Auto-immune Haematological Complications Occurring during the Treatment of Malignant Lymphoproliferative Diseases

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SUMMARY

Auto-immune haematological complications occurring during treatment for malignant lymphoproliferative diseases are described in 5 patients. There appeared to be a temporal relationship between the development of these complications and the administration of chemotherapeutic drugs or extensive radiotherapy.

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Immunohaematological disorders may complicate the clinical course of patients with chronic lymphocytic leukaemia, lymphocytic lymphoma and Hodgkin's disease.[1-7] Auto-immune haemolytic anaemia is the most common of these complications, occurring in approximately 10 - 25% of patients with chronic lymphocytic leukaemia,[8] and in about 2% with non-Hodgkin's lymphoma[4] and Hodgkin's disease.[4,6]

Less well appreciated, but adequately documented, is the occurrence of immune thrombocytopenia in patients with either chronic lymphocytic leukaemia or the lymphomas.[3-5] More recently, pure red cell aplasia has been described in patients with chronic lymphocytic leukaemia;[9] an auto-immune basis for this manifestation has been suggested, since it is now well established that certain patients with primary pure red cell aplasia have evidence of immune injury to their erythroblasts.[10] Because of the chronological relationship between the treatment of lymphoproliferative neoplasms and the onset of auto-immune complications, several workers have suggested that either radiotherapy or alkylating agents may 'trigger' the onset of such immune-mediated disturbances.[7,11,14,15] While it is clear that auto-immune haemolytic anaemia, or a positive direct Coombs test in the absence of overt haemolysis, may precede, coincide with, or follow the diagnosis of a lymphoproliferative neoplasm,[1,7] it is important to recognise the possibility that treatment may itself precipitate or unmask these manifestations.

This article reports 5 patients with malignant lymphoproliferative diseases, in whom either auto-immune haemolytic anaemia or immune thrombocytopenia, or both, developed after the initiation of therapy with either alkylating agents or extensive radiotherapy. The temporal association between treatment and the onset of these complications strongly suggests a more than fortuitous relationship between the two.

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CASE REPORTS

A retrospective study was made of the records of 62 patients with Hodgkin's disease, 54 with lymphocytic lymphoma, and 28 with chronic lymphocytic leukaemia who attended the Haematology Clinic of the Johannesburg General Hospital between January 1970 and January 1972. Of these 144 patients, 5 developed either auto-immune haemolytic anaemia or immune thrombocytopenia. The auto-immune haematological complications appeared after the initiation of extensive radiotherapy or after the administration of alkylating agents in all 5 instances and in no patient was there evidence of a pre-existing immune disturbance.

Case 1

A 61-year-old White male presented with rigors, night sweats and significant weight loss. Examination showed the liver to be enlarged 6 cm and the spleen 8 cm below the costal margin. The blood count showed: haemoglobin 11,1 g/100 ml; leucocyte count (WBC) 35 900/mm^3 (90% mature lymphocytes); platelets 170 000/mm^3. The direct Coombs test was negative. A diagnosis of chronic lymphocytic leukaemia was made and treatment was commenced with chlorambucil 6 mg daily.

Therapy was continued for 3 months, at which time the patient became jaundiced with further hepatic enlargement. A blood count showed: haemoglobin 10,6 g/100 ml, WBC 6 000/mm^3, platelets 12 000/mm^3 and reticulocyte count 6%. The direct Coombs test, previously negative, was now positive. A bone marrow examination showed erythroid hyperplasia and abundant megakaryocytes. Auto-immune haemolytic anaemia was diagnosed and immune thrombocytopenia suspected. Corticosteroid therapy (60 mg prednisolone/day) was commenced, but the haemo-

globin level fell to 6,2 g/100 ml and the platelet count to 10 000/mm³. A splenectomy was undertaken. Postoperatively both the haemoglobin and platelet values returned to normal levels and the corticosteroid therapy was discontinued.

Case 2

A 76-year-old White female presented with mental confusion, abdominal pain and weight loss. The liver and spleen were both enlarged to 6 cm below the costal margin. There was marked cervical lymph node enlargement. A blood count showed the following: haemoglobin 12,1 g/100 ml, WBC 4 000/mm³, and platelets 138 000/mm³. The direct Coombs test was negative. A diagnosis of Hodgkin's disease was established on lymph node biopsy. The patient was considered to have clinical stage IVB disease because of the hepatomegaly.

Combination chemotherapy using nitrogen mustard, vincristine, procarbazine and prednisolone (MOPP)[12] was commenced. Immediately after the second cycle of MOPP, the Coombs test became weakly positive. The platelet count, which prior to therapy was 138 000/mm³, fell to approximately 75 000/mm³ during the first 4 months of therapy and then suddenly dropped to 20 000/mm³. The fall in platelet count was out of proportion to any decline in the granulocyte count. Bone marrow examination revealed a mild increase in megakaryocyte numbers. The spleen was palpable 1 cm below the left costal margin at this time. Immune thrombocytopenia was suspected and therapy was commenced with 40 mg prednisolone daily. The platelet count rapidly rose to 65 000/mm³ and then gradually rose to normal values.

Case 3

A 63-year-old White male presented with a facial rash, lymph node enlargement and weight loss. The spleen was palpable 2 cm below the costal margin and there was enlargement of the axillary, submental, submandibular and inguinal lymph nodes. A blood count showed the following: haemoglobin 13,4 g/100 ml, WBC 100 000/mm³ (the majority of cells were well-differentiated lymphocytes) and platelets 275 000/mm³. The direct Coombs test was negative. A diagnosis of chronic lymphocytic leukaemia was made.

The patient was treated with total body irradiation to a mid-sacral dose of 190 rads over a 3-month period. Approximately 2 months after the completion of this therapy, he was admitted to hospital in congestive cardiac failure with a haemoglobin of 7,5 g/100 ml and a reticulocyte count of 14,2%. The total bilirubin was 3,3 mg/100 ml and urobilinogen was present in the urine. The direct Coombs test was now positive and the haemoglobin fell progressively to 4,9 g/100 ml. He was transfused with 6 units of blood and treated with prednisolone in a dose of 80 mg/day. The haemoglobin rose to 13,9 g/100 ml on this medication, but the patient died 13 days later from septicaemia.

Case 4

A 54-year-old White male presented with weight loss, diarrhoea and a productive cough. Physical examination revealed a 2-cm enlargement of both liver and spleen; the axillary lymph nodes were also enlarged. The presence of nodular well-differentiated lymphocytic lymphoma was demonstrated on a lymph node biopsy. Blood findings were as follows: haemoglobin 12,2 g/100 ml, WBC 4 100/mm³, and platelets 106 000/mm³. The direct Coombs test was negative.

The patient received radiotherapy to the axillae, abdomen and groins over a 2-month period, to a total dose of 2 400 rads. Three months after the commencement of radiotherapy the platelet count fell dramatically to 15 000/mm³. A bone marrow aspirate showed increased megakaryocyte numbers. At the time the spleen was just palpable below the costal margin. A ^{51}Cr platelet survival study, carried out by the Department of Haematology of the South African Institute for Medical Research, demonstrated a platelet survival of under 24 hours. Prednisone in a dose of 60 mg daily was commenced, and the platelet count rose to 175 000/mm³ over a period of one month. The Coombs test remained negative. Elective splenectomy (weight 226 g) was subsequently done and the platelet count remained normal.

Case 5

A 27-year-old White female presented to another hospital with enlarged lymph nodes in the left axilla, supraclavicular fossa and mediastinum. The blood count showed: haemoglobin 12,8 g/100 ml, WBC 5 000/mm³ and platelets 164 000/mm³. The spleen was enlarged to 1 cm below the costal margin. A diagnosis of Hodgkin's disease was established on lymph node biopsy. She was treated initially with cyclophosphamide and mediastinal irradiation. The disease subsequently relapsed, with swelling of the lymph nodes in the left axilla and left side of the neck. The patient was then referred to this hospital, where a lymph node biopsy demonstrated Hodgkin's disease of the mixed cellularity type.

Therapy with the MOPP regimen was instituted. After three courses she suddenly developed epistaxis and extensive purpura. These manifestations occurred 6 weeks after she had last received chemotherapy and at a time when all clinical evidence of disease had disappeared. The spleen was not palpable. Blood findings were as follows: haemoglobin 11,7 g/100 ml, WBC 3 500/mm³ (67% neutrophils) and platelets 18 000/mm³. The Coombs test was negative. The patient refused to allow a bone marrow aspirate to be performed. Prednisone in a dose of 60 mg daily was given, and the platelet count rose promptly to 90 000/mm³. At this point, elective splenectomy was undertaken, and the platelet count rose to 205 000/mm³, and remained stable in this region. She received a further 6 courses of MOPP after splenectomy, without the development of untoward thrombocytopenia.

DISCUSSION

Of 144 patients with malignant lymphoproliferative disorders, 5 developed either auto-immune haemolytic anaemia or immune thrombocytopenia, or both. Of the 5, 2 had chronic lymphocytic leukaemia, 1 a nodular well-differentiated lymphoma and the remaining 2 had Hodg-

kin's disease. In all 5 instances the haematological complications appeared after the exhibition of alkylating agents or wide-field radiotherapy. The over-all incidence of immunohaematological complications in this small series was 3,5%. This figure is in keeping with the incidence published in other reports,[4,6] although it might have been anticipated that more patients with chronic lymphocytic leukaemia would have developed auto-immune haemolytic anaemia.[13] None of our patients had evidence to suggest the presence of auto-immune disease prior to the initiation of treatment, and the chronological sequence of events strongly suggests that extensive radiotherapy or chemotherapy may have led to the formation of antibody directed against components on the surface of red cells or platelets. Alternatively, it may have unmasked such antigens. The possible role of X-irradiation and alkylating agents as 'trigger' mechanisms for auto-immune complications in patients with malignant lymphoproliferative diseases has been commented on by several investigators.[11,14,15]

Lewis *et al.*[11] reported 5 patients in whom auto-immune haemolytic anaemia and 1 in whom both auto-immune haemolytic anaemia and immune thrombocytopenia developed during or after the initiation of therapy with alkylating agents or irradiation. Other workers, however, have not witnessed a temporal relationship between treatment and the onset of such complications.[4,6] While the relationship may be coincidental, it is not unreasonable to suppose that such an association may exist, since both radiation[16] and alkylating agents[17] are able to enhance antibody synthesis.

The mechanism whereby the immune system may be enhanced under these circumstances is not known. Cellular breakdown products, such as nucleic acids, may play a role in the enhancement of antibody synthesis after exposure to cell-damaging X-rays or radiomimetic drugs,[18] and it has been suggested that an 'overshoot' of cellular proliferation may occur during restoration of lymphoid tissue after injury by such agents.[11] There is the further possibility that alkylating agents and X-rays may cause auto-immune manifestations by a suppression of immunological tolerance. Such a phenomenon has certainly been observed in mice and rats made tolerant to foreign erythrocytes.[19] Thus, these agents could 'trigger' auto-immune disease in patients with lymphoproliferative disorders, either by enhancing a pre-existing, subliminal auto-immune process, or by reducing immunological tolerance between neoplastic lymphocytes and self-antigens.

Whether the relationship between the use of alkylating agents or radiotherapy and the subsequent occurrence of immunological aberrations in patients with malignant lymphoproliferative disorders is a statistically significant one or not, the available evidence strongly indicates that such a relationship may be more than fortuitous. Physicians should therefore be aware of the possibility of auto-immune complications supervening, often with fatal consequences, in patients whose underlying disorder may not have required active treatment in the first instance. The possible benefits of therapy must be carefully weighed against the potential hazards.

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