Dear Sir,

We report a case of pure red blood cell aplasia (PRBCA) induced by azathioprine (AZA) in a renal transplant recipient. K.L.T., a 30-year-old male, presented with chronic glomerulonephritis with end-stage renal failure in 1984 and underwent renal transplantation in March 1985. He was put on prednisolone and AZA (2 mg/kg/day). On the 15th postoperative day he developed leucopenia. The dose of AZA was temporarily decreased to 1.5 mg/kg/day. In spite of his normal renal function, his haemoglobin (Hb) continued to remain low near 7-8 g% even 6 months after transplantation. Slowly his Hb picked up, but in November 1986 it dropped again to 8.3 g%. At this time detail investigations revealed: Hb 8.5 g%, total leucocyte count 6,300/mm³, reticulocyte count 3.3%, red cells showed anisocytosis, poikilocytosis and macrocytes. Mean corpuscular volume was 108 mm³. Red blood cell count was 5.2 million/mm³. Coomb’s test was negative. Bone marrow aspiration was normal. In view of the macrocytosis, a trial of vitamin B₁₂ and folic acid was given. His Hb slowly increased to normal within 2 months. The Hb remained normal till 8 months later, when it dropped to 8.2 g%. Treatment with vitamin B₁₂ and folic acid was restarted, but this time his Hb did not increase. Considering AZA-induced toxicity cyclosporine was started in the dose of 2 mg/kg/day, and AZA was decreased to 0.75 mg/kg/day. His Hb increased to 12.5 g%, but to avoid long-term nephrotoxicity, cyclosporine was stopped, and the patient was put again on AZA (2 mg/kg/day). Within a few months his Hb dropped again to 7.6 g% with a reticulocyte count of 1.5%. Bone marrow biopsy at this time revealed normal myeloid and megakaryocytic elements but severe paucity of erythroid cells. AZA was stopped, and cyclosporine was started (2 mg/kg/day). His Hb became 12.6 g% in a month’s time. At this time a repeat bone marrow biopsy was normal.

AZA can commonly cause leucopenia, predominantly granulocytopenia and megaloblastic erythropoiesis [1], but PRBCA has also been reported in the past. The first 2 cases of PRBCA
due to AZA were reported by McGrath et al. [2] in 1975. Since then only 4 more cases of AZA-induced PRBCA have been reported so far. All developed PRBCA after many years of AZA therapy, which suggests that a cumulative dose of the drug is responsible for it.

Previous studies [2, 3] had suggested that an increase in mean corpuscular volume can be used as a marker for impending erythrocyte aplasia. However, Old et al. [4] reported 2 cases of PRBCA due to AZA in which mean corpuscular volume was normal.

PRBCA is known to be caused by chronic haemolytic diseases, chronic infections, autoimmune diseases, severe nutritional deficiency, thymoma, haematological malignancy and drugs like anticonvulsants, iso-niazid and chloramphenicol [5]. None of the above causes was present in our case. The mechanism of selective erythroid hypoplasia is poorly understood. The high level of erythropoietin activity in some cases reported so far suggests that AZA does not inhibit erythropoietin [1]. Aplasia can be cured only once AZA has been stopped. Hb improves very rapidly, and in most of the cases the patient becomes normal in a month’s time. McGrath et al. [2] and Declerck et al. [1] could manage their patients after restarting AZA in low doses, but in the patients reported by Hogge et al. [3] and in the present case, even a lower dose of AZA continued to keep Hb at a low level. Old et al. [4] and Hogge et al. [3] ultimately started cyclophosphamide.

We conclude that AZA can cause PRBCA in renal transplant patients. It is a complication which is related to cumulative doses of AZA and requires its withdrawal for complete recoveries. Once aplasia recovers, a trial of a low dose of AZA can be given, but usually other drugs have to be used in place of AZA.

References