Classic signs revisited

White-centred retinal haemorrhages (Roth spots)

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Summary

Roth spots (white-centred retinal haemorrhages) were classically described as septic emboli lodged in the retina of patients with subacute bacterial endocarditis. Indeed many have considered Roth spots pathognomonic for this condition. More recent histological evidence suggests, however, that they are not foci of bacterial abscess. Instead, they are nonspecific and may be found in many other diseases. A review of the histology and the pathogenesis of these white-centred haemorrhages will be provided, along with the work-up of the differential diagnosis.

A history of Roth spots

In 1872 Moritz Roth, a pathologist at the University of Basel, published two papers describing a retinal condition he termed *retinitis septica* that occurred in patients who were gravely ill with bacteraemia.^{1,2} He observed scattered retinal haemorrhages in patients with subacute bacterial endocarditis. These haemorrhages were round, oval, or flame-shaped, with a white spot in their centre (figure 1). Roth assumed that the white centres represented disseminated foci of bacterial abscesses, products of emboli from the infective vegetation on heart valves.

It was not until 1878 that Litten assigned the name 'Roth spot' to these white-centred retinal haemorrhages, and gave further detailed description of these lesions.³ He observed that these white spots may appear and disappear with great rapidity (within half an hour) in successive crops, resulting in an ever-changing fundal picture. He also claimed that they occurred in 80% of cases of subacute bacterial endocarditis. This was how the Roth spot became a pathognomonic hallmark of subacute bacterial endocarditis, and Moritz Roth's name was immortalised.

Conditions with Roth spots

Subacute bacterial endocarditis is not, however, the only condition in which Roth spots are seen. Indeed, white-centred retinal haemorrhages have been observed in a bewildering variety of conditions with no obvious single underlying aetiology (box 1).

How is it that such diverse conditions produce retinal haemorrhages of the same morphology? Excluding patients with systemic sepsis, it is inconceivable that the white centres in all the other cases represent infected embolic foci of septic infiltrates. Furthermore, with the exception of patients with leukaemia, it is difficult to imagine that these lesions represent a concentration of leukocytes.

The answer lies in a closer histological examination of the white centre of the Roth spot.

Histopathology of the Roth spot

Early investigators were surprised by the lack of definite aggregations of bacteria and leukocytes in the white centre of the lesions in specimens of patients who died of sepsis.⁴ Instead, they observed areas within the lesions where cellular staining is faint and the endothelium of capillaries becomes indefinite and shows hyaline changes. These histological observations were inconsistent with the proposed explanation of a bacterial abscess as the white centre of a Roth spot.

Recent investigators have given prominence to the presence of fibrin in the lesions. Wong and Bodey had noted fibrin in their aplastic anaemia patients.⁵ Von Barsewisch observed in perinatal retinal haemorrhages that the electron microscopic appearance of white-centred haemorrhages corresponds to fibrin fibrillae and concluded that the white centre of Roth spot represents a fibrin thrombus at the site of a vessel rupture.⁶ Duane *et al* confirmed the observation of the fibrin and platelet aggregate in the white centre of Roth spots in leukaemic patients and further alluded to the fact that the haemorrhage in one leukaemic eye came from a centrally located aneurysm, with 'symmetrical distribution of fibrin, platelets and infiltrating red blood cells' arising from the aneurysm.⁷

The pathogenesis of Roth spots: a unifying theory

White-centred haemorrhage may thus result from the rupture of retinal capillaries and the extrusion of whole blood. Subsequent platelet adhesion to damaged endothelium and the platelet release reaction initiates the coagulation cascade

Conditions in which Roth spots are observed

- subacute bacterial endocarditis
- leukaemias
- anaemia
- anoxia
- carbon monoxide poisoning
- prolonged intubation during anaesthesia
- hypertensive retinopathy
- pre-eclampsia
- diabetic retinopathy
- neonatal birth trauma
- mothers who have undergone traumatic deliveries
- battered children / shaken baby syndrome
- intracranial haemorrhage from arteriovenous malformation
- ocular decompression following trabeculectomy

Box 1

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Case report

A 62-year-old Caucasian woman presented to the eye clinic complaining of visual disturbance. She reported seeing 'half moon' shaped shadows over both eyes since an episode of flu-like illness 2 months earlier. She also complained of fatigue. She was being treated for hypertension. There was no other significant medical history. On ophthalmic examination, her visual acuity was 6/4 in both eyes. She was noted to have pale conjunctiva. Fundal examination revealed multiple white-centred retinal haemorrhages scattered in the posterior poles of both eyes (figure 2). General examination revealed a blood pressure of 150/90 mmHg, a 2-cm liver edge and multiple purpuric spots over both legs.

Laboratory investigations showed a pancytopenia (haemoglobin 5.8 g/dl, leucocytes $3.9 \times 10^9/l$, platelets $4 \times 10^9/l$), and the presence of blast cells in the peripheral blood film suggestive of acute myeloid leukaemia. The diagnosis was confirmed by a bone marrow biopsy later the same day. She was entered into the Medical Research Council UK Acute Myeloblastic Leukaemia XI Trial and was randomised to receive the MAC schedule (mitoxantrone, arabinoside, cytosine).

Box 2

Diagnostic features and investigations in adults with Roth spots

History

- subacute bacterial endocarditis, leukaemias: fever, night sweat, weight loss
- anaemia, fatigue, shortness of breath on exertion
- hypertension and diabetes

Examination

- subacute bacterial endocarditis: fever, signs of anaemia, cardiac murmurs, clubbing, splinter haemorrhages, Osler's nodes
- leukaemias: hepatosplenomegaly, signs of thrombocytopenia (mucosal and skin petechiae and purpura)
- blood pressure

Laboratory investigations

- full blood count (FBC): anaemia, thrombocytopenia
- peripheral blood film: may be indicated if FBC is suggestive of leukaemia
- erythrocyte sedimentation rate, C-reactive protein: raised in subacute infective endocarditis
- blood culture: if subacute bacterial endocarditis is suspected
- random blood glucose: undiagnosed diabetes mellitus

Box 3

Figure 1 Typical appearance of Roth spots

Figure 2 Fundus appearance of the patient in the case report with acute monocytic leukaemia

that results in the formation of a platelet-fibrin thrombus. Morphologically, this fibrin thrombus appears as a pale white lesion in the centre of the haemorrhage. It is difficult to account for the relative rarity of a white centre in the retinal haemorrhages seen in common diseases. It may be argued that they reflect a relatively acute systemic change rather than the more gradual changes seen in diabetes and hypertension.

A variety of insults can result in retinal capillary rupture. The conditions listed in box 1 in which white-centred haemorrhages are observed, can be subclassified according to common underlying mechanisms resulting in capillary rupture. In subacute bacterial endocarditis, for example, thrombocytopenia secondary to a low grade disseminated intravascular coagulopathy can predispose to capillary bleeding in the retinal vasculature. Similarly, thrombocytopenia in acute leukaemia can cause haemorrhages in the retina, on mucosal surfaces and in the skin. Indeed, there is an association between the presence of retinal haemorrhages and thrombocytopenia in leukaemia at the time of diagnosis.⁸ Anaemia may cause further anoxic insult to retinal capillaries in patients with subacute bacterial endocarditis and leukaemia.

Ischaemic insults to the capillary endothelium of whatever aetiology, perhaps associated with elevated venous pressure, also lead to retinal haemorrhages. It is therefore not surprising that anaemia, anoxia, carbon monoxide poisoning and prolonged difficult intubation are all associated with Roth spots.

Hypertension, pre-eclampsia and diabetes are all conditions associated with increased capillary fragility. Micro-aneurysms have been found at the centre of many diabetic white-centred retinal haemorrhages.⁹ An elevated venous pressure is the common predisposing factor for retinal haemorrhages in neonatal birth trauma, traumatic deliveries in mothers, battered baby syndrome and intracranial haemorrhages. It is also interesting that Roth spots have been found in eyes that have undergone acute surgical reduction of intracranial pressure,¹⁰ perhaps the clearest illustration that mechanical trauma to the delicate retinal vasculature underlies the development of Roth spots.

Conclusion

Roth spots occur in a wide variety of conditions. Although seemingly diverse and unrelated, they show a common predisposition to retinal capillary bleeding. It is important to remember that the Roth spot is a morphological manifestation of retinal capillary rupture and the ensuing reparative process, and as such is a nonspecific sign. The underlying cause must be carefully sought by a systematic approach in history taking, clinical examination and the judicious use of laboratory investigations (box 3).

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