LETTERS TO THE EDITOR

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Fludarabine in the treatment of an active phase of a familial haemophagocytic lymphohistiocytosis

Editor,—Familial haemophagocytic lymphohistiocytosis (FHL) is a lethal disease with an uncontrolled activation of T lymphocytes and macrophages due to a perforin gene defect.¹ The only current curative treatment is bone marrow transplantation. However, favourable outcome is associated with clinical remission status at the time of the procedure.¹ Unfortunately, the use of steroids, etoposide (VP16), cyclosporin A, and antithymocyte globulins alone or in association frequently fails to control recurrent active phases.

BL, a 2 month old boy, was admitted in June 1999 for an active phase of FHL. His elder brother had died of FHL. The diagnosis was established on clinical (vomiting, fever, pallor, hepatosplenomegaly) and biological features (pancytopenia, hypertrophic- cedema (3.82 mmol/l), haemodilution, hypofibrinemia (0.65g/l), a moderate elevation of aspartate transaminases (2N) and haemophagocytosis on bone marrow aspirates). No central nervous system abnormality was observed on cerebrospinal fluid analysis and cerebral magnetic resonance imaging.

A first remission was obtained with the combination of steroids: prednisolone (2 mg/kg/day), VP16-phosphate (150 mg/kg/day, d1–d3), cyclosporin A (4 mg/kg/day, continuous infusion), and antithymocyte globulins (10 mg/kg/day, d1–d5) three weeks after diagnosis. Despite maintenance treatment, relapse occurred one month later with severe pancytopenia. No remission was obtained with a second course of steroids, VP16-phosphate, and antithymocyte globulins. Two and a half months (day 76) after diagnosis, a course of fludarabine (30 mg/m²/day for four days) was initiated and dramatically improved our patient’s condition regarding the clinical and all biological criteria of FHL. An additional course was given on day 92. Transient neutropenia and a noticeable lymphopenia were observed. After a busulfan (120 mg/m²/day for four days) and cyclophosphamide (30 mg/kg/day for four days) conditioning regimen one month after the last course of fludarabine, we performed a haematopoietic stem cell transplant with the father’s CD34+ HLA-half-identical peripheral cells (Miltenyi, Germany). Haematological reconstitution was observed from day 24 post transplant. There was transient grade II acute graft versus host disease (skin, liver). No relapse of FHL has occurred to this date (day 330 post transplant).

Treatment of active phases of FHL is based on drugs killing immunocompetent cells. Fludarabine is a purine antimetabolite with a strong immunosuppressive action.² During treatment with fludarabine for B cell malignancies, an important decrease in the T cell subpopulations, particularly of the natural killer phenotypes (CD16/56+), was observed. Our patient’s response to the first course of this drug was dramatic and allowed bone marrow transplant when in good clinical condition. Nevertheless a series of patients is needed to assess the efficacy of fludarabine for the treatment of active phases of FHL.

We thank Dr JL Stephan for his helpful clinical advice.

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Visceral leishmaniasis: also beware of these deceptive microbes in non-endemic countries!

Editor,—We read with interest the report by Grech et al.³ From their population based study, it seems that the annual incidence of visceral leishmaniasis (VL) declined considerably in Malta as a result of the eradication of stray dogs. VL is still endemic around the Mediterranean Sea and sporadic cases are reported in children living in Northern Europe. It seems likely that with increasing tourism the incidence of VL will also increase in areas where until recently this condition would not even be thought of. During the last 18 months, we have diagnosed three children with VL. As the presentation features can be fairly dramatic and physicians in Northern Europe are not always alert to the possibility of this condition, we would like to call attention again to the possibility of VL in non-endemic countries.

The main clinical features of the patients are shown in table 1. All three children presented with spiking high fevers, anorexia, hepatosplenomegaly, and pancytopenia. The onset of the symptoms was insidious and it took 3–12 weeks to establish the diagnosis. In all three patients this was achieved through bone marrow aspiration and the demonstration of the typical amastigotes in macrophages. The diagnosis was further confirmed through the demonstration of antibodies to the leishmania parasite. All three patients needed erythrocyte transfusions and patient three also needed platelet transfusions. A 5–10 day course of liposomal amphotericin-B was given to all three children. The treatment was well tolerated, and they all became afebrile within a week. Pancytopenia subsided over the ensuing 2–3 weeks and the children gradually returned to normal activity.

Table 1 Patient characteristics

<table>
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<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<tr>
<td>Age (years)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>South of France</td>
<td></td>
<td>Elba</td>
</tr>
<tr>
<td>6</td>
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<tr>
<td>7</td>
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<td>Interval from exposure to appearance of symptoms (months)</td>
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<td>2</td>
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<tr>
<td>6</td>
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<tr>
<td>Interval between appearance of symptoms and diagnosis (weeks)</td>
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<td>3</td>
<td>12</td>
</tr>
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<td>6</td>
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<td>Hepatomegaly (cm)</td>
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<tr>
<td>Splenomegaly (cm)</td>
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<td>Hb (mmol/d)</td>
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<td>WBC (×10⁹/cm³)</td>
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<td>Platelets (×10³/cm³)</td>
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<td>Serum IgG (g/l)</td>
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LDH = lactate dehydrogenase
Intestinal inflammation in cystic fibrosis

EDITOR,—Following their studies of whole gut lavage fluid, Smyth et al have suggested that a non-idiopathic intestinal inflammation occurs constitutively in patients with cystic fibrosis (CF), as a consequence of a proinflammatory effect of the patient’s CFTR mutations. They reported marginally elevated excretion of IgG, IgM, interleukin 1 (IL-1), neutrophil elastase, and eosinophil cationic protein, and much more significant increase in excretion of IL-8 and albumin, but no increase in excretion of α1 antitrypsin or IgA. In this study where lavage fluid was administered continuously, and intestinal effluent was collected in discrete samples, pooling of the effluent before analysis would have allowed small differences in calculated inflammatory marker outputs to be interpreted as representative of gastrointestinal output. Of all the inflammatory markers presented, only IL-8 shows a range of cytokine outputs in CF patients with or without fibroscopy, colonoscopy that did not extend into the range seen in controls, in these non-parametric databases. The author’s evidence for intestinal inflammation therefore relies heavily on the validity of their IL-8 Quantikine assay (R&D Minneapolis) protocol.

I have explored the validity of this assay for use in supernatants of faecal homogenates in children with cystic fibrosis and found it wanting. Recovery of a 500 pg/ml spike of IL-8 progressively increased from 41% in samples which were a 12-fold dilution of faeces to 180% in samples which were a 120 000-fold dilution of faeces, when used according to manufacturer’s instructions. Prediluting the samples 50/50 in newborn calf serum, and using calf serum for further dilutions gave this assay (R&D catalogue no DB000) mean (SD) spike recovery of 92.1 (12.5%) and coefficients of variation of 3.46% (intra-assay) and 6.85% (interassay). Without knowledge of the IL-8 ELISA validation data of Smyth et al, I assume that this assay returns similarly spuriously high IL-8 concentrations in polyethylene glycol based whole gut lavage fluid to my 120 000-fold dilution faecal supernatant. The absence of a significant difference between CF patients and controls in their α1 antitrypsin outputs suggests that intestinal inflammation was not present in the CF patients. Overestimation of the WCLF IL-8 concentration would explain the apparently implausibly large volumes of swallowed sputum that the authors estimate would be required to account for their results. In this study which could not turn off the involuntary eructor, but did dramatically increase the rate of intestinal transit and exclude exogenous pancreatic enzymes, swallowed sputum is the most likely explanation for the results.

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The potential benefits of lumbar puncture include making a diagnosis of meningitis and cerebral spinal fluid (CSF). The antibiotic regimen is no different for either meningococcal meningitis or septicaemia, with seven days of a third generation cephalosporin being the treatment of choice because of improved CSF penetration. There are no reports of meningococcal resistance to this treatment in the UK, so performance of a lumbar puncture for bacterial sensitivity testing appears to be unnecessary.

Prospective therapy while awaiting results of culture or PCR from blood seems to be a small price to pay in this life threatening illness. An analogy could be drawn from the management of epiglottitis. It is generally accepted that throat swabs should not be taken from children with epiglottitis until the child’s airway has been protected, because of the risk of clinical deterioration. It is time that textbooks of emergency paediatrics stated clearly that lumbar punctures on children with a haemorrhagic rash, and clinical signs of meningococcal infection, should not be carried out until the clinical condition has been stabilised, and only if the procedure will add further valuable information that cannot be obtained elsewhere.

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Editor,—I was dismayed to see your publication of the letter by Dr Sam regarding the need to be weighed against the risk of causing unnecessary harm. While fully understanding the need to get as much information as possible, the benefits of isolating the causative organism are undoubtedly greater than the potential risks of blood borne infections such as hepatitis B and C are obvious, especially in the current climate of the AIDS epidemic. The role of parental antischistosomal therapy in the prevention of malaria infection in children with high risk related admission rates and the type of preventive measures used to keep such infants out of hospital is a matter for further consideration. I would like to emphasise the “biggest picture” also warrants further consideration.

During the winters of 1998–99 and 1999–2000, we recorded our admissions who were RSV positive and had a Cambridge “CB” postcode. “At risk” infants—that is, ex-preterm infants who are physically and financially able. In our area, the potential e...