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Anaemia – More than Meets the Eye

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ABSTRACT

Anaemia is a commonly encountered medical condition, although associated ophthalmic manifestations are not often sought or recognised. The authors present a case report of a patient with severe vitamin B_{12} deficiency anaemia with florid retinal changes classical of anaemic retinopathy. A review of the ocular involvement in anaemia is also presented.

Keywords: anaemia, vitamin B_{12} deficiency, anaemic retinopathy

INTRODUCTION

Anaemia is defined as a decrease in the circulating red blood cell mass. The lower limit of the normal haematocrit value in males is 40% (equivalent to haemoglobin 14 g%) and 37% (haemoglobin 12 g%) in females. This abnormality may be associated with a reduction in one or more of the other blood elements, for example, platelets. Many causes of anaemia have been described, although one can broadly classify them into deficiency of red blood cell production, anaemias secondary to blood loss and haemolytic anaemias (Table I).

We present, in this article, a case report of a patient diagnosed with vitamin B_{12} deficiency, who presented with deterioration of vision and was referred for ophthalmological assessment. We also review the various ocular manifestations reported in literature, and their clinical significance, which might be useful to haematologists and general physicians in their management of anaemic patients.

CASE REPORT

The patient is a 37-year-old Indian male chronic alcohol drinker of 12 years, and diagnosed with alcoholic liver cirrhosis five years ago, who was admitted with severe anaemia of haemoglobin 2.1 g%. He complained of blurring of vision of both eyes for a duration of several weeks.

On ophthalmic examination, his best-corrected visual acuity was 6/30 OD and 6/24 OS. There was marked conjunctival pallor but no haemorrhages were noted. The intraocular pressures were normal. There was no relative afferent pupillary defect, and no lenticular opacities were found. Extraocular eye movements were full in all directions. Visual fields by confrontation was normal.

There were significant fundal changes in both eyes (Figs 1 & 2). Multiple flame-shape and blot haemorrhages were scattered throughout the posterior pole. There were several Roth's spots seen, as well as marked venous engorgement and tortuosity. No frank central retinal vein occlusion was present. Cotton-wool spots and exudates were absent. The discs were not choked and there was no macular oedema. A diagnosis of anaemic retinopathy was made.

Systemic examination revealed mild hepatomegaly, with no splenomegaly or lymphadenopathy. There were no skin petechiae or mucous membrane haemorrhages noted. No peripheral neuropathy was detected. He did not demonstrate any other neurological deficits. The patient refused a gastroscopic examination and bone marrow aspiration.

Table I – Classification of anaemia

A. Inadequate erythropoiesis
- 1 lack of essential nutrients eg. iron, vitamin B_{12}, folic acid
- 2 bone marrow injury eg. ionising radiation
- 3 marrow inhibition eg. cytotoxic drugs
- 4 marrow replacement eg. neoplasm, fibrosis, myelodysplasia
- 5 hereditary defect
- 6 endocrine deficiency eg. hypothyroidism, hypopituitarism, renal failure
- 7 idiopathic – "refractory"

B. Bleeding
- 1 Acute
- 2 Chronic

C. Haemolytic
- 1 Intracorpuscular defect
  - a abnormal haemoglobin (S,C,D,E)
  - b defective globin synthesis (thalassaemia)
  - c defective haem synthesis (porphyria)
  - d defective enzyme (G6PD, pyruvate kinase)
  - e membrane defect (hereditary spherocytosis, elliptocytosis)
  - f paroxysmal nocturnal haemoglobinuria
- 2 Extracorpuscular defect
  - a Primary, idiopathic, usually autoimmune
  - b Secondary to
    - i physical agents eg. water, thermal injury, microangiopathy
    - ii chemical agents eg. venom, drugs
    - iii infection eg. malaria, septicaemia
    - iv neoplasm eg. lymphoma
    - v collagen vascular disease eg. systemic lupus erythematosus
    - vi splenomegaly
    - vii paroxysmal cold haemoglobinuria

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Investigations

Haemoglobin	:	2.1 g% (Haematocrit: 6.1%)
MCV	:	89.5 fL
MCHC	:	34.5 g/dL (normocytic, normochromic)
Platelets	:	30,000/mm^3
Total white	:	5,900/mm^3
Differential count	:	normal
Peripheral blood film	:	most of the red blood cells were normocytic with a few macrocytes. No blasts were seen and features of myelodysplastic disease were absent
Serum B_{12}	:	106 pmol/L (132 – 835)
Serum folate	:	4 nmol/L (5 – 38)
Serum iron, TIBC (post-transfusion)	:	normal
Liver Function Test	:	AST, ALT, GGT, bilirubin all raised Albumin 38 g/L (normal) Total protein 61 g/L (low normal)

DIAGNOSIS

A clinical diagnosis of alcoholic liver disease with vitamin B_{12} and folate deficiency anaemia was made.

Treatment

A total of four pints of packed red blood cells were transfused and 3000 μg of cobalamin parenterally administered over two sessions.

DISCUSSION

Introduction

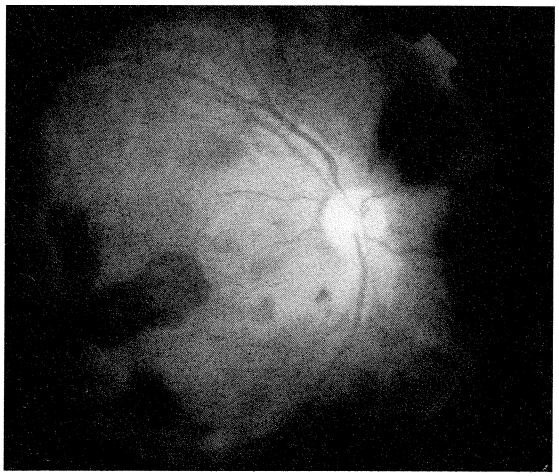
Retinal haemorrhages and exudates were already recognised and described in patients with blood disease during the latter part of the 19th century. Liebrich (1863) was cited by Gowers in 1904 as the first to describe retinal haemorrhages in acute leukaemia[1]. Some years later, Mackenzie described retinal haemorrhages in two patients with severe pernicious anaemia, although the clinical details suggested instead that one of these may have had acute leukaemia. In the first major review of the subject, Moore described the fundal features of nearly 100 patients afflicted with a variety of blood disorders, including anaemia[2]. One of the first to report retinal changes specific to anaemia was Fuchs, in his landmark work *Lehrbuch der Augenheilkunde* in 1926[3].

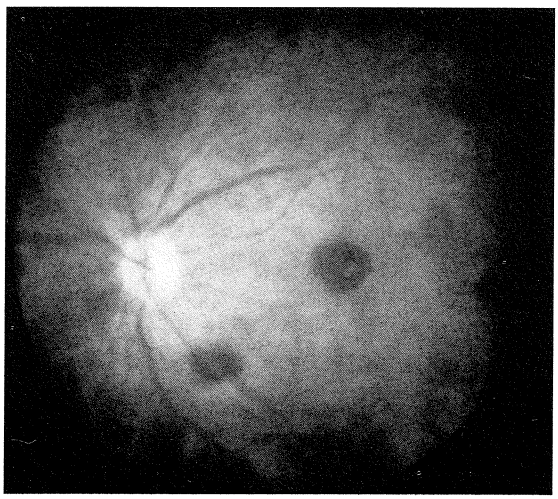
Since then, there have been several reports of the various retinal manifestations seen in anaemia. In a major study of 152 anaemic patients, Holt attempted to define the incidence of retinopathy in the various disorders of blood, whether lesions were of any diagnostic importance, and whether these abnormalities could be related to blood counts and prognosis. He found that 51 patients (about a third) had retinopathy, which were diagnostic of the underlying anaemia[4].

Clinical features of anaemic retinopathy

Merin's series described the various forms of haemorrhages in anaemia: streak (superficial retina), dot and blot (deeper retinal), round, splinter, flame-shaped, punctate, haemorrhages with pale centres (Roth's spots), boat-shaped subhyaloid, breakthrough vitreous haemorrhages; cotton-wool spots and hard exudates are occasionally seen as well[5]. Other clinical abnormalities observed are venous tortuosity and engorgement which may even develop into frank central venous occlusion[6,7].

There is evidence that severe anaemia may exacerbate diabetic retinopathy[8]. Shorb described the progression of three patients with mild to moderate diabetic retinopathy to severe proliferative disease when they developed severe iron deficiency anaemia. An exotic case of haemorrhagic retinoschisis was attributed to aplastic anaemia[9]. Rarely, perivascular sheathing can be seen and Marshal has reported a case with disc oedema[10]. Whether the latter sign is related to anaemia itself, or as a result of leukaemic infiltration is unclear and not elaborated. All these features should be looked for in a classical anaemic patient with conjunctival pallor. In fact, intraocular haemorrhages may have systemic counterparts in cutaneous and mucous membranes elsewhere, including the conjunctiva. Cranial nerve palsy has been known to occur in severe pernicious anaemia.





Figs 1 & 2 (above) – Colour fundus photographs of right and left eyes respectively, showing florid changes typical of anaemic retinopathy, including multiple flame shaped and blot retinal haemorrhages scattered throughout the posterior pole. Note the presence of Roth's spots (retinal haemorrhage surrounding an area of central pallor) and engorgement and tortuosity of the retinal veins.

Pathogenesis

Little is known of the pathogenesis of these lesions, but several causative factors have been implicated. Duke-Elder postulated that anaemia results in diminished capillary oxygenation, producing increased permeability and ultimately extravasation of blood and its products[11]. An alteration in vascular integrity features prominently in most theories, among them that put forward by Ballantyne[12]. Others have speculated that the natural aging process of retinal vessels predisposed an individual to the deleterious effects of anaemia on the retina. Venous changes, such as alterations in calibre and tortuosity, are certainly not unique to anaemia. A variety of disorders, including diabetes mellitus (pre-proliferative retinopathy), hypertension, leukaemia, multiple myeloma, Waldenstrom's macroglobulinaemia and sickle cell disease (Table II) are known to result in these same changes.

Table II – Causes of venous tortuosity

1. Carotid-cavernous fistula
2. Central retinal vein occlusion
3. Congenital tortuosity and dilatation of retinal vessels
4. Diabetes mellitus
5. Leukaemia
6. Lymphoma
7. Macroglobulinaemia (Waldenstrom syndrome)
8. Multiple myeloma
9. Polycythaemia vera
10. Sickle cell disease
11. Syphilis

Table III – Causes of Roth's spots

1. Collagen vascular disease
2. Blood disorders
   a) anaemias
   b) leukaemia
   c) multiple myeloma
3. Septic retinitis
   a) candida albicans
   b) rheumatic valvulitis
   c) infective endocarditis

Associated and contributing factors

There seems to be a correlation between the severity of anaemia and the presence of anaemic retinopathy. Fundal abnormalities probably do not occur unless the haemoglobin level falls to below 8 g%. Various arbitrary threshold haematocrits have been proposed: Ballantyne and Michaelson mentioned 50% as the critical haematocrit below which retinal haemorrhages occur. Kearns claimed that retinal changes occurred consistently if haematocrit fell to less than 35%[13]. Merin pointed out that the lower the haemoglobin, the more severe was the retinopathy[5]. All their patients with haemoglobin levels below 3 g% demonstrated some form of retinal change or other. Aisen's review suggests a significant correlation between venous length (a method of quantifying the degree of venous tortuosity) and haematocrit levels. This, ultimately, might be the more important significant feature of anaemic retinopathy, rather than the pure presence or absence of haemorrhages.

The coexistence of thrombocytopaenia is an important factor in determining the risk and severity of anaemic retinopathy. With anaemia alone, only 10% of patients developed retinal haemorrhages in Rubenstein's series, while in the presence of both anaemia and thrombocytopaenia, that incidence rose to 70%. Conversely, it is extremely uncommon to find retinal haemorrhages in purely thrombocytopaenic patients, as reports of idiopathic thrombocytopaenic purpura and other like conditions have revealed. The conclusion, therefore, that anoxia alone (anaemia) usually does not cause retinal haemorrhages as long as sufficient platelets are present to ensure the integrity of the capillary endothelium, does bear some merit.

Interestingly, children with a similar severity of anaemia seem to be more resistant to the development of anaemic retinopathy than adults. Merin and Freund found that none of their patients below 15 years of age had retinopathy, compared with an incidence of 46% in those above that age. Perhaps, as proposed by Fuchs and Duke-Elder, the aging of retinal blood vessels or prolonged exposure of adult vessels to the deleterious effects of anaemia may account for this phenomenon.

There does not seem to be any particular pathognomonic feature associated with specific aetiologies of anaemia. Identical abnormalities are found in leukaemia, haemolytic anaemia, aplastic anaemia, pernicious anaemia, iron deficiency anaemia, anaemia from blood loss and multiple myeloma. The much-touted Roth's spot is nothing more than a description of retinal haemorrhage surrounding an area of central pallor. This sign was originally thought to be diagnostic of leukaemic infiltrates in the retina, but since then, it has been seen in all other conditions causing anaemia, and even infective endocarditis and collagen vascular diseases (Table III). The white areas may represent true leukaemic infiltrates in some cases, or swollen degenerating nerve fibres in others. With particular reference to our case in question, no unique features associated with megaloblastic anaemia can be found. The retinal abnormalities invariably clear with treatment, usually within weeks of administration of vitamin B_{12}.

Loss of vision may result from retinal or pre-retinal bleeding, or from macular oedema in unusual cases in which a central retinal vein occlusion develops. However, if it is detected early, and when appropriate therapy is directed toward correcting the underlying systemic problem, visual problems can resolve within a period of weeks.

The next time you are faced with an anaemic patient, a look into the eyes may impart to you a wealth of pertinent information.

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