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CASE REPORT

Therapy-related acute myeloid leukaemia following immunosuppression with azathioprine for polymyositis

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Summary A 52-year-old man developed therapy-related acute myeloid leukemia (AML) following prolonged immunosuppression with azathioprine for polymyositis. Karyotypic analysis showed deletions of the short arm of chromosome 7 and the long arm of chromosome 5. The importance of recognizing this potential complication while treating benign rheumatological and immunological diseases with purine analogues like azathioprine is emphasized. Therapy-related AML is a poor prognostic group that does not respond favourably to standard induction therapy.

Keywords: polymyositis, azathioprine, acute myeloid leukaemia

Therapy-related acute myeloid leukaemia is a well recognized complication following cytotoxic therapy with alkylating agents (cyclophosphamide, busulfan, chlorambucil, melphalan and nitrogen mustards) in various malignant and benign conditions (Louie & Schwartz 1978; Frisch, Bartl & Chaichik 1986). Rarely, purine analogues like azathioprine have been known to cause lymphomas, solid tumours and acute myeloid leukaemia in patients on long-term immunosuppression for various conditions like primary biliary cirrhosis (Louie *et al.* 1978), rheumatoid arthritis (Seidenfeld *et al.* 1984), systemic lupus erythematosus (Vasquez *et al.* 1992), systemic sclerosis (Tulliez *et al.* 1974) and renal transplant recipients (Hoy, Packman & Freeman 1982).

We report a case of acute myeloid leukaemia following treatment of polymyositis with azathioprine.

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Case report

A 52-year-old man was admitted to the University of Michigan Medical Center in February 1993 with a four-week history of fever, night sweats, fatigue and cough associated with pancytopenia.

His past medical history was significant for polymyositis and Hashimoto's thyroiditis diagnosed in 1984 when he presented with neck muscle weakness, inability to keep his head up, difficulty in rising from the chair and raising his arms above his head. Examination was significant for decreased strength in the sternocleidomastoids, weak head extension, and decreased bulk in the shoulder muscles and biceps. Electromyography was consistent with a chronic myopathy and muscle biopsy showed mild focal degeneration and mononuclear cell infiltration.

Creatine phosphokinase (CPK) levels were 346 U/l (normal 30–225). Thyroid function tests were consistent with hypothyroidism with TSH of 12 mU/l (normal 0–7) and serum T_4 0.04 mmoles/l (normal 0.06–0.15). He also had high titre anti-microsomal antibodies with titres of 1 in 6400 (normal less than 1 in 400). ESR was 54 mm/h. Autoantibody screen was negative. Complement levels were normal. He was initially treated with prednisone and thyroxine replacement and subsequently changed to azathioprine because he developed diabetic coma while on the steroids. He was started on 250 mg of azathioprine daily in 1984 and reduced to 100 mg in 1989 and tapered to 50 mg in 1991. The symptoms of polymyositis were well controlled on this immunosuppressive regime but repeat electromyography continued to show evidence of ongoing inflammation and denervation in the form of high amplitude fibrillation potentials in the paraspinal muscles. He was hence maintained on azathioprine. He was regularly followed up with CPK levels and full blood counts. The counts were normal till February 1993 when he was found to have pancytopenia.

Physical examination in 1993 revealed an obese man who was febrile with a temperature 100.4°F, pulse 78/min, respiratory rate 16/min and blood pressure 138/70 mm Hg. He had oropharyngeal petechiae and a 1 cm mobile right axillary lymph node. There was no hepatosplenomegaly. There was no obvious muscle weakness.

Laboratory examination revealed haemoglobin 8.6 g/dl, WBC 2.7×10^9/dl, platelets 13×10^9/dl and a differential count of segs 14%, bands 5%, blasts 7%, eosinophils 3%, monocytes 3% and lymphocytes 57%. The absolute neutrophil count was 0.5×10^9/dl. Liver function tests were normal. Bone marrow examination was consistent with acute myeloid leukaemia (FAB-AML, MO). Flow cytometric immunophenotypic analysis showed CD 13, CD 33, CD 34, CD 45, HLA Dr, CD 11c and CD 15 positivity consistent with acute myeloid leukaemia. Cytogenetics (Figure 1) identified 13 of 18 cells analysed to be abnormal with the karyotype 46, XY, del (5) (q 21), der (7) t(7;?) (p 22; ?); −12, −17, +mar, +mar. Five cells had a normal karyotype with a normal male chromosome complement. The presence of abnormalities in addition to those on chromosomes five and seven were interpreted as signifying a poor prognosis.

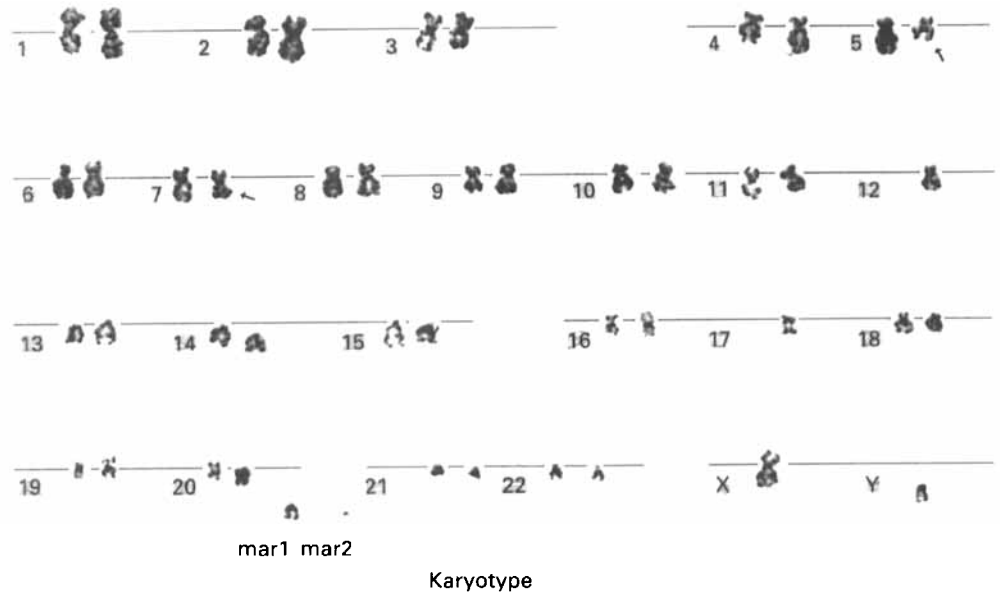

Figure 1. Karyotype showing the deletion of part of the long arm of chromosome 5 and derivative chromosome 7 (arrows) and the two marker chromosomes, labelled mar1 and mar2. These abnormalities were seen in 13 of 18 cells; a 46, XY, normal karyotype was seen in the remaining five cells.

He was treated on a standard induction regime with daunorubicin at 45 mg/m^2 on days 1 to 3 and cytosine arabinoside at 100 mg/m^2 on days 1 to 7. The repeat bone marrow examination performed after the counts had recovered following induction showed hypercellularity and the presence of all three cell lines with no residual leukemia; in addition there was hyperplasia, atypicality and clustering of megakaryocytes consistent with either a myelodysplastic process or an effect of cytotoxic drugs. Repeat cytogenetics revealed the persistence of the abnormal karyotype in 1 of 15 cells studied. He received two cycles of consolidation chemotherapy with daunorubicin and cytosine arabinoside and was in complete remission for two months when he relapsed. All the courses of chemotherapy were complicated by severe hypotension and febrile neutropenia.

Discussion

The occurrence of therapy-related acute myeloid leukaemia in the setting of prolonged immunosuppression for benign rheumatological and immunological conditions is an important complication to be recognized (Levine & Bloomfield 1992). The occurrence of this complication following administration of cytotoxic agents especially alkylating agents for a primary malignancy have been previously described (Sheibani *et al.* 1980). The alkylating agents have been the main agents responsible in causing MDS/AML in nonhaematological diseases. Recently, epipodophyllotoxins and cisplatinum have also been implicated (Levine *et al.*

1992). Occurrence of secondary myelodysplastic syndrome or acute myeloid leukaemia (MDS/AML) following the use of fluorinated pyrimidines, cytidine analogues, antifolates, purine analogues like 6-mercaptopurine and azathioprine, anthracyclines and plant alkaloids have been rare, published as isolated case reports.

The occurrence of AML in azathioprine treated patients was first described in 1974 (Silvergleid & Schrier 1974) and since then there have been only few cases reported (Alexson & Brandt 1977; Gilmore, Holden & Rodan 1977; Vismans *et al.* 1980). We describe a patient who presented with pancytopenia and acute myeloid leukaemia following nine years of treatment with azathioprine for polymyositis. We were not able to document morphologically any preceding myelodysplastic process in this patient. The minimal dysplastic changes seen in the post-induction marrow could be due to the cytotoxic drugs used during induction therapy. The presence of cytogenetic abnormalities of chromosomes 5 and 7 are seen both in therapy-related MDS and AML and cannot be used to distinguish them reliably (Johansson *et al.* 1991; Heim 1992).

Long term immunosuppression with purine analogues could be complicated by acute myeloid leukaemia. Prognosis of therapy-related AML is poor and only allogenic bone marrow transplantation offers a curative approach (Longmore *et al.* 1990).

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