Cryptosporidiosis and acute leukaemia

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Abstract

Six children with cryptosporidiosis, concurrently receiving chemotherapy for acute leukaemia (n=5) and lymphoma (n=1), are described. Two died with evidence of persistent infection. Modification of the chemotherapy regimens in the other four children was associated with successful eradication of the pathogen and permitted continued treatment of the primary disease.

Although the protozoal coccidian parasite, cryptosporidium, was first described as an animal pathogen in 1907, in more recent times it has been recognised increasingly as an important cause of diarrhoea in man. Surveys have shown it to be as frequent a cause of gastroenteritis as campylobacter, and more common than giardia, shigella, and salmonella. Cryptosporidiosis is a self limiting, although debilitating, disease in otherwise healthy people, but it may cause severe, intractable diarrhoea and malabsorption in immunosuppressed patients, and has been associated with a high mortality. Treatment with spiramycin, and bovine colostrum, has been used but with inconsistent results, and in the patient who remains immunocompromised, cryptosporidium has proved difficult to eradicate. Successful treatment has been documented in patients undergoing treatment for leukaemia, but at the expense of cessation of chemotherapy.^{1 2} Only one study has reported a spontaneous remission without alteration of treatment.³ However, this child was receiving an intermittent rather than a continuous chemotherapy regimen at the time.

We present our experience of the management of cryptosporidiosis occurring in children rendered immunosuppressed by antileukaemic treatment.

Patients and methods

Over the three year period from April 1986 to

April 1989, six children treated in our department developed cryptosporidiosis. Five were receiving chemotherapy according to the Medical Research Council United Kingdom acute lymphoblastic leukaemia (UKALL) protocol, and the sixth had undergone allogeneic bone marrow transplantation for acute myeloid leukaemia. Patient details are as shown in the table. In all cases, oocysts of cryptosporidium were detected in the same local laboratory by a cold Ziehl-Neelsen technique.

Management and outcome

Of the six infected children presented here, four were managed by modification but not cessation of chemotherapy, and there was successful eradication of the pathogen. Two (cases 1 and 6) became chronically unwell with the infection, and were intolerant of continuous oral maintenance treatment. Transfer to a less immunosuppressive intermittent intravenous regimen, as described for the treatment of B cell non-Hodgkin's lymphoma, was associated with a rapid resolution of symptoms, decline in oocyst excretion, and improved well being, thus permitting continued treatment of their malignancy. Two further children (cases 3 and 5) did not exhibit such florid chronic symptomatology, and were managed successfully by stopping methotrexate, which is known to have associated gastrointestinal side effects. The remaining two cases died with evidence of persistent infection, despite cessation of immunosuppressive agents, confirming the potentially lethal nature of this pathogen.

Discussion

These cases represent the wide range of disease process that can occur, the severity being highly dependent upon host factors. By means of treatment modification in four of the cases the pathogen was successfully eradicated. In addition, all but one of our patients were treated

Summary of patient details, management, and outcome in six cases of cryptosporidiosis occurring in childhood leukaemia

Case No	Sex	Diagnosis	Age (years)	Management	Outcome
1	Male	T cell lymphoma	4.1	Spiramycin, changed to intermittent treatment†	Well. Off treatment 18 months
2	Male	Acute lymphoblastic leukaemia	4.5	Spiramycin	Died. Cryptosporidiosis and cytomegalovirus pneumonitis found at necropsy
3	Female	Acute lymphoblastic leukaemia	11.3	Spiramycin, omission of methotrexate	Well. Off treatment 12 months
4*	Male	Acute myeloid leukaemia	3.8	Nil	Died. Cryptosporidiosis found at necropsy
5	Female	Acute lymphoblastic leukaemia	1.8	Spiramycin, omission of methotrexate for 4 months	Well. Remains on treatment
6	Male	Stem cell leukaemia	1.5	Spiramycin, changed to intermittent treatment†	Well. Remains on treatment

All children, excluding case 4, treated according to the UKALL X protocol.

*Allogeneic bone marrow transplantation after chemotherapy with daunorubicin, cytosine and thioguanine.

†As described in the United Kingdom children's cancer study group (UKCCSG) non-Hodgkin's lymphoma maintenance protocol.

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Accepted 27 October 1989

with spiramycin. Portnoy *et al* reported symptomatic improvement in five of 10 immunocompromised infected patients, most of whom had the acquired immunodeficiency syndrome,⁴ and other anecdotal reports exist. In our cases, however, there was little evidence for the success of spiramycin alone, without manipulation of the chemotherapeutic regimen to reduce immunosuppression.

Neutropenia was an associated finding in most of our cases, both at presentation of the infection, and also on attempted reintroduction of oral treatment. One reason for this could be an increased toxicity from chemotherapy. Methotrexate exerts its greatest toxic effects on the gastrointestinal tract and the bone marrow. It has been suggested that gut damage predisposes to a greater enterohepatic circulation of methotrexate.⁵ This could produce further epithelial damage as a result of high intraluminal concentrations, aggravating a pre-existing enteropathy as might occur in cryptosporidiosis. This presumed increased enterohepatic circulation might conceivably lead to greater marrow toxicity as well.

Infection with cryptosporidium can occur by varied routes. Although primarily a zoonosis, with some cases traceable to infected livestock or domestic pets, person to person spread within families, day care centres, and hospital are well documented. More recently waterborne outbreaks have also been recognised.

No animal contact was established for any of our cases. Two of the children (cases 1 and 2) had overlapping admissions on the same ward, and may demonstrate nosocomial infection. In two further children (cases 4 and 5), asymptomatic excretion of oocysts was discovered after a prolonged period of hospitalisation, with previously negative stools, which might again suggest a hospital acquired infection. Although there were no other documented cases of

cryptosporidiosis on the wards at those times, the oocysts are known to be resistant to many commonly used disinfectants and may even survive for many months at 4°C. Thus in wards where care of immunocompromised patients is undertaken, special precautions should be taken with known cases of infection to help prevent nosocomial spread.

Minor outbreaks of cryptosporidiosis were documented in the Bristol district during the winters of 1987 and 1988. In neither outbreak could a specific source be identified (S F Gray, personal communication). Only case 6 falls within the time period of one of these outbreaks, and therefore might represent a community acquired infection.

In summary, cryptosporidiosis remains a life threatening infection in children who are immunosuppressed by chemotherapy, as documented by two deaths among the six cases described. Modification rather than cessation of chemotherapy regimens may lead to successful eradication of the organism, however, without leaving the child vulnerable to the primary disease.

We wish to thank Dr SF Gray for details of community outbreaks of cryptosporidiosis in the Bristol area, and the department of microbiology, Bristol Royal Infirmary, for help with laboratory diagnosis.

Dr ABM Foot is supported by the Alex Wolton Trust.

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