*). Vitreous haemorrhage (stage IV) is a frequent complication, occurring in 23% of SC patients, but only 3% of those with SS haemoglobin (Elagouz et al, 2010). Retinal detachment (stage V) in proliferative sickle retinopathy is commonly secondary to tractional bands and membranes between the vitreous and retina after years of transudation and haemorrhage.

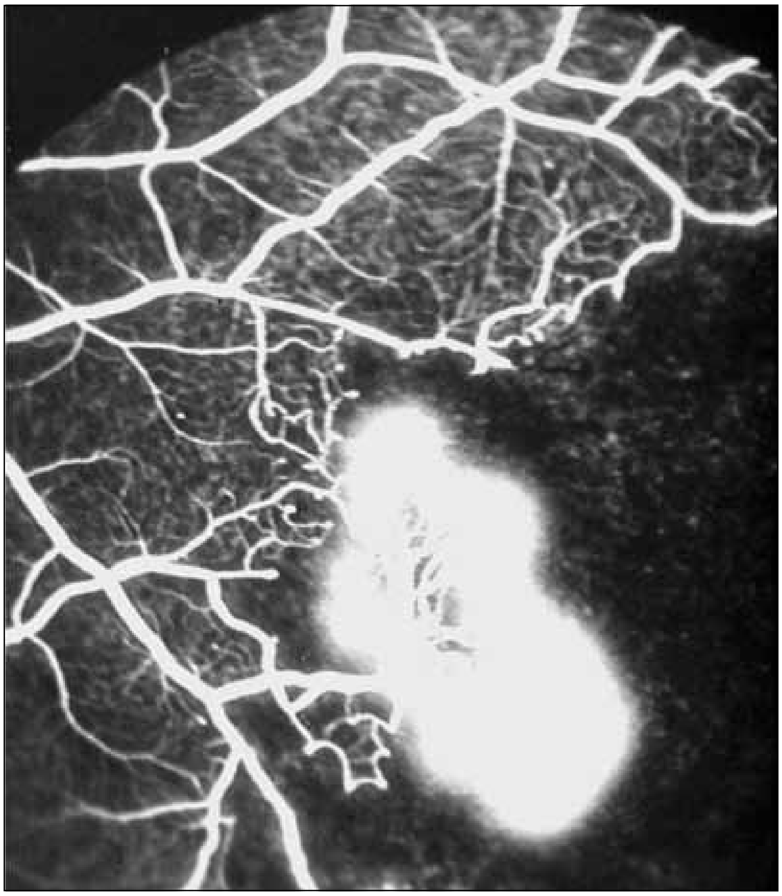
Table 1. Stages of proliferative sickle retinopathy

Stage I	Occlusion of peripheral arterioles
Stage II	Formation of arteriolar-venular anastomoses
Stage III	Formation of neovascular sea-fan complexes (*Figure 1*)
Stage IV	Vitreous haemorrhage
Stage V	Retinal detachment

From Goldberg (1971)

Non-proliferative sickle cell disease encompasses several entities that may lead to visual loss, including central retinal artery occlusion. Bleeding between the neurosensory retina and internal limiting membrane results in salmon patch haemorrhages that resolve leaving black sunburst scars.

Figure 1. Fluorescein angiogram showing peripheral retinal vascular closure with new vessel formation which leak fluorescein.



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The severely ischaemic nature of proliferative sickle retinopathy mean that many patients are spared visual loss as proliferated vessels auto-infarct, ending any localized neovascular drive. Nevertheless, proliferative sickle retinopathy causes blindness in 12% of eyes. Vitrectomy may be required to treat non-clearing vitreous haemorrhage, retinal detachment or epiretinal membranes.

A better understanding of sickle cell disease has also offered novel treatments for proliferative sickle retinopathy. Increasing levels of haemoglobin F with hydroxyurea inhibits haemoglobin S polymerization and resultant erythrocyte sickling (Claster and Vichinsky, 2003). Furthermore, vascular endothelial growth factor (VEGF) is known to play an integral role in proliferative sickle retinopathy, and anti-VEGF agents such as bevacizumab have been used in proliferative sickle retinopathy with significant success.

The eye in thalassaemia

While sickle cell disease represents a qualitative abnormality of haemoglobin, in the thalassaemias there is a quantitative reduction or complete absence of a globin chain leading to deficient erythropoiesis and haemolysis. Patients with thalassaemia major become transfusion-dependent and require treatment with iron-chelating agents to prevent cardiac and hepatic failure from iron overload.

Desferrioxamine is widely used in the management of chronic iron overload. However, the drug has been linked to serious ocular toxicity, including pigmentary retinopathy (*Figure 2*), optic neuropathy and cataract. It is not clear whether these adverse effects are caused by a direct effect of desferrioxamine or secondary to removal of copper and zinc that are necessary for normal ocular function. Regular screening of patients on desferrioxamine therapy has been recommended as cessation or reduction of drug dose reverses visual loss in some cases.

The incidence of ocular toxicity in those on desferrioxamine varies widely, and is likely to be dose-related. Taher and colleagues (2006) studied 67 patients with thalassaemia major in Lebanon, where 29.9% had evidence of retinal pigment epithelium degeneration and 19.4% had visual acuity worse than 20/40. On the other hand, a 10-year study of 84 children with transfusion-dependent thalassaemia on desferrioxamine in Toronto found only one case of ocular toxicity which reversed fully on reduction of the treatment dose (Baath et al, 2008).

Concerns about the adverse effects of desferrioxamine as well as its invasive subcutaneous mode of administration have led to the search for newer chelation agents. Deferiprone has been shown to be just as effective, but can be taken orally and has no reported ocular toxicity, making it useful in those who have demonstrated ocular toxicity on desferrioxamine.

Figure 2. Pigmentary retinopathy in a patient on desferrioxamine for prevention of iron overload.

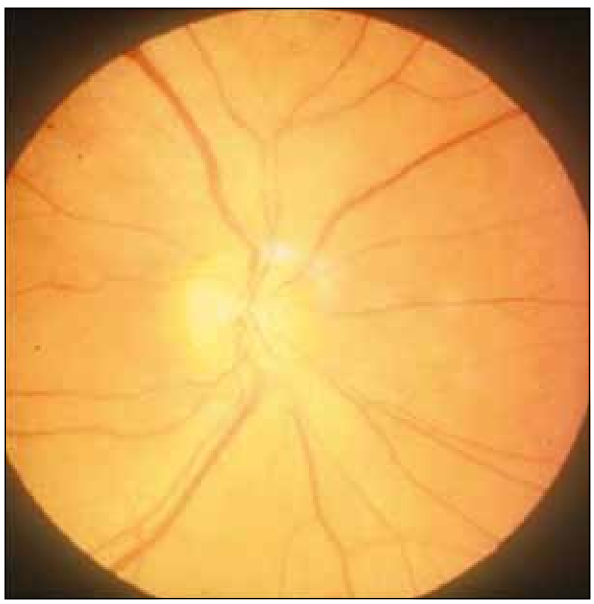
Anaemia and ischaemic optic neuropathy

The optic nerve possesses an elaborate system of vascular autoregulation, but this fails in the extremes of low blood pressure. This occurs in ischaemic optic neuropathy (*Figure 3*) secondary to severe anaemia, usually in combination with hypotension.

Perioperative visual loss describes loss of vision resulting from non-ocular surgery under general anaesthetic, and commonly occurs as a result of ischaemic optic neuropathy. Cardiac and spinal fusion surgery have been shown to pose the highest risk of perioperative visual loss, with intraoperative anaemia posing 60% excess risk, and those requiring at least a single blood transfusion a 68% increased risk (Shen et al, 2009).

Despite the rarity of perioperative visual loss, the American Society of Anaesthesiologists (2006) has published preventive guidance that low perioperative haematocrit be corrected and arterial blood pressure maintained, particularly in spine surgery with prone-posturing.

Figure 3. Anterior ischaemic optic neuropathy. Notice the marked disc pallor.



Optic neuropathy in pernicious anaemia

The optic nerve is sensitive to low levels of vitamin B_{12} (cobalamin), which is solely diet-derived. Intrinsic factor is secreted by gastric parietal cells to facilitate ileal vitamin B_{12} absorption.

In pernicious anaemia, anti-gastric parietal cell antibodies cause failure of production of intrinsic factor. The condition is associated with other autoimmune disorders, including vitiligo, Addison's and thyroid disease. Ineffective erythropoesis leads to a megaloblastic anaemia, as well as a host of neurological disorders, including a peripheral sensory neuropathy, subacute combined degeneration of the spinal cord as well as optic neuropathy. Vitamin B_{12} deficiency may also be the result of poor dietary intake, gastrectomy or ileal disease.

In pernicious anaemia, optic atrophy presents insidiously with reduced central vision and a centrocaecal scotoma. There may also be temporal disc pallor with loss of nerve fibres in the papillomacular bundle. A similar picture is seen in vitamin B_1 (thiamine), vitamin B_2 (riboflavin) and folate deficiency. These substances are essential in oxidative phosphorylation in neuronal mitochondria, and their absence leads to impaired energy metabolism and the generation of free radicals (Sadun, 2002). Replacement of the deficient vitamins halts visual loss but rarely normalizes vision.

Disorders of leucocytes

Leukaemia

Almost any structure within the eye may be affected by leukaemia. The effects may be the result of primary infiltration or secondary to the complications of leukaemia or its often aggressive treatment. In fact, before the advent of bone marrow biopsy, an ophthalmic examination was often required for the diagnosis of leukaemia.

Figure 4. Widespread retinal infiltrates and haemorrhages in leukaemia.

The eye in leukaemia

The retina is commonly affected in leukaemia. Fundal examination may reveal white clumps representing leukaemic infiltrates, or retinal haemorrhages, frequently with a white centre composed of leukaemic cells and debris (*Figure 4*). Complications of leukaemia, such as anaemia and thrombocytopenia, affect the eye in approximately 39% of patients (Stafford et al, 2001). Pre-retinal and vitreous haemorrhage cause significant visual morbidity. Hyperviscosity secondary to leukaemia may cause retinal cotton wool spots and retinal vein occlusion. Rarely, peripheral retinal neovascularization similar to that seen in sickle cell disease may develop. The vitreous may also be infiltrated by leukaemic cells, gaining access via the optic nerve head.

Although the choroid may appear normal in leukaemic patients, autopsy studies have documented leukaemic infiltration in 65% of those affected (Kincaid and Green, 1983). Serous retinal detachment may occur, with secondary photoreceptor loss and cystoid macular oedema. The iris may also be affected, manifesting as a change in colour, pseudohypopyon or spontaneous hyphaema. Infiltration of the trabecular meshwork can cause significantly elevated intraocular pressure.

In CNS leukaemia, symptoms may include diplopia secondary to cranial nerve palsies. Optic disc swelling may appear as a result of raised intracranial pressure, or as a result of direct nerve infiltration (*Figure 5*). The orbit is commonly involved in leukaemia, causing lid oedema and exophthalmos. When the conjunctiva is affected, corkscrew vessels similar to those seen in sickle cell disease appear.

Figure 5. Optic disc swelling secondary to direct infiltration with leukaemic cells.

Drugs used to treat leukaemia

Systemic chemotherapy causes significant ocular morbidity. Vincristine, for example, leads to corneal anaesthesia, ocular motor neuropathy and optic atrophy. Cataract is induced by radiotherapy, systemic steroids and busulphan. Ciclosporin may cause retinal toxicity. One of the feared complications of bone marrow transplantation is graft *vs* host disease. This may lead to failure of the graft as well as a host of ophthalmic manifestations, including keratoconjunctivitis sicca. This presents as a Sjögren's-like illness, progressing to pseudomembranous conjunctivitis, cicatricial lagophthalmos and corneal ulceration.

Ocular opportunistic infection in leukaemia

The disease process and aggressive chemo- and radiotherapy in leukaemia can lead to profound immunocompromise, making ocular structures susceptible to infections that are rarely problematic in health.

Cytomegalovirus causes a full-thickness necrotizing retinitis that is characteristically sectoral (*Figure 6*). Visual loss can result from involvement of the optic nerve or macula, rhegmatogenous retinal detachment or cystoid macular oedema (Kramer et al, 2003).

Acute retinal necrosis typically occurs in immunocompromised patients and is primarily caused by varicella zoster virus. White, well-demarcated retinal lesions are seen together with optic disc swelling and vitritis. Severe visual loss secondary to macular involvement or retinal detachment commonly occurs unless intravenous aciclovir is started immediately.

Fungal endophthalmitis may complicate fungal septicaemia and can be a significant threat to vision. Immunocompromised individuals may be affected by atypical fungi. Vitrectomy with injection of intraocular amphotericin B is required when the vitreous is affected (Sallam et al, 2008). Thankfully, better management of neutropenic sepsis is making fungal entry into the circulation increasingly rare.

Figure 6. Full-thickness herpetic retinitis.

Lymphoma

Lymphoma is a malignant clonal proliferation of lymphoid cells in the lymphoid tissue. It can affect either the ocular adnexae or the contents of the globe (intraocular lymphoma).

Ocular adnexal lymphoma

The ocular adnexae consist of the orbit, extraocular muscles, conjunctiva, eyelids, lacrimal gland and lacrimal apparatus. Lymphoma of these sites comprises 7–8% of all extranodal lymphomas (Freeman et al, 1972). Most ocular adnexal lymphoma is primary, and almost all are of B cell lineage. Lymphoma of mucosa-associated lymphoid tissue (MALT) is by far the commonest type, accounting for up to 80% of cases.

Ocular adnexal lymphoma presents at a median age of 65 years and shows a female preponderance (M:F=1:2) (McKelvie, 2010). Patients present with eyelid swelling (33%), diplopia (13%) or proptosis (13%) (Demirci et al, 2008). They may also show a conjunctival salmon patch lesion or lacrimal gland enlargement. At presentation, most patients with ocular MALT lymphoma have disease confined to the orbit.

Radiotherapy has a high success rate, even in high-grade lymphomas, achieving 86–100% local control with 0–15% local recurrence rates (McKelvie, 2010). Treatment is complicated by ocular toxicity, including cataract, ischaemic retinopathy and neovascular glaucoma. The use of the radioimmunoconjugate Y-90 ibritumomab tiuxtan greatly reduces side effects as the dose of radiation needed is only a tenth of that required for radiotherapy alone (Esmaeli et al, 2009).

The prognosis in ocular adnexal lymphoma depends greatly on histological subtype. Adverse prognostic markers include non-MALT histology, age over 60 years, non-conjunctival location, nodal involvement and raised serum lactate dehydrogenase (Jenkins et al, 2000).

Intraocular lymphoma

Intraocular lymphomas are a heterogeneous group affecting different structures with strikingly different prognoses.

Retinal lymphomas account for the majority of intraocular lymphomas. They are high-grade malignancies that are closely associated with CNS lymphomas, with disease presenting in both tissues simultaneously in many cases. The most common tumour type is diffuse large B cell lymphoma.

Retinal lymphoma most commonly presents in individuals over 60 years. Younger patients are frequently immunocompromised and most disease is bilateral at presentation. Patients typically present with floaters and painless reduced vision, and examination may reveal vitiritis together with chorioretinal infiltrates (*Figure 7*).

Those without CNS involvement can be treated with low-dose external beam radiotherapy or intraocular methotrexate. Both are effective at inducing remission in most cases. The prognosis depends on the involvement of the CNS. Survival is greater in those treated aggressively with chemoradiotherapy at the first sight of ocular disease.

Uveal lymphomas may be primary or secondary. Primary choroidal lymphoma is most commonly extranodal marginal zone B cell lymphoma. The peak incidence is at 50–60 years, and patients present with symptoms of blurred vision and metamorphopsia as a result of recurrent serous retinal detachment. Examination reveals diffuse thickening of the choroid with extraocular extension in some cases. Treatment with low-dose radiotherapy is very effective at inducing remission.

In patients with known non-ocular non-Hodgkin's lymphoma, secondary ocular disease commonly involves the choroid. This leads to reduced vision, and can be bilateral. The most commonly encountered tumour subtype is diffuse large B cell lymphoma. Other lymphoproliferative disorders that may affect the choroid include multiple myeloma, extramedullary plasmacytoma and Waldenstrom's macroglobulinaemia.

The eye in amyloidosis

Amyloidosis is characterized by the deposition of fibrillar insoluble protein and may be primary (idiopathic or hereditary) or secondary to multiple myeloma or chronic inflammation. A mutation in the amyloid protein transthyretin gene causes familial amyloidotic polyneuropathy, inherited as an autosomal dominant condition. Amyloid deposition leads to restrictive cardiomyopathy, a peripheral and autonomic neuropathy as well as respiratory and gastrointestinal tract complications.

The eye may be affected in both primary and secondary amyloidosis. Amyloid deposition in the vitreous is particularly common in inherited disease. It leads to visual loss unless treated with vitrectomy. Glaucoma results when amyloid is deposited in the trabecular meshwork. When deposition occurs in the eyelids it can manifest as purpura, whereas conjunctival involvement typically demonstrates a yellow-pink mass with propensity for recurrent subconjunctival haemorrhage (Demirci et al, 2006). Diplopia and proptosis may result when the extraocular muscles or cranial nerves are involved. In lacrimal gland amyloidosis, severe sicca syndromes are observed.

Disorders of platelets

Blood hyperviscosity and retinal vein occlusion

Retinal vein occlusion is common, with a prevalence of 1–2% in those over 40 years. However, younger individuals and those with bilateral disease are more likely to have an underlying systemic condition that leads to hyperviscosity.

The factor V Leiden R506Q mutation produces factor V that is resistant to protein C degradation, creating a hypercoagulable state that increases the risk of retinal vein occlusion. In fact, 29% of patients with central retinal vein occlusion have the mutation, significantly higher than the 9% prevalence of the mutation in the general population (Greiner et al, 1999). Retinal vein occlusion is also 8.9-fold more common in those with raised serum homocysteine levels and 3.9-fold more prevalent in those with anti-cardiolipin antibodies, such as in patients with antiphospholipid syndrome (Janssen et al, 2005) (*Figure 8*).

Figure 7. Retinal lymphoma with chorioretinal infiltrates. The view is hazy as a result of secondary vitritis.

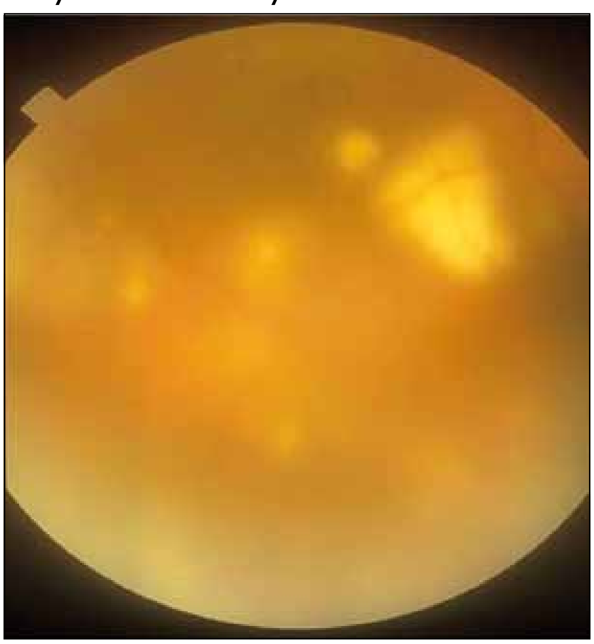
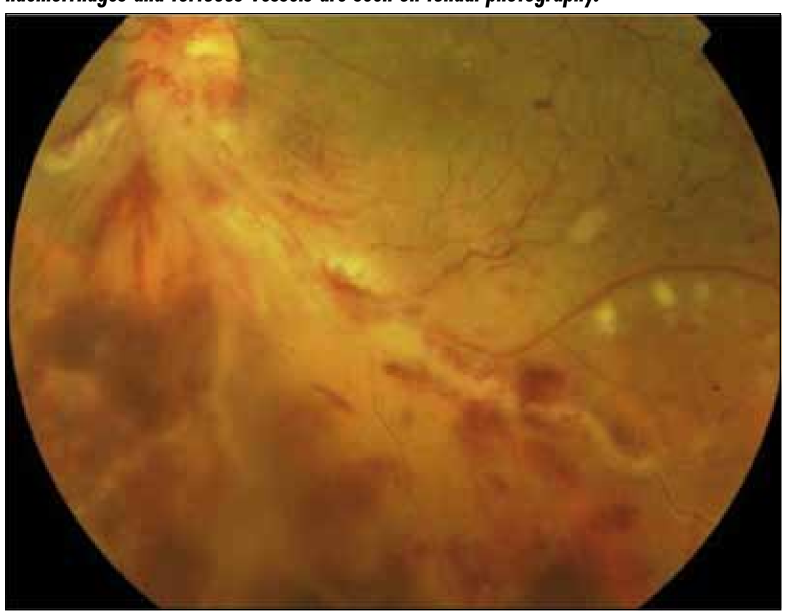


Figure 8. Branch retinal vein occlusion in antiphospholipid syndrome. Widespread haemorrhages and tortuous vessels are seen on fundal photography.



Hyperviscosity is a feature of haematological malignancy, and retinal vein occlusion is commonly seen in leukaemia, multiple myeloma and Waldenstrom's macroglobulinaemia. Bilateral central retinal vein occlusion has been reported in Eisenmenger's syndrome, where pulmonary hypertension leads to elevated erythropoietin production, polycythaemia and hyperviscosity.

Thrombocytopenia

Thrombocytopenia may be the result of reduced platelet production or excessive peripheral destruction. Impaired production may be the result of leukaemia, myelofibrosis or metastatic infiltration, or secondary to marrow failure (aplastic anaemia). Increased platelet loss occurs through immune-mediated means, such as immune thrombocytopenic purpura, or secondary to thrombotic thrombocytopenic purpura. Bleeding is the primary complication and presents a considerable threat to sight.

Aplastic anaemia (bone marrow failure)

Aplastic anaemia is characterized by pancytopenia with hypocellular bone marrow, presenting with the triad of anaemia, recurrent infections and bleeding. Ophthalmic manifestations are seen in 78% of patients, with vision of counting fingers or worse in both eyes in 28% as a result (Mansour et al, 2000). The ocular manifestations are primarily the result of haemorrhage, occurring when the platelet count is below $50x10^9$/litre. In severe cases, widespread retinal haemorrhages with venous engorgement are seen giving the appearance of retinal vein occlusion, although fluorescein angiography excludes venous impedance. Vitreous and subconjunctival haemorrhages are also seen, as is eyelid ecchymosis.

The ophthalmic manifestations of aplastic anaemia rarely require treatment in themselves but may be the presenting features of serious systemic disease. Patients with retinal haemorrhages of unknown cause should be investigated with a full blood count, clotting profile and fasting serum glucose. A human immunodeficiency virus test should also be considered.

Immune thrombocytopenic purpura

Immune thrombocytopenic purpura, previously termed idiopathic thrombocytopenic purpura, involves the immune destruction of platelets. It may present acutely, usually occurring in children after a viral infection, or chronically, which mostly affects adult females. Patients typically have features of purpura with bruising on minimal trauma.

Immune thrombocytopenic purpura rarely causes ocular symptoms, but when they occur, they can be serious. Manifestations include retinal, pre-retinal and vitreous haemorrhage. Vision typically recovers with systemic therapy to raise the platelet count.

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura occurs as the result of a genetic mutation that leads to reduced degradation of von Willebrand factor. It is characterized by profound thrombocytopenia that results in purpura, delirium, fever and haemolytic anaemia with secondary renal failure.

It has been estimated that up to 14% of patients with thrombotic thrombocytopenic purpura show ocular features (Percival, 1970), although this may be an underestimate as many are too unwell to report visual symptoms. The clinical features are caused by ischaemia as well as defective clotting. Serous detachments of the neurosensory retina are consistently reported in thrombotic thrombocytopenic purpura patients, and these are bilateral in most cases. When the fovea is affected, vision can be significantly reduced. Detachments improve markedly within days of systemic treatment. It is hypothesized that circulating fibrinous debris leads to ischaemia of the choriocapillaris with resultant retinal pigment epithelium dysfunction and neurosensory detachment. Haemorrhagic ocular manifestations have also been reported in thrombotic thrombocytopenic purpura, including both choroidal and retinal bleeding.

KEY POINTS

- The eye provides a unique window for observing haematological disease.
- Disorders of erythrocytes, leucocytes and platelets have dramatic ocular manifestations and may pose a significant threat to vision.
- The eye may be affected as a direct result of blood disorders or secondary to the aggressive drugs used in their management.
- A close working relationship between ophthalmologists, haematologists, oncologists and general physicians is essential for the diagnosis and management of many haematological disorders.

Conclusions

It is often said that the eye reflects the state and general health of the body. That is particularly true for haematological disease, where disorders of erythrocytes, leucocytes and platelets can often show dramatic ocular features and cause significant ophthalmic disease.

Recent advances in the treatment of haematological disease not only mean affected patients can expect to live longer, but the often aggressive drugs used can themselves induce ocular pathology. Tomorrow's ophthalmologist will therefore be required not only to help make the diagnosis of systemic disease, but also to work closely with other specialties to manage increasingly complex ocular manifestations. BJHM

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