Correspondence

Another cause of anaemia

Sir,

Renal impairment is commonly associated with normocytic anaemia, due to relative deficiency of erythropoietin, and it is now standard practice to treat this with recombinant human erythropoietin (r-HuEPO) once other causes of anaemia have been excluded. Recurrent anaemia in this setting may be due to occult gastrointestinal blood loss, and this is the most common cause of anaemia, but pure red cell aplasia (PRCA) secondary to an antibody to human recombinant erythropoietin also needs to be considered. We present such a case.

An 80-year-old man, with a 19-year history of non-insulin-dependent diabetes mellitus complicated by diabetic retinopathy, diabetic nephropathy, obesity and congestive heart failure, was admitted to our hospital with lethargy and haemoglobin (Hb) of 6.7 g/dl. His red cell indices (MCV 92.7 fl, MCH 33.7 pg, MCHC 35.8 g/l) and haematocritics (B12 673 ng/l, folate 6.5 ng/ml) were within the normal range. White cell count was 4.3 × 10^9/l and platelets were 64 × 10^9/l. Iron (41.9 μmol/l), ferritin (626 μg/l) and transferrin index (1.67%) were elevated, but he was known to be receiving iron infusion at a Renal Unit in a different hospital, where he had also been receiving Eprex (human recombinant erythropoietin α) injections. Blood film showed normocytic normochromic picture with low platelets, a few burr cells and rouleaux formation. Reticulocytes were absent (Figure 1). There was no obvious cause of an acute blood loss, although his Hb dropped significantly from the baseline value of 10.5 g/dl, and urea almost doubled from its baseline value of 34.0 mmol/l. An upper gastrointestinal endoscopy showed no source of bleeding, and he was transfused with three units of blood, resulting in Hb rising to 8.1 g/dl. However, he remained lethargic and in 3 weeks his Hb dropped to 5.1 g/dl, requiring eight units of blood in total to correct it to 10.0 g/dl. A myeloma screen was negative, as was a direct Coombs test. Barium enema showed minor diverticular disease in the sigmoid region. Erythropoietin levels were undetectable (<2.5 U/l). Bone-marrow aspiration showed complete absence of erythroid activity, but normal leucopoiesis and megakaryopoiesis (Figure 2). The trephine confirmed this, and a diagnosis of pure red cell aplasia was made. The results of serological tests for parvovirus B19, Epstein-Barr virus, hepatitis viruses and cytomegalovirus were negative. Eprex was stopped and a sample taken for anti-erythropoietin antibody. He was re-admitted with heart failure and sepsis, and unfortunately died, despite correction of his anaemia. A report of positive neutralizing anti-erythropoietin antibody was received after his death. Immunosuppressive therapy was considered, but as our patient had significant comorbidities, it was felt that this would not be appropriate, and we instead chose to correct his anaemia by regular blood transfusions totalling 17 units over 3 months.

r-HuEPO is widely used in renal medicine, oncology and haematology, and until recently its main side-effects were said to be hypertension, accelerated atherosclerosis, thrombotic events, headache, confusion and flu-like symptoms. It is now established that the treatment of anaemia with r-HuEPO in patients with chronic renal failure may cause pure red cell aplasia (PRCA).1 So far there have been 182 cases reported of suspected PRCA occurring in patients with chronic renal failure who have been treated with r-HuEPO, of whom 88% received Eprex (personal communication, Janssen-Cilag). The mechanism of r-HuEPO induced PRCA is not clear, but seems unrelated to the type of renal disease, dose of r-HuEPO, or whether patients are on renal replacement treatment or not. There is however some concern that the route of administration may affect the likelihood of developing anti-rHuEPO antibodies, as most of the patients received r-HuEPO subcutaneously. Our patient had diabetic nephropathy and deteriorating renal function, but was not on renal replacement therapy. He received 2 years of subcutaneous Eprex before developing PRCA.

PRCA is a progressively developing anaemia, with a near absence of red-cell precursors in bone marrow, while megakaryocytes and white-cell precursors are usually present at normal levels.2 The most common form of PRCA is an acute self-limiting form secondary to viral (particularly...
parvovirus B19) or drug-induced impairment of erythroid progenitor cells. The chronic form is associated with thymomas and autoimmune disorders. The diagnosis of PRCA must be made on assessment of the bone marrow after exclusion of other causes of anaemia. The diagnosis of EPO-induced PRCA should be based on the clinical presentation, the absence of red-cell precursors in the bone marrow and the presence of anti-EPO antibodies, whilst regular checking of the reticulocyte count may be an easy repeatable test for early detection of anaemia in patients on rHuEPO therapy.

Figure 1. Blood film.

Figure 2. Bone-marrow aspirate.

References

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