Dermatomyositis Associated with Acute Myeloid Leukaemia: A Paraneoplastic Association or a Drug-Induced Phenomenon?

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Sir,

Dermatomyositis (DM) is a relatively rare disease of unknown aetiology characterized by an inflammatory condition involving primarily the skin and the striated muscle and its associated vessels. The relationship of DM and neoplastic disease in adult patients was first reported in 1916 by Stertz and Kankeleit. Carcinomas are the most common malignancies found and parallel those observed in the general population: tumours of the lung, breast, uterus, ovary, prostate and gastrointestinal tract. Association with haematological disorders is highly uncommon and the presence of leukaemias in conjunction with DM is extremely rare.

We report here a patient affected by a severe and treatment-resistant DM who, 8 years after receiving multiple immunosuppressants, developed a myelodysplastic syndrome that subsequently transformed into acute myeloid leukaemia.

CASE REPORT

In 1991, a 56-year-old man was admitted to our hospital with periorbital oedema and heliotrope erythema, and erythematous rash over the dorsum of his hands and trunk that had appeared 3 months before. He also complained of progressive diffuse muscle weakness and myalgia.

Initial laboratory examination showed high levels of serum creatine kinase (1077 IU/l; normal range <80 IU/l), serum transaminases (AST 92 IU/l, ALT 52 IU/l; normal ranges <40 IU/l), aldolase (32 IU/l; normal value <3.1 IU/l) and lactic dehydrogenase (778 IU/l; normal range 120–240 IU/l). Mild but persistent haematological abnormalities were also present at diagnosis (leukocytes 3800/μl, neutrophils 2200/μl and lymphocytes 730/μl). Serum antinuclear autoantibodies were absent. No evidence of antibodies to extractable nuclear antigen (ENA) or to anti-aminoacyl-transfer-RNA-synthetase (Jo-1) was found. Skin and muscle biopsies and electromyogram findings confirmed the diagnosis of DM. A search for possible malignancies was carried out with negative results in the initial investigations.

The patient was first treated with oral prednisone at a dose of 1 mg/kg per day for 3 months, but azathioprine and chloroquine (100 and 150 mg/day, respectively) were added to the regimen due to unresponsiveness of severe cutaneous lesions. As no improvement was observed, the regimen was subsequently changed to oral prednisone and oral cyclosporine (2.5–3 mg/kg daily). High-dose intravenous immunoglobulin therapy was also attempted, due to severe treatment-resistant DM. Nine cycles were administered 4 days per month at a monthly dose of 2 g. Cyclophosphamide treatment was initiated when immunoglobulin was ineffective, and it was administered over 2 years, always in combination with oral prednisone ranging between 0.5 and 1 mg/kg. Despite the combined therapy, it was not possible to taper off the corticoids and the patient even required different adjuvant treatments on several occasions due to the presence of life-threatening flare-ups and multiple complications.

Ever since the initial diagnosis the patient presented persistently high serum enzyme values, and haematological abnormalities in peripheral blood, including relapsing episodes of severe thrombopenia, anaemia with anisocytosis requiring blood transfusions, eosinophilia and pancytopenia. Periodic complementary studies, including bone marrow analyses, were performed to rule out solid or haematological malignancies over this time. As no malignancies were found, the haematological alterations were considered to be drug-induced. A monoclonal κ-type gammapathy of undetermined significance was the only feature found during this period.

In 1999, while still on cyclophosphamide and prednisone, the patient presented a severe DM exacerbation with erythroderma, and was admitted to our hospital with high fever and malaise. Severe pancytopenia was detected. Finally, a myelodysplastic syndrome, refractory anaemia with excess of blast type (RAEB), was confirmed after repeated bone marrow aspirations and biopsies. Eight months later the RAEB transformed into an acute myeloid leukaemia (AML). The karyotype showed a deletion involving chromosome 7.

The patient received induction chemotherapy with idarubicine, cytarabine and etoposide. Complete response of both DM and AML was observed and the patient remained in remission for a whole year. He then presented a new erythrodermic flare-up of the DM coinciding with a recurrence of AML and died of acute, massive pulmonary bleeding at the age of 66.

DISCUSSION

As patients with DM are often treated with immunosuppressive and even cytostatic agents over many years, it has been suggested that these drugs may heighten the risk of developing cancer, especially haematological disorders (1–3).

Myelodysplastic syndromes (MDS) are myeloid

clonal haemopathies where up to 30% of patients develop a secondary acute leukaemia (usually AML) within 6 months of diagnosis. Cytogenetic abnormalities are common in MDS, and define specific subsets of the disease (4). MDS can be subclassified as primary and secondary or therapy-related MDS. Primary MDS is diagnosed as *de novo* disease while secondary MDS corresponds to cases arising in patients who have previously received leukaemogeneic chemotherapy and/or irradiation. The number of cases in this latter category is increasing: examples are therapy-related MDS secondary to alkylating agents or secondary to DNA topoisomerase II inhibitors.

Only seven cases of leukaemia have been reported in relation to DM. Two of them were paediatric cases with acute lymphoid leukaemia (5, 6). Two others were adults with Philadelphia chromosome positive chronic myelogenous leukaemia, who developed DM subsequently (7, 8). The three remaining cases were adult patients with DM who subsequently developed an AML. The first case was a 38-year-old man who developed an acute granulocytic leukaemia 11 months after diagnosis of DM which was resistant to treatment (9). The second was a 30-year-old man who had DM associated with metastatic seminoma. Four years after surgical excision and chemotherapy, he developed an acute promyelocytic leukaemia (10). The authors discussed the most likely causes of this association, ruling out a therapy-related leukaemia, as no alkylating agents had been used, and no cytogenetic abnormalities were present. The third case was a 62-year-old man with DM, who developed an AML 3 months after diagnosis (11). In this case the authors noted that the DM was probably associated with the AML, as haematological abnormalities were already present at initial evaluation and AML may be aleukaemic initially. No alkylating drugs were administered, and the diagnoses were almost coincidental.

Our patient had received several immunosuppressive agents, among them cyclophosphamide and azathioprine. Both drugs have been associated with MDS development, with monosomy 7 abnormality being described as one of the most frequent chromosomal abnormalities. Thus, prolonged use of azathioprine treatment for autoimmune diseases has been involved in the development of myelodysplasia and subsequent AML with a characteristic association in the karyotypic analysis (12, 13).

In conclusion, we report a case of adult DM who died due to a neoplasia directly related to DM. Although a therapy-related leukaemia seems to be the most likely cause in our case, some events may suggest a paraneoplastic association, especially as haematological abnormalities and a monoclonal gammapathy were present from the onset of the disease.

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