Cefuroxime induced lymphomatoid hypersensitivity reaction

S A M Saeed, M Bazza, M Zaman, K S Ryatt

Abstract
An 84 year old women developed erythematous blotchy erythema and purpuric rashes over the lower limbs three days after being started on intravenous cefuroxime for acute diverticulitis. A skin biopsy specimen showed a mixed infiltrate of lymphoid cells and eosinophils; many of the lymphocytes were large, pleomorphic, and showed a raised mitotic rate. Immuno-histochemistry showed the infiltrate to be T cell rich, with all the large cells being CD30 positive. Typical mycosis fungoides cells, marked epidermotropism, and Pautrier’s abscesses were not seen. The rash disappeared 10 days after cessation of cefuroxime and the patient remained asymptomatic 15 months later. This apparent cutaneous T cell lymphoma-like reaction is best described as lymphomatoid vascular reaction. The drug induced immune response with an atypical cutaneous lymphoid infiltrate mimics a cutaneous pseudolymphoma.

Case report
An 84 year old women, with established diverticula disease, presented as an emergency with a short history of fever, acute abdominal pain, and diarrhoea. On examination she was found to be toxic, febrile, dehydrated, with a tachycardia of 110/min and blood pressure 80/40 mm Hg. The left iliac fossa was tender. Haemoglobin, full biochemistry profile, including serum amylase, chest radiography, plain abdominal radiography, and an abdominal ultrasound scan were normal. Her white cell count was raised at 20.4 × 10^9/l with marked neutrophilia at 14.2 × 10^9/l.

A provisional clinical diagnosis of acute diverticulitis with septic shock was made and she was started on intravenous (IV) fluids, IV metronidazole 500 mg eight hourly, and IV cefuroxime 750 mg three times a day in a sequential manner. Three days later and after five doses of IV cefuroxime, purpuric and erythematous macular rashes developed over the lower limbs. Cefuroxime was considered to be responsible and was discontinued; metronidazole was continued for another week. The rashes were treated with flucinolone acetonide 0.00625% cream. Further investigations at this stage showed normal immunoglobulins, antinuclear factor, antineutrophil cytoplasmic antibodies, and autoantibody profile. A haematoxylsin and eosin stained section of representative skin biopsy showed a mixed dermal infiltrate of lymphoid cells and eosinophils, marked red blood cell extravasation indicative of ongoing small vessel damage, minimal focal vacuolar interface.
change and some basement membrane hyalinisation, both within the papillary dermis of the inflamed skin and in the immediate vicinity. The lymphoid cells were predominantly lymphocytic, with many of these being large and polymorphic and showing hyperchromatic and irregular nuclei and mitoses (fig 1). Epidermotropism was only mild and focal and there were no Pautrier’s abscesses. Immunohistochemistry showed the infiltrate to be T cell rich, with virtually all of the large cells being CD30 positive (fig 2). Direct immunofluorescence showed fine linear deposition of IgG along the dermoepidermal junction.

Pyrexia, diarrhoea, tachycardia, and hypotension improved rapidly with supportive measures and the rashes began to fade quickly and cleared within seven days. She was completely asymptomatic and clear of all rashes when reviewed more than 15 months after the initial episode.

Discussion
Cephalosporins are widely used for the treatment of septicaemia, pneumonia, meningitis, biliary and urinary tract infection, and peritonitis. Both the old and new third generations of cephalosporins are generally well tolerated at standard recommended dosage. The sequential cefuroxime regimen was chosen as it has been shown not only to be an effective treatment for severe infections but also easier to administer. The incidence of adverse effects is approximately 2.5%, the most common being gastrointestinal—for example transient, mild to moderate nausea, diarrhoea, increase in serum transaminases and alkaline phosphatase, and very rarely Clostridium difficile induced pseudomembranous colitis. Other adverse reactions include central nervous system complaints—for example headache, dizziness, somnolence, confusion, hyperactivity, and reversible encephalopathy and transient haematological changes—for example leucopenia, thrombocytopenia and eosinophilia, serum sickness reaction, and renal failure. Cutaneous reactions are observed less frequently but urticaria, angio-oedema, erythema multiforme, exanthema, pruritus, pustular eruptions, fixed drug eruptions, glossitis, oral ulceration, and vaginitis have been described. Henoch-Schönlein purpura with systemic manifestations, including renal involvement and acute generalised exanthematic pustulosis have recently been reported. Phenytoin, carbamazepine, phenothiazine, angiotensin converting enzyme inhibitors, β-blockers, antidepressants, and benzodiazepines have already been reported to cause atypical cutaneous lymphoid infiltrates, mimicking pseudolymphoma but cephalosporins, to our knowledge, have not been previously linked with this tissue response. Unlike the blotchy macular erythema and purpuric rashes as observed in our case, the more common mode of presentation was with solitary erythematous or purple nodules, a few infiltrated plaques or multiple infiltrative papules. Some diagnostic confusion, both clinical and histological, occurs most commonly with mycosis fungoides and lymphomatoid vascular reaction (table 1).

The precise mechanism of this drug induced lymphomatoid vascular reaction is unknown. However, the β-lactam ring of cephalosporins is well known to impart a degree of instability to the cephalosporin molecule; the ring can open up, conjugate with proteins, become a hapten and immunogenic, and thus induce a delayed type of hypersensitivity reaction. Indeed, moderate spongiosis, keratinocyte necrosis, papillary dermal oedema, the presence of angiocentric infiltrate of atypical lymphocytes, absent or minimal vessel wall damage, minimal

Table 1 Comparison between microscopical features of Mycosis fungoides and lymphomatoid vascular reaction

<table>
<thead>
<tr>
<th>Microscopical characteristic</th>
<th>Mycosis fungoides</th>
<th>Lymphomatoid vascular reaction</th>
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<tr>
<td>Epidermotropism</td>
<td>Marked and diffuse</td>
<td>Minimal and focal</td>
</tr>
<tr>
<td>Pautrier’s microabscesses</td>
<td>Usually present</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Minimal or absent</td>
<td>Moderate</td>
</tr>
<tr>
<td>Basilar vacuolopathy</td>
<td>Usually absent</td>
<td>Usually present</td>
</tr>
<tr>
<td>Marked spongiosis, dermal oedema, and keratinocyte necrosis</td>
<td>Usually absent papillary dermal fibrosis rather than oedema is the rule</td>
<td>Usually present</td>
</tr>
<tr>
<td>Intraepidermal population of cells</td>
<td>Markedly atypical cytomorphology</td>
<td>Mildly atypical cytomorphology</td>
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and focal exocytosis of cells in the epidermis overlying the inflamed dermal papillae observed in this case are well recognised features of delayed type hypersensitivity reaction. Such a delayed type reaction with a cutaneous T cell lymphoma-like morphology has been described as lymphomatoid vascular reaction. 10–16 Most of the large lymphocytic cells in the infiltrate stained CD30 positive. In the context of neoplasia, CD30 is positive in Reed-Sternberg cells of Hodgkin’s disease, the cells of lymphomatoid papulosis and in anaplastic large cell lymphoma (Ki1 lymphoma). This has been shown to carry an excellent prognosis. 10–17

The close temporal association of starting cefuroxime and the appearance of the rash, the cutaneous T cell lymphoma-like histology with more features of a lymphomatoid vascular reaction than mycosis fungoides and rapid resolution of rash on cessation of the suspected drug, all favour lymphomatoid hypersensitivity reaction to cefuroxime as the most likely diagnosis. This reaction pattern, not previously described with cephalosporins, appears to be a benign reaction, with there being no relapses for more than a year after cessation of the original offending drug. Our patient remains well and clear of her rash as well as showing no sign of developing any cutaneous or systemic lymphomatous pathology 15 months after her discharge.

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Colonic carcinoma after ureterosigmoidostomy

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Abstract
Urinary carcinogens promote late malignant transformation of the colon after a ureterosigmoidostomy. An unusual case is presented where, despite the early removal of the latter and hence cessation of urine flow, a colonic carcinoma developed at the site of previous anastomosis. The importance of surveillance of all patients who have undergone this procedure to avoid an iatrogenic cancer is emphasised. (Postgrad Med J 2000;76:579–581)

Keywords: rhabdomyosarcoma; ureterosigmoidostomy; colonic carcinoma

Colonic carcinoma arising from the site of a functioning ureterosigmoidostomy anastomosis is a recognised late complication. If the anastomosis is subsequently taken down with no further urine flow into the bowel, the risk of neoplasia is reduced. We describe a rare case where a colonic carcinoma developed coincidentally at the site of a previous ureterosigmoidostomy after a long latent period.

Case history
A 41 year old man presented with rectal bleeding without bowel habit changes. At the age of 3 he underwent cystectomy with ureterosigmoidostomy formation for a rhabdomyosarcoma. Due to recurrent pyelonephritis the ureters were divided near the sigmoid colon and implanted in an ileal conduit seven years later. Two short segments of ureters were left attached to the colon.

Physical examination was normal and a barium enema revealed a lesion in the sigmoid colon. At laparotomy a circumferential cancer was found at the exact site of previous ureteric implantation (fig 1). Histological examination revealed a moderately differentiated adenocarcinoma with two short segments of residual...