Myelodysplasia and Acute Myeloid Leukaemia in a Case of Rheumatoid Arthritis with Secondary Amyloidosis Treated with Chlorambucil

C Balakrishnan*, E Pathan*, S Khodaiji**, A Dasgupta**, G Mangat*, VR Joshi*

Abstract
Immunosuppressive therapy related secondary haematologic malignancy is well reported. A 52 years lady with established rheumatoid arthritis developed reactive amyloidosis. This was initially treated with colchicine and cyclophosphamide and later with chlorambucil. Ten months after stopping chlorambucil she developed pancytopenia and vitamin B12 deficient megaloblastic anaemia. The pancytopenia was refractory to vitamin B12 supplements and a repeat bone marrow confirmed myelodysplasia (FAB1 RAEB-T). Within three weeks of this diagnosis she evolved into acute myeloid leukaemia and expired due to refractory thrombocytopenia and uncontrolled bleeding. This case stresses the need for long term follow up of RA patients treated with alkylating agents.

INTRODUCTION
Increased incidence of malignancies has been reported in rheumatoid arthritis (RA) patients treated with disease modifying agents and immunosuppressive therapy. We have already published our experience with chlorambucil therapy in RA patients with reactive AA amyloidosis.1 We report one such patient who developed refractory anaemia, myelodysplasia (MDS) and acute myelogenous leukaemia after treatment with chlorambucil and, discuss the relevant literature.

CASE REPORT
Mrs. KJ was a 52 years lady, when first seen at our clinic in 1988, had established RA of 12 years duration. The arthritis was controlled on non-steroidal anti-inflammatory drugs (NSAIDs) and d-penicillamine 250 mg daily. There were no extra-articular features. Since then till 1997, she visited the clinic intermittently. During this period the disease control was variable and she received small dose prednisolone, injectable gold, d-penicillamine, methotrexate, chloroquine and levamisole singly or in combination with variable responses. She underwent bilateral knee replacement in 1990. In 1994, she developed angina and was found to have triple vessel coronary artery disease, which was treated conservatively.

In March 1997, the arthritis was stable but she developed proteinuria (1.76 gm/day) and mildly elevated creatinine of 1.2 mg/dl (0.5-0.9). Kidney biopsy confirmed amyloidosis. She was treated initially with colchicine (0.5 mg/bd), prednisolone (5 mg/d) and oral cyclophosphamide (2 mg/kg/d). In October 1997, cyclophosphamide was stopped since it produced recalcitrant oral ulcers and odynophagia. In February 1998, chlorambucil 2 mg/d was started. By May 1998, the optimal dose of 6 mg/d was reached. However, chlorambucil had to be discontinued in August 1998 due to progressive leucopenia (WBC = 3800/mm³). From September 1998 till May 2000 efforts were made to re-introduce chlorambucil but recurrent leucopenia prevented administration of optimal dosage for an adequate period. From then onwards she was treated with prednisolone 5 mg daily and colchicine 0.5 mg daily.

In April 2001, she complained of fatigue and asthenia. The arthritis was quiescent; and the proteinuria had persisted (24 hour proteinuria = 1.04 g/day). Investigations showed: Hb:8.8 gm/dl (MCV : 106.7 fl), WBC:6800/mm³, platelets: 54,000/mm³, serum B12:167 pg/dl (200-950) and RBC folate: 2019 ng/ml (175-700). Bone marrow revealed megaloblastic erythropoiesis. There was no clinical evidence of malabsorption. She was treated with parenteral cyanocobalamin. Although by August 2001, the haemoglobin improved to 9.4 gm/dl, the macrocytosis (MCV = 113.5 fl) and thrombocytopenia persisted.

In November 2001, she was admitted with fatigue, dyspnoea, cough, blood-streaked expectoration, anaemia and thrombocytopenia. Chest radiograph revealed bilateral fluffy...
opacities. High resolution CT was suggestive of bronchiolitis obliterans with obstructive pneumonia (BOOP). Bronchoalveolar lavage fluid was negative for infection. Transbronchial biopsy was avoided because of thrombocytopenia. Treatment with high dose steroid therapy resulted in complete resolution of the chest shadows in three days time.

Reports of haematological investigations at this stage were- Hb: 5.7 gm/dl (MCV: 124.7 fl, MCH: 41.4 pg, MCHC: 33.2%), WBC: 8800/mm³ (N70 L11 M19), platelet count: 41,000/mm³. Peripheral smear showed macrocytic anaemia and reduced platelets. The reticulocyte count was 0.04%. Iron binding studies showed serum iron: 71 microgram/dl (Normal range (NR): 40-130), TIBC: 434 microgram/dl (NR: 235-400), transferrin saturation: 16.4% (RN:20-40%). Coomb’s test: negative, serum B12: 8126 pg (NR: 200-950) and RBC folate: 2893 ng (NR:175-700). The bone marrow examination was repeated. It confirmed refractory anaemia with excess blasts in transformation (20-28%) (FAB, RAEB-t) (Fig. 1). Peripheral blood showed an excess of monocytes (17%). She was treated with packed red cell and platelet transfusions and discharged on 40 mg/day prednisolone (started for BOOP).

After discharge she evolved into frank acute myeloid leukaemia. Cytarabine A and thalidomide were started after consultation with a haemat-oncologist. However within three weeks of discharge she was readmitted with refractory thrombocytopenia and succumbed to uncontrolled bleeding. Her peripheral smear at this point showed 70% monocytes and promonocytes. Serial haematologic parameters and treatment are shown in Table 1.

## DISCUSSION

Malignancies reported in rheumatoid arthritis (RA) include leukaemia, non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, lung carcinoma, skin carcinoma, colorectal and breast malignancies.²

Patients with RA have a two-fold higher rate of leukaemia than expected.³ Immune aberration due to RA and the immunosuppressive drugs used in its management have both been implicated. Although the patient was initially treated with cyclophosphamide for a short period, the temporal profile and the rapidity of progression makes us suspect chlorambucil as a cause of the MDS/leukaemia.

Alkylating agent-induced myelodysplasia/leukaemia has been reported in rheumatology literature.³ These agents cause cessation of DNA replication, chromosome loss and change in sterometric configuration of DNA bases leading to mutagenesis and leukaemogenesis. Therapy related acute non-lymphocytic leukemias are preceded by MDS in 70% of cases. Cytogenetic studies show loss of whole chromosome 5 and/or 7 or various parts of the long arms of these chromosomes.⁴ cytogenetic studies were not done in our patient.

Therapy-related acute leukaemias have a dismal prognosis. Therapy with cytosine arabinoside, danazol and growth factors GM-CSF and G-CSF, has added little to the survival of these patients.⁴ Unfortunately many of these patients are ineligible for bone marrow transplantation due to advanced age, co-morbid conditions or lack of an appropriate HLA-matched donor.

Marrow stromal derangements in MDS include increased paracrine production of inhibitory cytokines like TNF alpha.
Recently, encouraging results have been obtained with TNF alpha blockers and thalidomide both of which diminish the inhibitory effects of TNF alpha.5

Chlorambucil has been used effectively in a proportion of patients with reactive secondary amyloidosis.6 In our patient one could not attain optimal therapy with chlorambucil due to leucopaenia. The interval between the initiation of therapy and development of MDS was 38 months and acute leukemia developed 9 months after the diagnosis of MDS. MDS has been reported previously to occur within 24 onths of chlorambucil therapy.6 Although thalidomide and cytarabine were tried in our patient, the MDS ran an uncontrolled course ending fatally. This communication highlights the oncogenic potential of chlorambucil and patients treated with this drug should be followed up carefully.

REFERENCES