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Short reports

Fatal pulmonary toxic effects of lomustine

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Lomustine (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; CCNU) is a synthetic orally active nitrosourea marketed in the past few years for the chemotherapy of carcinoma, particularly of the brain. The major toxic effects are bone marrow suppression with leucopenia and thrombocytopenia and gastrointestinal effects with nausea and vomiting. Progressive lung changes resulting from cytotoxic drugs such as busulphan and bleomycin are now well recognised and recent reports have documented the pulmonary toxicity that may result from the use of BCNU (bischloroethyl nitrosourea).[1 2] I report a case in which lomustine treatment was followed by fatal pulmonary changes.

Case report

A 52-year-old machine operator presented in April 1976 with increasing neck pain, vomiting, and loss of balance. On examination he had early papilloedema and a left hemiparesis. Computed tomography showed a space-occupying lesion on the left side of the posterior fossa and in September 1976 a large tumour was resected, the microscopic appearance being highly suggestive of a medulloblastoma. Radiotherapy was given; the cranial contents received a minimum tumour dose of 3000 rads (30 Gy) with 6MeV x-rays but the dose to the posterior fossa was taken to 4500 rads. Spinal treatment was also given with 6MeV x-rays at a dose of 2000 rads by a single posterior portal.

In February 1980 the symptoms returned and a subtotal excision of recurrent tumour was performed. Following discharge from hospital the patient received three doses of 200 mg lomustine (2·5 mg/kg) orally at six-weekly intervals, starting on 21 March. After each dose he vomited for six hours, but had no fever. The total white cell count fell to $2{\cdot}3 \times 10^9/1$ after the first dose but otherwise there was no evidence of bone marrow depression. The patient requested that treatment should be discontinued in view of the severity of the vomiting.

In August 1980 symptoms and signs of raised intracranial pressure returned and dexamethasone 2 mg thrice daily was given with some improvement. One month later the patient complained of a dry cough and increasing breathlessness, which progressed despite the addition of digoxin and diuretics by his general practitioner. On admission to hospital two weeks later he was Cushingoid and breathless at rest and had intermittent carpopedal spasms. There was no evidence of cardiac failure. Chest expansion was minimal and on auscultation there were widespread fine end-inspiratory crackles. The chest radiograph, which had been normal previously, showed widespread reticulonodular shadowing throughout both lungs (fig 1). Blood gas measurements were: Po_2 4·5 kPa (34 mm Hg); Pco_2 3·4 kPa (28 mm Hg) (the patient was too ill for any other assessment of lung function). Sputum smears showed no acid-fast bacilli and cultures for bacteria and fungi gave negative results. He was treated with 30% oxygen and an increased dose of dexamethasone but he died 48 hours after admission.

Necropsy showed recurrence of medulloblastoma in the cerebellum. The lungs were uniformly firm with a homogeneous pink texture to the cut surface and microscopically the alveolar walls were thickened with hyaline

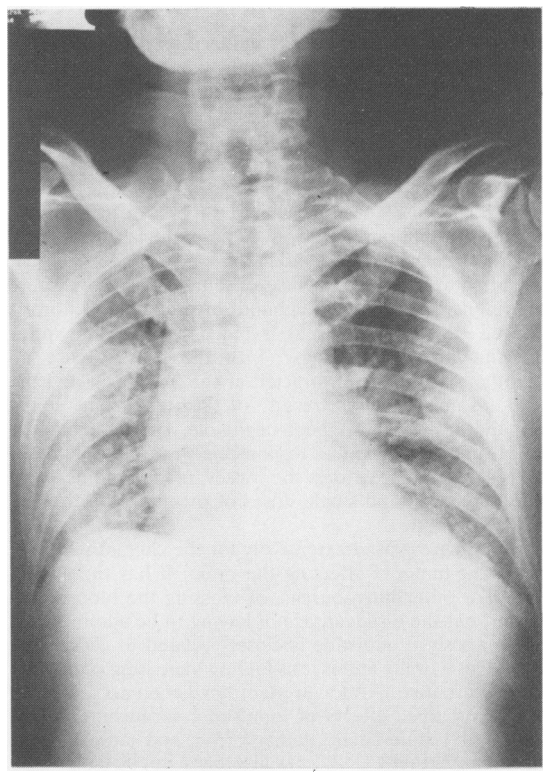

Fig 1 *Chest radiograph showing widespread reticulonodular shadowing: antero-posterior film at time of admission to hospital.*

No reprints of the paper will be available.

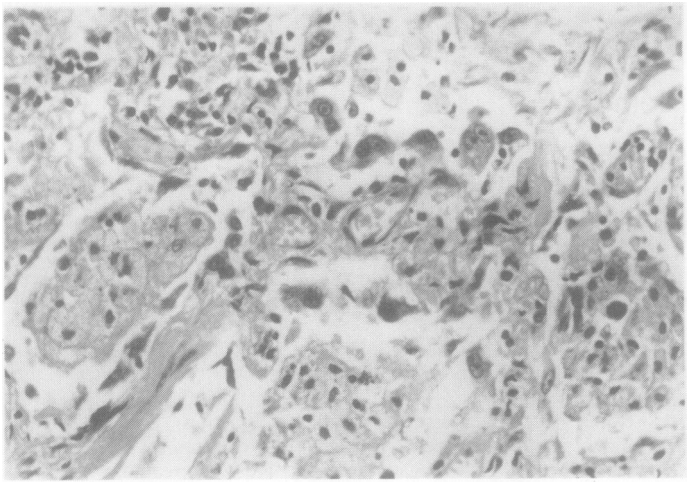

Fig 2 *High-power view of lung at necropsy showing thickening of alveolar walls and desquamation of atypical alveolar lining cells (haematoxylin and eosin, × 480).*

membrane and fibrous tissue. Abundant shed pneumocytes and foamy macrophages were present in the air spaces (fig 2).

Discussion

Reports of pulmonary disease induced by cytotoxic drugs have been reviewed.[1] The symptoms and signs present in our patient were similar to those described in the previously reported cases of pulmonary damage induced by carmustine—(1,3-bis(2-chloroethyl)-1-nitrosourea; BCNU)—namely, dry cough, dyspnoea, and widespread fine end-inspiratory crackles. The histological appearances were also typical of damage induced by cytotoxic drugs. Although radiation may produce an identical histological picture, the changes observed in this case were generalised, extending well beyond the field of spinal irradiation. There is evidence that the likelihood of pulmonary fibrosis induced by cytotoxic drugs is much enhanced by prior radiotherapy to the lungs.[3 4] In the present case no radiotherapy had been directed at the lung itself and the dose received as a result of scatter from spinal radiotherapy must have been negligible. There can be little doubt that lomustine was responsible since the only other drugs prescribed before the onset of symptoms were dexamethasone and single doses of prochlorperazine and metoclopramide.

Carmustine is used extensively for the chemotherapy of malignant tumours affecting the brain: it has the advantage, like other nitrosoureas, of crossing the blood-brain barrier, but the disadvantage of having to be administered intravenously. Lomustine is closely related to carmustine but is active orally and is thus finding increasing popularity as an alternative. Although there have been no reports of pulmonary toxic effects of lomustine, carmustine is well known to cause lung damage[1 2 5–7] and another nitrosourea, methyl CCNU, has also been implicated.[8]

The total cumulative dose of lomustine given in this patient was small and it seems likely that the pulmonary damage, like that due to carmustine, is not dose dependent.[5] The interval between the start of treatment and the development of symptoms of lung disease was only six months, which is the shortest interval reported for carmustine. The damage was more rapidly fatal than that described previously for nitrosoureas.

The use of serial tests of lung function to detect early lung damage resulting from cytotoxic treatment has been advocated, the typical changes being a restrictive ventilatory defect with a decrease in diffusing capacity. The development of such changes or a suggestive clinical picture or radiograph should lead to the discontinuation of treatment since some patients suffering from the toxic effects of carmustine recover spontaneously.[5] Corticosteroid treatment has occasionally been followed by radiological improvement in cases where carmustine has been implicated.[5 9] Our patient was receiving dexamethasone at the time he developed evidence of pulmonary damage and an increase in the dose did not lead to any improvement.

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