Bronchiectasis in acute leukaemia

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Summary

Five children in remission from acute lymphoblastic leukaemia developed bronchiectasis when on chemotherapy. Persistent collapse or consolidation on chest radiographs was helpful in suggesting the diagnosis. Necropsy established the diagnosis in one child who died of massive haemoptysis when in complete remission, and bronchography confirmed the diagnosis in three. In a further child the diagnosis was based on clinical and chest x-ray findings alone. The surviving children were treated with prophylactic rotating antibiotics.

Routine chest radiographs are recommended in children with acute lymphoblastic leukaemia, as bronchiectasis may otherwise be underdiagnosed.

Introduction

Infection is a major threat to children being treated for acute leukaemia and is an important cause of death in patients whose long-term prospects of cure are real.¹ Life-threatening respiratory infections tend to be caused by opportunistic organisms in remission,¹ and by pathogenic bacteria in relapse.² The incidence and severity of bronchiectasis in childhood have declined in the past 20 years,³ and it is now rare. Moreover, acute leukaemia is not considered to be among the predisposing factors for bronchiectasis.⁴ We describe here four children with bronchiectasis and acute lymphoblastic leukaemia, including one child who died of massive haemoptysis when in complete continuous remission. Another child had very similar clinical findings and his chest x-ray appearances were consistent with bronchiectasis, but he has not been included here because a bronchogram was not performed.

Details of patients

Three boys and one girl, aged 2 to 4 years, presented initially with acute lymphoblastic leukaemia confirmed by bone marrow aspirate. All four children had initial total leucocyte counts less than $20 \times 10^9/l$ and no evidence of central nervous system involvement. Chest radiographs taken in two children were normal. Lumbar punctures were not performed at diagnosis: the cerebrospinal fluid findings were obtained after remission (in case 2 after the second remission), but before intrathecal methotrexate had been given. At the time of writing two children were off cytotoxic treatment in complete remission, one had relapsed on treatment 20 months after diagnosis, and the fourth child died in complete remission (see case report).

Bronchiectasis was diagnosed in these four children (and in the fifth child not included here) in 1974-6. The symptoms and signs (tables I and II) of bronchiectasis had an insidious onset and developed when all four children were on treatment. Apart from mild finger clubbing

in two children, the remaining clinical features of recurrent respiratory tract infections are often found in children on combination chemotherapy. The diagnosis was established by bronchogram in three cases and at necropsy in the fourth (table III). Repeat chest radiographs showing persistent segmental collapse or consolidation suggested the possibility of bronchiectasis in three children. The child who died had similar x-ray findings. All four children had opaque sinuses on radiography. Immunoglobulin levels were measured by single radial immunodiffusion using commercially available tripartigen plates from Hoechst.

TABLE I—Respiratory symptoms

Case No:	1	2	3	4
Cough	Daily	Monthly	Weekly	Nocturnal
Haemoptysis	0	0	Once	Terminal
Sputum	Daily-weekly	Monthly	Daily	Monthly
Nasal discharge	Monthly	Monthly	0	Daily
Wheeze	Slight	Slight	0	Slight
Breathlessness	0	0	0	0
Others	Otorrhoea		Otorrhoea	Husky voice; halitosis

Predisposing factors—Possible predisposing factors to bronchiectasis complicating the course of leukaemia treatment are listed in table IV. Two children had progressive weight loss associated with gastrointestinal symptoms in the first six months of treatment. Barium meal and follow-through examinations showed malabsorption. Their nutrition and symptoms improved after a course of prednisolone and vincristine but they remained on suboptimal doses of chemotherapy because of myelosuppression. One patient (case 4) had episodes of diarrhoea and vomiting, which were apparently related to chemotherapy. The four children had no respiratory problems before the onset of leukaemia.

Treatment for leukaemia was based on the St Jude total V protocol,⁵ but reinduction courses were not given. One patient (case 1) had initially been treated by monthly courses of combination chemotherapy for 23 months and subsequently by three-weekly reinduction courses of prednisolone and vincristine every three months for 15 months. Haematological relapse occurred nine months after treatment stopped. After three years in complete continuous remission on a modified St Jude total V protocol this patient was again receiving no treatment at the time of writing. Cyclophosphamide was stopped in case 2 20 months after diagnosis. Cyclophosphamide was omitted altogether in case 3, and for the first 12 months thioguanine was given instead of mercaptopurine.

Treatment for bronchiectasis—Once the diagnosis of bronchiectasis had been established in three children prophylactic antibiotic treatment was started. This consisted of rotating co-trimoxazole, amoxycillin, erythromycin, and cephalixin at two-weekly intervals.

CASE 4

This boy was found to have acute lymphoblastic leukaemia when he was 3 years old. Subsequent treatment was according to the total V protocol except that reinduction courses of prednisolone and vincristine were not given. In the first year of treatment chemotherapy was interrupted four times, three times because of bone marrow depression and once because of unexplained diarrhoea and vomiting. Recurrent upper respiratory tract infections and otitis media were a persistent problem. Clinical and chest x-ray findings consistent with bronchopneumonia were first noted eight months after diagnosis and were associated with a neutropenia of $0.6 \times 10^9/l$. The chest x-ray changes improved but were still detectable six months later. He remained in complete remission confirmed by repeated bone marrow examinations under general anaesthetic, though hepatosplenomegaly was noted intermittently. Twenty-eight months after diagnosis he complained of pain in the left submammary region. Later that day he collapsed after

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TABLE II—Physical signs of bronchiectasis detected at outpatient clinic

Case No:	1	2	3	4
Posture	Normal	Normal	Normal	Normal
Chest shape	Harrison's sulci	Harrison's sulci; pectus carinatum	Normal	Normal
Chest expansion	2 cm	1.5 cm	2.2 cm	Not done
Clubbing	Early	Early	None	None
Adventitia	Persistent crepitation at left base	Intermittent bilateral crepitations	Chest clear	Intermittent crepitations at right base
Others	Recurrent otitis media; chronic serous otitis media; left tympanoplasty		Recurrent otitis media; chronic serous otitis media	Recurrent otitis media; chronic serous otitis media; splenomegaly; left Bell's palsy

TABLE III—Investigations performed to establish diagnosis

Case No:	1	2	3	4
Sputum cultures	<i>Streptococcus viridans</i> , <i>Neisseria</i> spp, <i>Haemophilus influenzae</i> , <i>Pneumococcus</i> spp	<i>Streptococcus viridans</i> , <i>Neisseria</i> spp, <i>Haemophilus influenzae</i>	<i>Streptococcus viridans</i> , <i>Neisseria</i> spp, <i>Haemophilus influenzae</i>	<i>Streptococcus pneumoniae</i>
Chest radiographs	Persistent collapse of left lower lobe	Persistent collapse of right middle lobe ± widespread pneumonitis	Persistent collapse of right middle lobe; patchy opacities at bases	Persistent opacities at right lung base
Bronchogram	Bronchiectasis of left lower lobe and lingula	Fusiform dilatation and crowding of right middle lobe bronchi	Slight saccular dilatation of right lower lobe and right middle lobe; crowding and saccular dilatation of left lower lobe and segmental bronchi	Not done
Maxillary sinus radiograph	Opaque	Opaque	Opaque	Opaque
Immunoglobulins (g/l):				
IgA	0.98	Not done	1.09	Not done
IgG	7.9		13.0	
IgM	2.2		1.01	

TABLE IV—Possible predisposing factors

Case No:	1	2	3	4
Neutropenia $<0.5 \times 10^9/l$ (No of episodes)	3	2	1	0
Recurrent upper respiratory tract infections	Yes	Yes	Yes	Yes
Recurrent pneumonia (No of episodes)	1	4	1	1
Weight loss and gastrointestinal symptoms	No	Yes	Yes	Yes

a massive haemoptysis. He was rushed to hospital but was dead on arrival.

Necropsy showed bronchiectasis and a large cast of blood in the right middle lobe. There was slight intra-alveolar haemorrhage throughout both lungs. Pus from the bronchiectatic lobe grew *Staphylococcus aureus* and *Bacteroides* spp. There was no gastrointestinal haemorrhage. The liver was enlarged to 820 g and showed fatty change. On microscopy there was portal cirrhosis of the liver, bronchiectasis, pneumonia, and emphysema but no evidence of leukaemia. The bone marrow was hypoplastic. Megakaryocytes were present and there was a relative eosinophilia. The spleen was enlarged to 105 g and histological examination showed excess fibrous tissue, histiocytes, and eosinophils.

Discussion

The mortality of children in complete remission when still on cytotoxic drugs is affected by the type of regimen and the length of survival, and may be as high as 16%.¹ The most common causes of death in remission are infections due to *Pneumocystis carinii*, viruses, and fungi.¹ Pulmonary haemorrhage, often associated with pneumonia, is a common cause of death in relapse² and has presented as unexplained infiltrates on chest radiographs.⁶ Death in remission from bleeding must be exceptional, apart from haemorrhagic cystitis due to cyclophosphamide.¹ Bronchiectasis causing massive haemoptysis can be added to this rare group of non-leukaemic causes of death.

Malnutrition,⁵ recurrent chest infections, myelosuppression, and immunosuppression⁷⁻⁹ are all well-recognised complications of cytotoxic therapy, which by its nature impairs tissue repair. The four children had evidence of chronic upper respiratory tract infections. The relative importance of all these factors is

impossible to evaluate, but bronchiectasis is not a surprising outcome. The clinical pattern of recurrent upper and lower respiratory tract infections associated with failure to thrive and gastrointestinal symptoms, which was present in three of our cases, is also a feature of combined immune deficiency states.¹⁰ Bronchiectasis has been reported in two out of six children with the syndrome of cellular immunodeficiency with immunoglobulins.¹¹ Immunoglobulin levels were normal in two of our children. Antibody responses are impaired in children on combination chemotherapy, though the total immunoglobulin concentration may not be reduced.¹² The diagnosis of five cases in two years suggests that bronchiectasis may be underdiagnosed or less common in other centres. Important variables elsewhere may be the use of intermittent schedules and the inclusion of reinduction courses.

A high frequency of pneumonitis (in 38 out of 93 patients) has been reported in children whose sole maintenance treatment consisted of methotrexate twice a week.¹³ In that study two children were found to have bronchiectasis but no further details were given. Methotrexate has also been implicated in mucosal abnormalities found on jejunal biopsy¹⁴ and may have been responsible for the abnormal barium meal and follow-through findings in cases 2 and 3. The portal cirrhosis in case 4 has been described in association with methotrexate therapy¹⁵ and may have been aggravated by the three-monthly general anaesthetics. Methotrexate-induced inflammation, of the respiratory tract unrelieved by regular steroids may have been a factor in establishing the bronchiectasis, just as radiation pneumonitis can be aggravated by cytotoxic drugs but is relieved by corticosteroids.¹⁶ Nevertheless, severe pneumonia, associated with myelosuppression, probably played a critical part in initiating the bronchiectasis.

Prophylactic antibiotics were started once the diagnosis of bronchiectasis had been established. The improvement on the chest radiography seen since then may have been influenced by the antibiotics. The results of routine sputum cultures were unremarkable (table III), but sensitivity patterns to apparent commensals might have been important, as the normal flora may be pathogenic in the immunosuppressed child. Chest radiography should be taken routinely in the follow-up of children on

cytotoxic treatment. Early diagnosis and vigorous treatment of respiratory complications may help to avert chronic infection and deaths in remission.

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Vitamin D supplements and 25-hydroxy vitamin D concentrations in the elderly

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Summary

Serial 25-hydroxy vitamin D (25-OHD) concentrations were measured in long-stay geriatric patients treated with vitamin D. Comparison between a treatment and a control group showed that a daily dose of 500 IU vitamin D produced a significant increase in 25-OHD levels by two months. The supplement had a striking effect when the initial 25-OHD level was low and very little effect when it was high. 25-OHD levels in subjects on 2000 IU vitamin D daily were only marginally higher than those in subjects on 500 IU.

A dose of 500 IU vitamin D daily should therefore produce adequate blood 25-OHD concentrations in most old people, and probably prevent most cases of osteomalacia in the elderly—though a large-scale study is needed to confirm this.

Introduction

Many sick old people have osteomalacia.^{1,2} Even more have low plasma 25-hydroxy vitamin D (25-OHD) concentrations.^{3,4} The simplest preventive approach might be to give vitamin supplements, but Corless *et al*³ found that a group of patients in a long-stay geriatric hospital had low 25-OHD levels despite the fact that they had been on a long course of vitamin D supplements. We report the effects of varying doses of vitamin D on 25-OHD concentrations in sick elderly patients.

Subjects and methods

All subjects were in a long-stay geriatric unit and were aged 68 to

92 years. Plasma 25-OHD concentrations were estimated using the method described by Belsey *et al*.⁵ The study was in three parts.

Part 1—In July 1976 eight subjects with plasma 25-OHD concentrations of under 15 nmol/l (6 ng/ml) were given 500 IU of vitamin D daily as one tablet of calcium and vitamin D BPC. 25-OHD concentrations were estimated on plasma samples collected each week for one month.

Part 2—In August 1976 12 subjects with 25-OHD concentrations of under 30 nmol/l (12 ng/ml) were given 2000 IU of vitamin D daily, again as calcium and vitamin D tablets. Plasma 25-OHD concentrations were measured at each week for one month and again at the end of six months.

Part 3—In November 1976 30 patients with plasma 25-OHD concentrations of 5 to 57 nmol/l (2 to 22.8 ng/ml) were divided at random into two groups. Fifteen subjects were given 500 IU of vitamin D daily as calcium and vitamin D tablets. The rest had no treatment. Plasma 25-OHD concentrations were measured every month for four months.

Results

Part 1—One of the subjects was discharged from hospital. There was little change in the mean plasma 25-OHD concentrations of the remaining subjects (fig 1).

FIG 1—Log₁₀ mean (± SE of mean) 25-OHD concentrations in subjects taking 500 IU vitamin D daily.

Conversion: SI to traditional units—25-OHD: 1 nmol/l ≈ 0.4 ng/ml.

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