Relapsing *Salmonella enteritidis* infection in a young adult male with chronic granulomatous disease

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Summary: A case of chronic *Salmonella enteritidis* infection in a young adult patient is reported. Following an initial enteritis with bacteraemia, the illness lasted for a 7-year period and was characterized by recurrent pyrexia, anaemia, weight loss and marked hepatosplenomegaly.

Investigations revealed that the patient suffers from a mild form of chronic granulomatous disease presenting in adolescence.

Introduction

Chronic granulomatous disease (CGD) is a rare syndrome characterized by recurrent, often prolonged purulent infections associated with impaired neutrophil bactericidal activity. The disease usually arises in infancy with a fatal outcome by adolescence. However, several cases of young adults with CGD have been reported and recently there has been increased recognition of the mild form of the disease.

Infections are caused predominantly by catalase-positive micro-organisms such as staphylococci, *Escherichia coli*, Serratia spp., *Aspergillus* spp. and *Candida albicans*.

Described here is an unusual case of a young male patient with a mild form of CGD who presented with a chronic salmonella infection which ran a relapsing course over a 7-year period.

Case report

A 20 year old male patient presented in 1980 with acute diarrhoea and high fever. *Salmonella enteritidis* phage type 8 was isolated from blood and faeces. He was treated with intravenous ampicillin for 10 days and parenteral fluid replacement. In 1984 he was readmitted with a few weeks' history of anorexia, general malaise, weight loss and recurrent epistaxis. On examination he was anaemic with a temperature of 38°C. There were signs of consolidation at the lower lobe of the left lung with pleural effusion. Laboratory investigations were as follows: haemoglobin (Hb): 8.6 g/dl (normal range: 13.5–18), white cell count (WCC): 5.3 x 10⁹/l (normal range: 4–11), platelet count: 700 x 10⁹/l (normal range: 150–400) and erythrocyte sedimentation rate (ESR): 54 mm/h (normal range: 0–5). Monospot test was positive. Urea and electrolytes were normal and liver function tests showed mildly raised alkaline phosphatase (ALP) 320 IU/l (normal range: 30–120). Blood and pleural fluid cultures were negative but pleural fluid examination revealed sheets of lymphocytes associated with atypical mononuclear cells suggestive of Epstein–Barr virus infection. He was transfused with 4 units of blood and his general condition improved. He was discharged and followed up in the outpatient clinic.

A year later he was readmitted for investigation of anaemia and recurrent pyrexia. Liver function tests showed a normal bilirubin level but elevated values of enzymes; serum aspartate transaminase: 54 IU/l (normal range: 8–40), ALP: 703 IU/l. Blood, stool and urine cultures were negative. Hepatitis A and B, brucellosis, toxoplasmosis, cytomegalovirus infection and leptospirosis were all excluded by serological investigations. Trephine biopsy of the iliac crest showed an active marrow with non-caseating granulomata. He was transfused with 3 units of blood and followed up as an outpatient.

In March 1986 he was readmitted with fever, progressive weight loss and epistaxis. On examination he was pyrexial, there was marked anaemia and moderate hepatosplenomegaly. Liver biopsy showed non-caseating granulomata. Anti-tuberculous therapy was commenced with ethambutol, isoniazid and rifampicin. His fever settled with
clinical improvement and some regression of the hepatosplenomegaly but liver function tests continued to be abnormal with markedly elevated enzyme levels. Treatment was discontinued after 9 months in December 1986.

Three weeks later he presented again with fever, anaemia and weight loss. On this occasion S. enteritidis phage type 8 was isolated from both blood and stool. Co-trimoxazole 960 mg twice daily was commenced with remarkable improvement clinically and biochemically. There was marked reduction of the hepatosplenomegaly. Endoscopic retrograde cholangiography showed normal gall bladder and biliary tree. Bile cultures were negative. Bone scan and human immunodeficiency virus (HIV) screening were negative. Repeated echocardiography showed no evidence of endocarditis. Haemoglobin electrophoresis and immunoglobulin studies were normal. There was a normal response to the streptokinase-streptodornase and candidin skin tests indicating intact cell mediated immunity. T cell assay and complement studies were normal. The co-trimoxazole treatment was continued for 3 months. Three months after stopping treatment he relapsed and was admitted with fever and general malaise. S. enteritidis phage type 8 was again isolated from blood cultures. Co-trimoxazole was restarted and continued for another 6 months. He has now been clinically well for 18 months since stopping the antibiotics. On a recent physical examination the patient was well developed and the hepatosplenomegaly had fully resolved. His biochemical and haematological indices remain normal.

The patient's two siblings and parents were all in good health. The patient's maternal grandmother was in good health but his maternal grandfather had a life long history of skin infections and was said to have died of tuberculosis at the age of 62.

The patient had neutrophil function studies as described below.

Methods

Preparation of polymorphonuclear neutrophils (PMNs) PMNs were isolated from the patient's blood by sedimentation of red cells in the presence of dextran, centrifugation of the supernatant on Ficoll-Sodium metrizoate (Lymphoprep, Nycomed UK) and hypotonic lysis of the red cells remaining in the granulocyte pellet.4

Cytochrome b-245 was detected on Western blots of sodium dodecylsulphate-polyacrylamide gels of a cell extract from the patient's neutrophils. Normal cell extracts were used for comparison. Extracts were prepared by sonication of hypotonic suspensions of neutrophils. The immune-reaction on the blots was carried out using a specific antibody against the 22 KDa alpha subunit of the cytochrome.5

Superoxide anion generation was measured as the rate of superoxide dismutase-inhabitable reduction of cytochrome c, using phorbol myristate acetate (200 ng/ml) as the stimulus.6

Nitroblue tetrazolium (NBT) dye reduction Quantitative NBT determinations were performed by the method of Baehner and Nathan.7

Aerobic and anaerobic leucocyte bactericidal activity This was performed as described by Mandell.8 Four ml of a PMN suspension containing 5 x 10^6 bacteria and 5 x 10^6 PMN were used. Samples were removed at 0, 30, 60 and 120 minutes. PMNs from healthy adults were obtained as controls and were always run parallel with the PMNs of the patients.

Results

Cytochrome b The haem-containing alpha sub-unit of the cytochrome was not detectable immunologically on Western blot.

Superoxide generation The patient's neutrophils generated superoxide at 1.3 nmol/min/10^7 cells, that is, approximately 1% of the normal rate.

Reduction of nitroblue tetrazolium When examined under the microscope, nearly all the phorbol myristate acetate-treated granulocytes from the patient reduced NBT. However, as shown in Table I, the intensity of the reduction was low in comparison to the dark reaction products in control cells, and most of the cells presented only a faint blue granular appearance in their cytoplasm.

Staphylococcal bactericidal index Granulocytes from the patient showed defective in vitro bac-

Table I Reduction of nitroblue tetrazolium (NBT) by granulocytes of the patient and controls

<table>
<thead>
<tr>
<th>Degree of NBT reduction*</th>
<th>Subject (% granulocytes)</th>
<th>Carrier of CGD†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient (Patient) Normal control</td>
<td>45</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Weak</td>
<td>95</td>
<td>2</td>
</tr>
<tr>
<td>Strong</td>
<td>4</td>
<td>97</td>
</tr>
</tbody>
</table>

*Individual granulocytes were examined under direct microscopy. Lack of reduction was scored as 0, weak reduction as 1, and strong reduction as 2; †Mother of a patient with X-linked CGD.
tericidal activity against *Staphylococcus aureus*
502A on three occasions. In a typical experiment
normal granulocytes killed nearly all bacteria by 60
minutes; 3% of colony-forming units still survived
after 60 minutes, and 8% after 120. The patient's
granulocytes failed to kill 28% of bacterial colony-
forming units after 60 minutes, and 75% after 120
minutes.

These results indicate that this patient suffers from
a variant form of chronic granulomatous disease. It
would appear that the ability of the phagocytes to
generate a very low level of superoxide on
stimulation is sufficient to result in a milder form of
the disease.

**Discussion**

Systemic infection may follow salmonella gas-
troenteritis. This is more likely in immunosup-
pressed patients. In these cases chronic infection
characterized by recurrent bacteraemia and clinical
relapse may ensue. This has been particularly
associated with Hodgkin's lymphoma, asplenia
and acquired immune deficiency syndrome.

A further case is described here in an adolescent
patient who had a mild form of CGD. He exhibited
a chronic illness characterized by anaemia, weight
loss and relapsing febrile episodes. *Salmonella enteritidis* phage type 8 was isolated from blood
cultures on three separate occasions over a 7-year
period. Partial resolution of symptoms and signs
occurred following anti-tuberculous therapy, but
there was a relapse after the drugs were stopped.
More noticeable improvement was seen after a
3-month course of co-trimoxazole although relapse
was again seen after cessation of the drug. A
subsequent 6-month course was successful in
eradicating the infection.

The diagnosis of tuberculosis was suggested by
the presence of granulomata in the bone marrow
and the liver. In retrospect these were also consist-
ent with histological findings associated with
CGD and chronic salmonellosis. It is likely that
the response seen with anti-tuberculous therapy
was due to rifampicin which is active against
salmonella and has been used successfully in
combination with other antibiotics for treating
salmonella carriers.

The aetiology of the chest infection and pleural
effusion which occurred in 1984 is unclear. Pul-
monary involvement in Epstein-Barr virus infec-
tion is rare. Salmonellosis has been noted to
invoke the production of atypical mononuclear
cells and it is more likely that the episode
represented recurrence of salmonella infection
with a false positive monospot test.

The reported patient suffers from a very rare
variety of CGD. His cells did respond to maximal
stimulation, but with a minute proportion of the
normal production of superoxide. This would
explain why he was unable to eradicate the sal-
monella infection but has been relatively well apart
from that. Patients with a mild form of CGD
usually present with skin infection, but our patient
presented with recurrent invasive salmonellosis
which, as far as we are aware, has not been
previously described.

Recent study has demonstrated partial correc-
tion of the cellular defect in CGD by subcutaneous
interferon gamma. The results of the study sug-
gest a potential role for interferon gamma in the
prophylaxis of infections or as an adjunct to
conventional antimicrobial therapy for acute infec-
tions in patients with CGD.

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