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Case report

Stevens-Johnson syndrome associated with methotrexate treatment for non-Hodgkin's lymphoma

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In recent years methotrexate has been used increasingly in combination chemotherapeutic regimens for the treatment of aggressive non-Hodgkin's lymphoma.[1] Its principal toxic effects are bone marrow suppression, gastrointestinal mucositis, hepatitis, renal impairment, and erythematous rashes. The Stevens-Johnson syndrome has been reported previously in two children receiving high-dose methotrexate with leucovorin rescue for treatment of acute lymphoblastic leukaemia.[2] The syndrome is characterized by severe erythema multiforme associated with orogenital mucosal ulceration, and may be complicated by severe systemic upset and hepatic, renal and neurological disturbances.[3] We report a case of near-fatal Stevens-Johnson syndrome following intermediate dose methotrexate and leucovorin rescue in a patient receiving combination chemotherapy for diffuse large cell non-Hodgkin's lymphoma.

CASE REPORT. A 54-year-old man presented with cervical lymphadenopathy and an abdominal mass. Cervical lymph node biopsy demonstrated a diffuse large cell non-Hodgkin's lymphoma.[4] Extensive involvement of mesenteric lymph nodes was demonstrated by CT scanning. He was treated with BCHOP-M chemotherapy intravenously: bleomycin 10 mg, cyclophosphamide 1·4 g, doxorubicin 76 mg and vincristine 2 mg on day 1; followed by oral prednisolone 40 mg daily on days 1 – 5 and intravenous methotrexate 380 mg on day 15, and leucovorin 30 mg orally six-hourly for four doses on day 16.

On days 22 – 24 he developed a fever, a generalised erythematous itchy rash, and severe mucosal ulceration of the orpharynx, glans penis, and anus. He had epidermal ulceration of the scrotum, perineum, and upper medial aspect of the thighs. On days 25 – 30 the rash became confluent over the whole body surface and began to blister over the trunk, palms and soles, gradually resolving over days 33 – 40.

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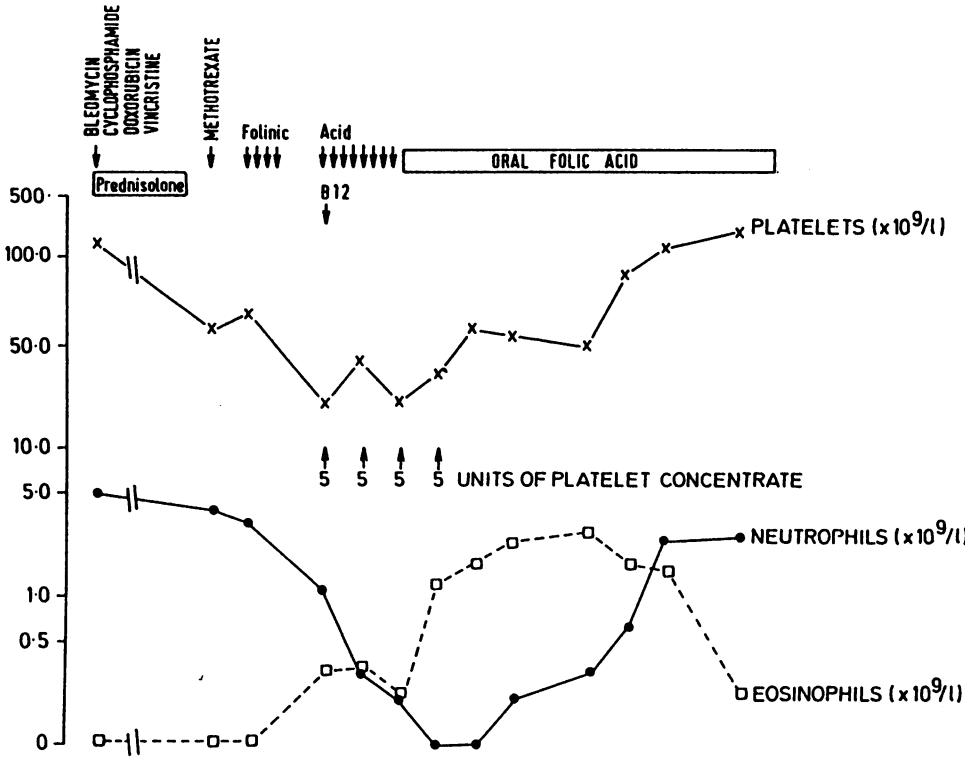

Figure. Neutrophil, eosinophil and platelet counts following methotrexate and leucovorin rescue. The haemoglobin fell gradually from 15·4g/dl on day 1 to 9·2g/dl on day 21, rising to 9·6g/dl on day 30. Blood transfusion was not required.

On day 18 he had been found to have pancytopenia associated with eosinophilia (Figure). The bone marrow was hypocellular with gross megaloblastic changes and no evidence of lymphomatous infiltration. He was given further doses of leucovorin intravenously (30mg six-hourly for 48 hours) followed by oral folic acid (15mg daily for 10 days), and hydroxocobalamin 1mg intravenously. The peripheral blood count gradually improved over days 20 – 24, but the eosinophilia persisted until day 29 and then gradually resolved. The period of pancytopenia was complicated by bleeding from the ulcerated oropharyngeal mucosa and a purpuric rash on the lower limbs. *Staphylococcus aureus, Escherischia coli,* and *Klebsiella pneumoniae* were isolated from the skin, throat, sputum and blood. He required support with platelet transfusions and intravenous antibiotics. During the acute illness he had reversible renal and hepatocellular damage, but ultrasound scan showed no evidence of ureteric or biliary obstruction.

By day 40 his temperature was normal and there was complete resolution of the rash, complete healing of the orogenital ulceration, and normal liver, renal, and bone marrow function. Subsequently he received five further pulses of BCHOP without methotrexate, and had no recurrence of the Stevens-Johnson syndrome. His non-Hodgkin's lymphoma remains in complete remission 36 months after completion of chemotherapy.

DISCUSSION

Although dermatological complications of methotrexate therapy appear to be relatively rare, they may be serious when they do occur. Bullous skin reactions have been reported in high-dose methotrexate regimens used in the treatment of non-Hodgkin's lymphomas,[5] and the Stevens-Johnson syndrome in two patients treated for childhood acute lymphoblastic leukaemia.[2]

This case demonstrates that the Stevens-Johnson syndrome can occur following intermediate dose methotrexate with leucovorin rescue in aggressive non-Hodgkin's lymphoma. In any severe drug reaction in patients receiving multiple agents, a cause-effect relationship can only be proven by selective re-challenge. The reaction in our patient was temporarily related to methotrexate administration, and did not recur when the patient received five further pulses of BCHOP without methotrexate. The syndrome was not present before the initiation of chemotherapy, suggesting that it was not part of the presenting features of his lymphoma. He did have evidence of infection manifested by triple organism septicaemia, but this occurred after the onset of the mucocutaneous reaction, and was therefore more likely a complication than the cause. These arguments provide strong support for a causal relationship between the Stevens-Johnson syndrome and methotrexate administration in this case.

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