examination, and the blast cells were Sudan-black positive, periodic acid Schiff-negative. Marrow chromosome analysis was normal. Cell surface markers showed that 85% of the cells were Ia positive, while 8% were TdT positive, suggesting that a small proportion of the blast cells were lymphoid.

He was nursed under laminar-flow conditions, with gut decontamination, and was started on the following chemotherapy: daunorubicin 40 mg/m² day 1, thioguanine and cytarabine 100 mg/m² twice a day on days 1 to 5. Despite two courses, his blood and marrow remained in florid relapse. Over these four weeks he had a right basal pneumonia, which responded to gentamicin and carbenicillin, and oesophageal candidiasis, which was treated with flucytosine. Treatment was changed to a seven-drug regimen, TRAMPCO¹ (prednisolone reduced to 40 mg/day). Two courses of this succeeded in reducing, but not eliminating, circulating myeloblasts.

After his last course, symptomatic candidiasis recurred when flucytosine was temporarily discontinued, and shortly thereafter he developed a left basal pneumonia with progressive deterioration, despite further broad-spectrum antibiotics. Within 48 hours signs of superior vena caval obstruction appeared with plethora, facial swelling, and distended neck veins. A chest radiograph showed a right-sided mediastinal mass with a right-sided subpleural effusion (see figure). Bronchoscopy showed splaying of the carina and narrowing of the right bronchus but no specific features; the results of mycological, cytological, and bacteriological examinations of the bronchial and pleural aspirate were negative, and a bronchial biopsy specimen showed nothing abnormal.

Chest radiograph showing consolidation medially in the right upper zone; appearances in the right lower zone were due to a subpleural effusion.

Though prednisolone 60 mg/day produced symptomatic and clinical improvement of the superior vena caval obstruction, his general condition deteriorated and within two weeks he developed a further homogeneous consolidation in the left mid-zone. All treatment was discontinued and he died one week later, 12 weeks after initial presentation.

At necropsy there was thrombosis of the superior vena cava, multiple thrombi within the pulmonary arteries with infarction of adjacent lung tissue, and thrombosis of the splenic vein and minor veins of the left kidney. Many broad hyphae, confirmed to be phycomycetes, were found on microscopic examination of the pulmonary infarcts and throughout the thrombus and walls of the superior vena cava.

Following a postmortem diagnosis of mucormycosis, direct culture of the dust and the outer surface of the air filter grew colonies of mucor and aspergilli, though air samples within the unit did not.

Comment

Mucormycosis represents an infection by any genus of the class of fungi phycomycetes. It has been the subject of few reports from Britain but is well recognised in North America as an opportunistic infection of increasing importance, especially in patients with leukaemia or lymphoma.² It is a frequent commensal in sputum but, in the invasive form, isolation is difficult, and diagnosis depends on the findings in a tissue biopsy specimen. *Candida*, particularly of the oesophagus, is a common associated infection.³ Fungal-induced

thrombosis, with consequent infarction of adjacent tissue, is characteristic of mucor and aspergillosis.² Obstruction of the superior vena cava, however, has been reported only with aspergillosis.⁴

Mucormycosis carries a high mortality and survival is rare unless the underlying disorder can be controlled.² Though flucytosine appears to be ineffective, amphotericin B has been reported to be beneficial.⁵

In the immunosuppressed patient, who develops features suggestive of widespread thrombosis and infarction and a fever unresponsive to antibacterial antibiotics, mucormycosis should be seriously considered. Treatment with amphotericin B may be indicated in these circumstances, though diagnosis should normally be confirmed histologically—if necessary by open lung biopsy.

We thank Dr R Reid of the university department of pathology and the medical mycology unit for establishing postmortem diagnosis of mucormycosis.

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Fatal pseudomembranous colitis despite eradication of *Clostridium difficile*

Pseudomembranous colitis is associated with toxin-producing *Clostridium difficile* in the stool.¹⁻³ Treatment with vancomycin usually results in rapid clearance of the organism and toxin from the stool, resolution of the diarrhoea, and prompt healing of the mucosal lesions.³ A high relapse rate, however, has recently been reported after vancomycin treatment.⁴ We report a case in which histological changes persisted despite elimination of *C. difficile* and its toxin by vancomycin.

Case report

A 49-year-old man presented in 1977 with erythema nodosum proved on biopsy, anaemia, fever, and a high erythrocyte sedimentation rate. Intensive investigation failed to discover the underlying cause. There was no response to a prolonged trial of specific antituberculous chemotherapy, and from August 1978 corticosteroids were required to control his symptoms.

In April 1979 he developed extensive pyoderma gangrenosum with severe secondary infection for which flucloxacillin 500 mg four times daily and amoxycillin 500 mg three times daily were prescribed. One week later he developed abdominal pain and severe diarrhoea, and the antibiotics were stopped. Sigmoidoscopy showed florid pseudomembranous colitis, and biopsy of the lesion confirmed the diagnosis. *C. difficile* and toxin were detected in faecal specimens, and on 17 May oral vancomycin 125 mg four times daily was started. His condition continued to deteriorate, and on 21 May the vancomycin dose was increased to 500 mg four times daily and metronidazole suppositories added. Subsequent laboratory tests showed that the organism and toxin had disappeared from the stool within two days after the start of treatment, and three further specimens taken at intervals up to the time of death were negative. Despite clearance of the organism there was no clinical response and repeat sigmoidoscopy showed persistent pseudomembranous colitis.

On 24 May he developed leucopenia, thrombocytopenia, and tinnitus and on 25 May vancomycin was stopped. The next day he collapsed and died. Postmortem examination showed advanced bronchopneumonia and

florid pseudomembranous colitis throughout the colon. Histological examination confirmed the diagnosis and showed superadded ischaemic necrosis.

Discussion

This patient developed pseudomembranous colitis within seven days of starting antibiotics. Despite adequate doses of vancomycin and clearance of both the organism and its toxin from the faeces he did not improve clinically or histologically. The reason for this is not clear, but possibly the underlying disease process or the corticosteroid treatment may have modified the therapeutic response.

Price and Davies⁵ divided the histological appearances of pseudomembranous colitis into three categories: type 1 is characterised by the "summit" lesion; type 2 by the pseudomembrane; and type 3, the most severe and advanced lesion, by structural necrosis and disease of the lamina propria. They suggested that the type 3 lesion may be due to a Shwartzman reaction with localised intravascular coagulation and microthrombosis leading to ischaemic necrosis. Our patient developed the type 3 lesion before vancomycin was started, and we suggest that by this stage the disease may be irreversible and unaffected by a bacteriological response. If this is so we think that in pseudomembranous colitis, especially in the presence of other serious disease, treatment with vancomycin should not be delayed.

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Sulphasalazine desensitisation

Sulphasalazine is extremely valuable in ulcerative colitis, particularly when used as maintenance treatment.¹ Rash, often associated with fever, occurs as a side effect in 1-5% of patients in different series. Svartz, who introduced sulphasalazine into therapeutics, indicated that some patients who experienced such a reaction could be desensitised,² but this observation has been forgotten or ignored, and most authorities state firmly that development of a rash is a contraindication to further use of the drug.³ I report that most patients who have had a rash or fever after taking sulphasalazine may be easily desensitised.

Methods and results

With the precedent of desensitisation regimens to penicillin,⁴ treatment was started in eight patients at one-thousandth of the normal therapeutic dose. Capsules were prepared containing 1 mg, 10 mg, and 100 mg of sulphasalazine. All patients started with 1 mg daily and the dose was progressively doubled; pauses in this dose increase occurred when 10 mg and 100 mg daily were achieved, each of these doses being taken for one week before doubling began again. The precise rate of increase varied, but 100 mg was never reached before 14 days and the normal tablet strength of 500 mg was never reached before 23 days. Patients were instructed that should any reaction develop, such as fever or skin eruption, the dose should not be increased further but should be continued until the reaction had settled down.

The table shows that of the eight patients studied, six had previously had a

rash, sometimes associated with fever, and two fever alone, as a reaction to treatment with the drug. In five patients the reaction had occurred while they were under observation as inpatients and was well documented. In the three others (cases 3, 5, 6) there was clear evidence of a reaction in the history. Desensitisation failed only one patient (case 8), who developed permanent light sensitivity, a rare, though well-recognised, reaction after treatment with sulphonamides.⁵ All other patients are now taking a normal maintenance dose of 2 g or 3 g daily.

Desensitisation was also tried in two patients whose reactions to sulphasalazine were abdominal pain, headache, and diarrhoea, rather than fever or rash. In both it was unsuccessful, diarrhoea and headache developing when 20 mg and 500 mg daily were reached.

Original reaction and duration of associated treatment and reaction on desensitisation. (Statements in quotation marks are summaries of patients' own descriptions)

Case No	Age (years)	Sex	Original reaction and duration of associated treatment	Reaction on desensitisation
1	21	F	Rash 7 days	
2	32	F	Fever 15 days; rash 26 days	
3	36	M	"Rash and fever" about 7 days	
4	40	F	Fever 8 days	
5	65	F	"Face swollen every time Salazopyrine taken"	
6	39	F	"Came out in blotches" about 7 days	
7	28	F	Abdominal pain and fever about 7 days	
8	11	M	Rash, fever, oedema, lymphadenopathy Residual permanent light sensitivity	Rash and vomiting at 100 mg daily Later reaction at 10 mg thrice daily

Comment

Desensitisation was successful in all except one of the patients who had previously developed rash or fever when taking the drug and were thought to be still likely to benefit from the drug for maintenance treatment. It is likely that the sensitivity is due to the sulphapyridine component of sulphasalazine; similar ease of desensitisation, except in patients with light sensitivity, has been recorded in patients sensitised to sulphonamides.⁵ Desensitisation is an easy outpatient procedure and requires only the co-operation of the hospital pharmacy to prepare capsules of appropriate strength. Corticosteroid cover is not needed: none of the patients who were successfully desensitised were taking steroids at the time, though several had been taking large doses when they developed their initial reaction.

Extrapolation from this study in one clinic suggests that there may be several hundred patients in Great Britain alone who are currently denied treatment with sulphasalazine in the mistaken belief that it is permanently contraindicated because of an initial skin eruption or drug fever. The only cautionary note is that should the drug be stopped in such patients, sudden readministration at full dosage would probably again be followed by an adverse reaction. Furthermore, desensitisation is not worth attempting for the more common side effects of sulphasalazine such as headaches, nausea, and abdominal discomfort.

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