Acute renal failure in visceral leishmaniasis treated with sodium stibogluconate

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Introduction

Visceral and cutaneous leishmaniasis are endemic in the Maltese islands. Leishmania infantum has been cultured from humans, dogs and the sandfly Phlebotomus perniciosus (Gradoni et al., 1991). Since 1955 the incidence of leishmaniasis has been about 10 local new cases per year compared with about 150 cases per year in the immediate post-war period (Cachia & Fenech, 1964; Ministry of Health, Malta, unpublished reports).

Parenteral sodium stibogluconate is still the standard treatment for leishmaniasis, despite considerable renal and cardiac toxicity (WHO, 1984). We report a case of visceral leishmaniasis with acute renal failure associated with the use of this drug, followed by successful treatment with a prolonged course of metronidazole.

Case report

A 53 year old white male weighing 70 kg was admitted to a general medical ward with visceral leishmaniasis. He also suffered from diabetic nephropathy and angina pectoris. Four years previously, cholecystectomy had been performed for acute cholecystitis at another hospital. He reported general ill health and low grade temperature with the former high dose intravenous stibogluconate. The satisfactory clinical response could only be the result of treatment with metronidazole.

Table 1. Haematological and renal changes during treatment of visceral leishmaniasis with sodium stibogluconate and metronidazole

<table>
<thead>
<tr>
<th>Day</th>
<th>Before stibogluconate</th>
<th>6 d after stibogluconate stopped</th>
<th>Start of metronidazole</th>
<th>After 5 d of metronidazole</th>
<th>After 12 d of metronidazole</th>
<th>Follow up at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Before stibogluconate</td>
<td>7-7</td>
<td>66 000</td>
<td>57 000</td>
<td>173 000</td>
<td>170 000</td>
</tr>
<tr>
<td>7</td>
<td>6 d after stibogluconate stopped</td>
<td>7-2</td>
<td>47 000</td>
<td>50 000</td>
<td>147 000</td>
<td>161 000</td>
</tr>
<tr>
<td>14</td>
<td>Start of metronidazole</td>
<td>6-5</td>
<td>57 000</td>
<td>89 000</td>
<td>213 000</td>
<td>160 000</td>
</tr>
<tr>
<td>19</td>
<td>After 5 d of metronidazole</td>
<td>8-8</td>
<td>57 000</td>
<td>89 000</td>
<td>213 000</td>
<td>170 000</td>
</tr>
<tr>
<td>26</td>
<td>After 12 d of metronidazole</td>
<td>7-2</td>
<td>173 000</td>
<td>173 000</td>
<td>173 000</td>
<td>170 000</td>
</tr>
<tr>
<td>50</td>
<td>Before second course of metronidazole</td>
<td>7-8</td>
<td>147 000</td>
<td>147 000</td>
<td>147 000</td>
<td>147 000</td>
</tr>
<tr>
<td>80</td>
<td>After 30 d of metronidazole</td>
<td>9-9</td>
<td>161 000</td>
<td>250 000</td>
<td>430 000</td>
<td>430 000</td>
</tr>
<tr>
<td>140</td>
<td>Follow up at 3 months</td>
<td>9-6</td>
<td>170 000</td>
<td>1900 000</td>
<td>440 000</td>
<td>440 000</td>
</tr>
</tbody>
</table>

He reported general ill health and low grade temperature for the previous 2 years. He was pale and the spleen was palpable 15 cm below the left costal margin. A chest X-ray and computerized tomography scan of the abdomen did not reveal any abnormality besides splenomegaly. Pancytopenia with a polyclonal gammopathy was present. Examination of bone marrow aspirate showed typical Leishmania intracellular parasites. Urine analysis revealed proteinuria (+ +), and serum creatinine was 175 µmol/litre.

A daily dose of 600 mg sodium stibogluconate was administered intravenously. Each infusion was followed by nausea and vomiting for 2 h. Stibogluconate was stopped after the third dose as, despite adequate intravenous hydration and normal serum amylase, the patient became oliguric with rising levels of serum creatinine (Table). His renal failure was treated conservatively and his daily urine output gradually increased.

Twelve days after stopping the stibogluconate, the patient was still febrile and the spleen was still palpable. Metronidazole was administered according to the regime suggested by Mishra et al. (1985), i.e. 500 mg intravenously 3 times a day for 5 d followed by 800 mg orally 3 times a day for 7 d. His temperature rapidly subsided and his spleen was no longer palpable at the end of the treatment course.

One month later the patient presented again with low grade temperature and falling platelet and white cell counts. Bone marrow examination was refused by the patient, but the clinical features strongly suggested recurrence of leishmaniasis. Metronidazole 400 mg 3 times a day orally was re-started for 30 d. The fever subsided and the platelet count returned to normal.

The patient was followed-up for one year and showed no clinical or haematological evidence of further relapse.

Discussion

This patient had diabetic nephropathy with renal impairment before treatment. Even though he received less than 10 mg/kg of stibogluconate he developed symptoms typically associated with toxic blood levels, with rapid deterioration of renal function. We could find only one similar case in the literature (Vega et al., 1983).

As sodium stibogluconate is excreted similarly to insulin (Rees et al., 1980), it was calculated that most of the circulating stibogluconate had been excreted within 72 h of the last dose, even with a glomerular filtration rate as low as 5 ml/min. It is therefore very unlikely that the successful treatment of leishmaniasis could be attributed to the stibogluconate. The satisfactory clinical response could only be the result of treatment with metronidazole.

Different species of Leishmania in various parts of the world have different susceptibilities to metronidazole [a list of references is obtainable from the author on request]. L. donovani, L. infantum and L. mexicana seem to be the most likely to respond.

The promising results obtained by Mishra et al. (1985) with metronidazole were not confirmed by Thakur & Sinha (1989). The higher plasma levels achieved with the former high dose intravenous regime could explain these different results.

As most anti-leishmanial drugs in use today are nephrotoxic, and metronidazole is almost entirely metabolized in the liver, metronidazole is probably a first line drug for the treatment of leishmaniasis in the presence of renal compromise.

References

Short Report

Isolation of Leishmania infantum from the blood of a patient with AIDS using sandflies.

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Leishmaniasis associated with human immunodeficiency virus (HIV) infection is being increasingly reported in Mediterranean countries, mainly Spain (Altes et al., 1991; Berenguer et al., 1989; Montalban et al., 1989; Peters et al., 1990). Over 30% of the patients do not exhibit any specific anti-Leishmania antibodies despite the fact that parasites are present in bone marrow aspirates (Alvar et al., 1989). Leishmania infantum is usually scarce in the samples, making its demonstration by Giemsa staining difficult.

Therefore, alternative techniques, such as cultivation or the polymerase chain reaction (PCR), are being developed as methods to amplify the organisms. However, the peculiar clinical status of some patients presents difficulties in obtaining an adequate sample for diagnosis.

Here we report a patient suffering from acquired immune deficiency syndrome (AIDS) and anti-Leishmania antibodies at a titre of 1:64 by indirect fluorescent antibody testing. Treatment was immediately started with pentavalent antimonials. The low level of specific antibodies prompted an attempt to demonstrate the presence of amastigotes. Bone marrow aspiration and blood sampling were attempted 2 days after the beginning of treatment, but the former was impossible due to the clinical condition of the patient. Only 3 ml of blood were obtained: 1.5 ml was unsuccessfully used in an attempt to separate the buffy coat in a Ficoll® gradient for the PCR. Fifty-three female Phlebotomus perniciosus, from a sandfly colony established in our laboratory with specimens collected in Spain (Molina, 1991), were artificially fed on the remaining 1.5 ml of blood using a membrane feeding apparatus with the skin of a 3-day-old chicken as membrane (Ward et al., 1978). Thirty-five sandflies were dissected 7 days after feeding and 9 were infected with Leishmania (25-7%). The Leishmania stock was isolated in NNN medium and characterized by the analysis of 15 enzymes as L. infantum zymodeme 33.

The blood was handled according to the recommendations of the Centers for Disease Control, USA (CDC, 1988), and the membrane feeding procedure was carried out in a sealed room with double doors. The holding cage with the fed flies was kept in a chamber made of transparent plastic material and the unfed flies were removed with a mechanical aspirator and immediately killed.

We suggest this simple xenodiagnostic method as an alternative means of demonstrating Leishmania in specialized laboratories when the usual techniques have failed and the suspicion of leishmaniasis is strong.

Additionally, we emphasize the ease with which P. perniciosus was experimentally infected. This suggests, from the epidemiological point of view, that some immunodepressed patients suffering from leishmaniasis could serve as reservoirs of this parasitic disease.

References


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