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Short report

Procarbazine associated alveolitis

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Drug induced pulmonary toxicity is a well documented complication of treatment with cytotoxic agents—bleomycin, methotrexate, cyclophosphamide, and busulphan being most commonly implicated.[1] This report documents a severe alveolitis associated with administration of procarbazine.

Case report

A 44 year old man, an ex-smoker, presented with swelling in the neck, increasing fatigue, and night sweats. Supraclavicular lymph node biopsy showed lymphocyte depleted Hodgkin's disease stage IIIB, with hilar, right paratracheal, and para-aortic lymphadenopathy and splenic disease. The haematological and biochemical abnormalities were: erythrocyte sedimentation rate (ESR) 20 mm in one hour, alkaline phosphatase activity 120 IU/l (normal range 20–90 IU/l). Pulmonary function was normal except for a low KCO of 0·9 mmol min^{-1} kPa^{-1} l^{-1} (predicted normal 1·3–1·8 mmol min^{-1} kPa^{-1} l^{-1}).

MOPP chemotherapy was given (mustine 10 mg and vincristine 2 mg intravenously on days 1 and 8, prednisolone 40 mg and procarbazine 150 mg daily for 14 days). After an interval of 14 days a second course was given. There appeared to be a good clinical response after completion of the second course but the patient complained of arthralgia in the arms and knees, breathlessness on exertion, and night sweats of a week's duration. A chest radiograph showed a soft mid-zonal infiltrate. The third MOPP course, begun 14 days after the end of the second, contained reduced dosages of mustine (5 mg) and procarbazine (50 mg daily) and on this treatment these symptoms remitted. Twenty four hours after completion of the course, however, arthralgia recurred, and during the following two weeks he developed a dry cough, pains in the fingers and wrists, night sweats, and breathlessness at rest. At this time he was afebrile and had no signs of cardiac failure, but he was cyanosed and tachypnoeic and bilateral basal fine mid and late inspiratory crackles were audible. Haematological investigation showed: haemoglobin concentration 10·2 g/dl; white blood cells 2·2 × 10^9/l; neutropenia and eosinophilia (308/μl, 14%); ESR 44 mm in one hour. The arterial oxygen tension was found to be 7·2 kPa (54·1 mm Hg), carbon dioxide tension 4·3 kPa (32·3 mm Hg). A chest radiograph showed a bilateral basal and mid-zone diffuse alveolar infiltrate (fig 1). Pulmonary function tests revealed a restrictive ventilatory defect (FEV_1 2·6 l, forced vital capacity 3·6 l) with a reduced KCO (0·53 mmol min^{-1} kPa^{-1} l^{-1}). Culture of sputum for bacterial and fungal organisms and the results of serological tests for infectious agents were negative. The appearances at bronchoscopy were normal. The differential cell count of bronchoalveolar lavage fluid showed small lymphocytes 80%, neutrophils 4%, macrophages 4%, and eosinophils 3%. Examination of a transbronchial biopsy specimen showed an alveolar infiltrate with macrophages and plasma cells only.

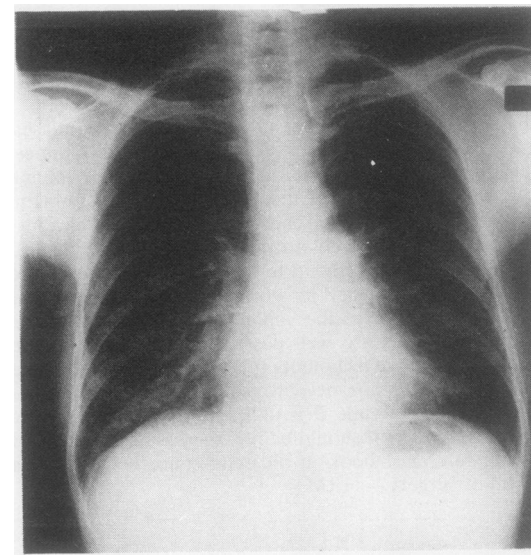

Fig 1 *Chest radiograph showing bilateral diffuse alveolar pattern of infiltrate.*

Treatment with prednisolone 60 mg/day was started and clinical improvement followed within 48 hours. Alternative chemotherapy of single dose combinations of adriamycin 65 mg, vinblastine 10 mg, and dacarbazine 600 mg (AVD) was begun. The improvement in pulmonary function, reduction in corticosteroid treatment, and the timing of five courses of AVD are shown in figure 2.

After completion of chemotherapy, restaging showed total resolution of the previous chest radiographic abnormalities and no evidence of lymphoma.

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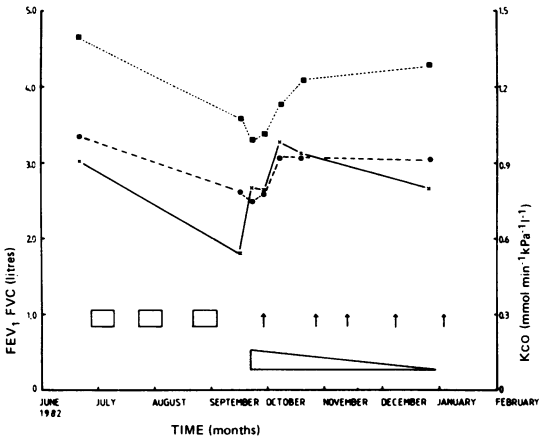

Fig 2 *Indices of pulmonary function and treatment.* ●—● *FEV*$_1$; ■—■ *forced vital capacity (FVC);* ×—× *transfer coefficient (KCO). The rectangular boxes represent MOPP chemotherapy: in the first periods the doses were mustine 10 mg and vincristine 2 mg on days 1 and 8 both intravenously, with prednisolone 40 mg and procarbazine 150 mg daily for 14 days; in the third period the schedule was similar except that the dose of mustine was 5 mg and of procarbazine 50 mg. The elongated triangle represents tapering doses of prednisolone, starting at 60 mg daily. ↑ represents chemotherapy with adriamycin 65 mg, vinblastine 10 mg, and dacarbazine 600 mg, all intravenously, as a single dose combination course.*

Discussion

The most usual manifestations of toxicity due to procarbazine are gastrointestinal disturbance, bone marrow depression, central nervous excitation, and skin changes. The association of procarbazine with pulmonary alveolitis is rare; only seven cases have been reported worldwide and a further atypical case may have occurred in the United Kingdom.[2] Seven patients had advanced Hodgkin's disease and were receiving MOPP and one had lymphosarcoma and was receiving cyclophosphamide, vincristine, and procarbazine. In only two cases was procarbazine rechallenge performed[3,4]; the diagnosis was substantiated in both. Rechallenge was not performed in the present case at the patient's request. It is just possible that the alveolitis was due to mustine or vincristine, though this seems unlikely and such reactions have not been previously reported.

Previously reported features of the syndrome, many illustrated by this case, include the onset after the second or third exposure to procarbazine of a dry cough, fever, breathlessness, arthralgia, and urticaria. Investigations show pleuropulmonary infiltrates, low transfer factor and a restrictive lung defect, and blood eosinophilia and eosinophils in lung biopsy specimens. Examination of bronchoalveolar lavage fluid in this case revealed considerable lymphocytosis, which is in keeping with a hypersensitivity pneumonitis. Drug withdrawal and corticosteroid treatment are followed by resolution of the abnormalities.

In patients treated with procarbazine who develop pulmonary infiltrates this reaction should be considered in the differential diagnosis.

I wish to thank Professor JR Trounce for allowing me to report one of his patients.

References

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