

indications for the drugs were not known. Finally, the exposure periods of 45 days or ever exposure may not adequately explore the temporal relation between exposure to topical preparations and gastrointestinal complications. The variables were chosen empirically and different exposure variables may yield different results.

With these limitations in mind we could find no significant independent associations between use of topical non-steroidal anti-inflammatory drugs and admission to hospital for upper gastrointestinal bleeding and perforation.

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Risk of pneumococcal septicaemia in patients with chronic lymphoproliferative malignancies

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Guidelines for the prevention of infection in patients with an absent or dysfunctional spleen have recently been prepared.¹ However, another group of patients (with intact spleens) is also particularly susceptible to such infections. Lymphoproliferative malignancies such as chronic lymphocytic leukaemia, myeloma, and low grade non-Hodgkin's lymphoma are associated with immune paresis.² Such patients are often treated with corticosteroids, and a combination of these two factors renders them vulnerable to infections with encapsulated organisms such as *Streptococcus pneumoniae*. These infections have a high morbidity and mortality. Over a period of 16 months we found that pneumococcal sepsis was a far greater problem in patients with lymphoproliferative disorders than in patients who had had a splenectomy; we decided to investigate further.

Patients, methods, and results

We studied all blood cultures that gave positive results from 1 July 1993 to 31 October 1994 in South Tees Health District (population 300 000). Forty seven cultures grew isolates of *S pneumoniae*. Seven of the samples were from patients with a lymphoproliferative disorder (table).

In South Tees district about 200 patients have a lymphoproliferative disorder, giving an annual incidence of pneumococcal infection of 2.6% during the study. Four of the seven patients were hypogammaglobulinaemic and four were receiving corticosteroids. None of the patients was neutropenic and none had had a splenectomy. Mortality was 43% (table).

In this district about 180 patients have had a splenectomy (30 000 nationwide). None developed pneumococcal septicaemia during the study period. Forty episodes of pneumococcal septicaemia thus occurred in the general population, giving an annual incidence of 0.01%. Of these 40 patients, only one was immunocompromised; this patient had ectodermal dysplasia and IgG₂ deficiency but survived. Mortality was 25% (10 patients died).

Comment

This report highlights the increased risk of pneumococcal septicaemia in chronic lymphoproliferative malignancies (table). These patients tend to be elderly; only one was aged under 65. Mortality in these patients was higher (43%) than that in patients of all ages from South Tees who were not immunosuppressed by disease or drugs (25%).

Measures should be implemented to prevent such infections or at least initiate prompt referral and treatment. Similar measures have been proposed in those at high risk of sepsis after splenectomy and in those at risk of varicella infection while taking corticosteroids.¹³ The patient should be educated in the same way as patients who have had a splenectomy or who have a dysfunctional spleen.¹ Patient information may be documented on a card, which the patient should carry at all times. General practitioners should

Details of patients with lymphoproliferative disorder and pneumococcal septicaemia

Case No	Age (years)	Sex	Diagnosis	Delay in admission or treatment (days)	Antibiotic prophylaxis	Corticosteroid treatment	IgG (g/l)*	Treatment before admission	Outcome
1	65	M	Chronic lymphocytic leukaemia	6	Yes	No	2.8	Ciprofloxacin	Survived
2	55	F	Multiple myeloma	1	No	Yes	3.2	None	Survived
3	71	F	Multiple myeloma	1	No	Yes	7.2	None	Died
4	71	M	Non-Hodgkin's lymphoma	7	No	Yes	11.7	None	Died
5	65	M	Non-Hodgkin's lymphoma	3	No	Yes	6.5	None	Survived
6	73	F	Chronic lymphocytic leukaemia	4	No	No	35.1	Ciprofloxacin	Died
7	74	F	Non-Hodgkin's lymphoma	2	No	No	14.6	None	Survived

*Normal range 7.2-17.0 g/l.

be informed of the risks to these patients and the need for prompt referral to hospital.

Patients may be given a supply of penicillin (or amoxicillin) to be kept at home and taken when symptoms of sepsis develop. However, patients must also be advised to obtain urgent medical attention. Ciprofloxacin has variable activity against pneumococcus and therefore should not be used as first line treatment unless later sensitivities indicate otherwise.⁴ The drug was ineffective before admission in two of our patients (cases 1 and 6).

Lymphoproliferative malignancies are associated with hypogammaglobulinaemia. Prophylactic intravenous immunoglobulin is beneficial, especially in those who have low concentrations of functional IgG and are susceptible to recurrent bacterial infections.⁵

Immunisation with pneumococcal vaccine is associated with an impaired response in immunocompromised patients. If such patients are to be immunised those that do not show a rise in antibody titre could be

considered for prophylactic intravenous immunoglobulin.

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Mechanisms behind hypocholesterolaemia in hairy cell leukaemia

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Hypocholesterolaemia is a common finding in various malignant disorders, such as acute myeloid leukaemia, chronic myeloproliferative disorders, and carcinoma of the colon.¹ It is unclear whether it is a risk factor for the development of malignancy or secondary to the cancer.¹ In acute myeloid leukaemia hypocholesterolaemia is the result of an increased uptake of cholesterol by leukaemic cells,² as indicated by an inverse correlation between cholesterol concentration and the activity of low density lipoprotein receptors in leukaemic cells. Hypocholesterolaemia is uncommon in lymphoid tumours, such as lymphoma and chronic lymphocytic leukaemia, but has been observed in patients with hairy cell leukaemia³—a rare disease affecting middle aged men that is clinically characterised by cytopenia, splenomegaly, and impaired immunity and may be fatal after an infection.

Patients, methods, and results

To evaluate mechanisms behind the development of hypocholesterolaemia in patients with hairy cell leukaemia, we analysed serial serum lipid concentrations after treatment with 2-chlorodeoxyadenosine in 24 patients with active disease.⁴ Total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglyceride concentrations all rose significantly after treatment ($P < 0.00001$, $P = 0.00002$, $P = 0.0001$, and $P = 0.02$, respectively). The figure shows the pattern for low density lipoprotein cholesterol concentration. The mean difference in low density lipoprotein cholesterol concentration from baseline values was 0.90 mmol/l (95% confidence interval 0.55 to 1.25 mmol/l) in 24 patients at three months ($P < 0.001$) and 0.98 mmol/l (0.62 to 1.33 mmol/l) in 18 patients at six months ($P < 0.001$). In one patient repeated serum cholesterol and haemoglobin concentrations before diagnosis showed that the

hypocholesterolaemia developed in parallel with anaemia, a marker for hairy cell leukaemia.⁵

We also analysed low density lipoprotein receptor activity by the cellular degradation of low density lipoprotein labelled with iodine-125 in isolated blood mononuclear cells from 12 patients with circulating hairy cells.² Only one patient showed increased low density lipoprotein degradation, and this patient was not hypocholesterolaemic.

Comment

Hypolipidaemia, mainly due to a low concentration of low density lipoprotein cholesterol, is a frequent finding in advanced hairy cell leukaemia, but values revert to normal after successful treatment. Thus it is a disease related phenomenon and not a predisposing factor for tumour development. Hypocholesterolaemia in patients with active disease was not caused by low density lipoprotein receptors being more active in hairy cells than in normal blood leucocytes; this indicates that the disease mechanism is different in hairy cell leukaemia and acute myeloid leukaemia, in which leukaemic cells show increased uptake of cholesterol.²

The lipid concentrations were related to the size of the spleen,⁵ and hypocholesterolaemia is more common in patients with splenomegaly than in those with a normal sized spleen or those who have had a splenectomy. Hairy cell leukaemia may influence the lipid metabolism of the reticuloendothelial system through cytokines such as granulocyte-macrophage colony stimulating factor and platelet derived growth factor, both of which influence lipid metabolism.

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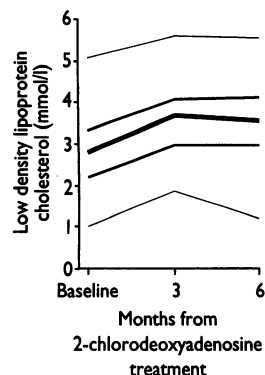
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Median low density lipoprotein cholesterol concentrations with quartile and extreme values in patients with hairy cell leukaemia after 2-chlorodeoxyadenosine treatment