had been isolated from the survey specimen in heavy growth. Stool cultures taken when she returned to work the next week proved negative.

Comment

S. flexneri has the smallest infecting dose of enteropathogenic bacteria—namely, about 200 viable cells for healthy volunteers—so that infections in laboratory workers are not uncommon.² Interestingly, laboratory-acquired infections of all kinds have in general occurred most often in trained bench workers in diagnostic services, and spills and sprays have equalled hypodermic needles as the commonest mode.¹

In this case gargling with copious water followed by thorough washing of the face and hands with soap and water might have been more effective than the brief exposures to antiseptics. The State Health Commission recommends a phenolic disinfectant for laboratory fixtures but offers no guidance on measures for people who become contaminated.³

¹ Pike RM. Laboratory-associated infections: incidence, fatalities, causes and prevention. *Ann Rev Microbiol* 1979;33:41-66.

² Hornick RB. Shigellosis. In: Hoeprich PD, ed. *Infectious diseases: a modern treatise of infectious processes*. 2nd ed. New York: Harper and Row, 1977:549-54.

³ Health Commission of New South Wales. *Code of safe practice in clinical laboratories*. Sydney, NSW: Health Commission of NSW, 1980.

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Fatal pulmonary fibrosis occurring during treatment with cyclophosphamide

Pulmonary fibrosis is an uncommon complication of drug treatment and has been reported in association with many cytotoxic drugs.¹ We describe two patients who developed pulmonary fibrosis while receiving cyclophosphamide for glomerulonephritis.

Case reports

Case 1—A 58-year-old man was admitted to hospital with rigors, anorexia, increasing dyspnoea, and a non-productive cough. For seven weeks he had been taking 100 mg cyclophosphamide and 30 mg prednisolone daily for a rapidly progressive glomerulonephritis, and his renal function had been improving (serum creatinine concentration 311 μ mol/l; 3.5 mg/100 ml). Examination showed fever, a tachycardia of 100/min, crepitations at both lung bases, and a left-sided pleural rub. Radiography showed left-sided basal shadowing. Intravenous cefuroxime 750 mg twice daily was given after specimens had been taken for culture. One week later he became acutely unwell, with cyanosis, tachypnoea, intercostal indrawing, a tracheal tug, and increase in intensity of the pleural rub. Blood gas analysis yielded P_{CO_2} 2 kPa (15 mm Hg) and P_{O_2} 4.7 kPa (35 mm Hg) on air. Chest radiography showed mid-zone and basal shadowing. Cyclophosphamide and cefuroxime were stopped and gentamicin, flucloxacillin, and co-trimoxazole introduced after bronchoscopy. Ventilatory support was required, initially with intermittent positive-pressure ventilation and later with positive end-expiratory pressure, between 60% and 100% oxygen being needed to maintain his P_{O_2} within the normal range. Ten days after admission an open-lung biopsy was performed without complication. Despite further treatment with high-dose steroids and co-trimoxazole, he continued to deteriorate and died in respiratory failure after a gastrointestinal haemorrhage 20 days after presentation.

Case 2—A 29-year-old man with a refractory nephrotic syndrome secondary to a diffuse proliferative glomerulonephritis (serum creatinine concentration 186 μ mol/l; 2.1 mg/100 ml) had been taking cyclophosphamide 200 mg daily and prednisolone 10 mg thrice daily for four months. He was admitted with a cough, rigors, and fever. There were signs suggestive of a left-sided bronchopneumonia. Radiologically this developed into a generalised micronodular pattern associated with a clinical deterioration over six days. Cyclophosphamide was stopped and intravenous cefuroxime 750 mg twice daily begun. Initially blood gas analysis on air yielded P_{CO_2} 2.3 kPa (17 mm Hg) and P_{O_2} 3.3 kPa (25 mm Hg). After bronchoscopy and transbronchial biopsy doxycycline 100 mg daily, co-trimoxazole 2 tablets

twice daily, and antituberculous treatment with rifampicin 600 mg and isoniazid 150 mg were introduced empirically and 70% oxygen via an Inspiron mask was required. Again further ventilatory support was needed, during which time an open-lung biopsy was performed, but respiratory failure progressed, with increasing hypoxia and decreasing lung compliance, leading to death 21 days after initial presentation.

Alveolus partly lined by bizarre epithelial cells and containing ingrowth of granulation tissue. Alveolar sputum contained heavy chronic inflammatory infiltrate. (Haematoxylin and eosin. Original magnification $\times 250$.)

Comment

In both patients no evidence of an infective agent was obtained. Cultures of sputum, urine, and blood all gave negative results, as did serological studies for legionellae, aspergillus, and candida. Viral titres remained insignificant. Biopsy material obtained in both cases at bronchoscopy and open-lung biopsy showed widespread severe interstitial fibrosis, less pronounced in case 2. There were newly formed reticulin fibres, organising and organised intra-alveolar exudates, and florid regenerative proliferation of alveolar epithelial cells, which were large, occasionally multinucleated, and often bizarre. A moderate, rather focal interstitial infiltrate of lymphocytes and plasma cells was present (fig). There was no evidence of malignancy, and staining for infective organisms, including *Pneumocystis carinii*, gave negative results. Necropsy in both cases showed diffuse pulmonary consolidation, histologically the same as that obtained at biopsy and considered to be similar to the fibrosis associated with busulphan treatment.² In the absence of any evidence of infection we believe that the progressive fibrosis was secondary to cyclophosphamide treatment. This reaction has been reported with low total dosage of cyclophosphamide after short courses³ but to our knowledge not in association with the treatment of renal disease. Only three cases of pulmonary fibrosis in association with cyclophosphamide have been reported to the Committee on the Safety of Medicines. World wide, eight cases have been documented. Resolution, however, often followed withdrawal of the drug.^{3,4} The mechanism of the reaction remains unsolved.

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¹ Brewis RAL. *Textbook of adverse drug reactions*. Ch 8. London: Oxford University Press, 1981.

² Batist G, Andreus JL. Pulmonary toxicity of antineoplastic drugs. *JAMA* 1981;246:1449-53.

³ Spector JJ, Zimble H, Ross JS. Early onset cyclophosphamide-induced interstitial pneumonitis. *JAMA* 1979;242:2852-4.

⁴ Patel AR, Shah PC, Rhee HL, et al. Cyclophosphamide therapy and interstitial pulmonary fibrosis. *Cancer* 1976;38:1542-9.

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