Haemolytic streptococcal gangrene and non-steroidal anti-inflammatory drugs

All patients with necrotising fasciitis seen at this hospital over 10 years were reviewed. Six cases were found in which non-steroidal anti-inflammatory drugs were suspected of having contributed to the infection; these cases are reported below.

Patients, methods, and results

The records of all 31 patients seen at this hospital during 1972-82 with a discharge diagnosis of necrotising fasciitis were reviewed. We considered for analysis only those who fulfilled strict criteria for acute dermal gangrene —that is, with a history of rapidly spreading euritic infection and evidence of extensive subcutaneous necrosis and oedema sparing of underlying muscle. To select patients who had not had a predisposing condition we excluded those with postoperative necrotising fasciitis or suprainfection of chronic venous or arterial leg ulcers and those with any debilitating underlying disease that could have affected normal defence mechanisms. Thus six previously healthy patients in whom severe necrotising fasciitis had developed apparently spontaneously or after minor trauma remained for analysis.

A history of recent minor trauma was noted in five of the six patients (table). When the initial symptoms arose non-specific inflammation or superficial phlebitis was diagnosed in all six cases and therapeutic dosages of non-steroidal anti-inflammatory drugs prescribed. Two patients were subsequently given steroids because of continued inflammation. Four patients received more than one anti-inflammatory agent, of whom two received a combination of three drugs including aspirin. Four to 10 days elapsed between the initial symptoms and referral to hospital, when extensive necrotising fasciitis was diagnosed.

In all patients except one (case 1), to whom benzylpenicillin had been given for 24 hours before admission, a Lancefield's A β-haemolytic streptococcus (Streptococcus pyogenes) has long been recognised as an agent of this infection and still accounts for many cases. Patients with the infection often have serious underlying diseases, including diabetes mellitus, severe cardiovascular disease, hepatic cirrhosis, and conditions requiring long term treatment with steroids. No underlying disease was present in our patients, but all had been given non-steroidal anti-inflammatory drugs. The sequence of events suggested that these compounds affected the development or extension of the disease in our patients as no other drugs were given. Activation of latent infections in debilitated patients treated with non-steroidal anti-inflammatory drugs was suspected by Solomom. In vitro studies support this hypothesis by suggesting that functions mediated by granulocytes, which are critical in the early stages of host defence against infection, may be impaired by non-steroidal anti-inflammatory drugs. In vitro chemotaxis, phagocytosis, and bactericidal activity of granulocytes are reduced by these drugs. Solberg et al observed reduced in vitro killing of Staphylococcus aureus and streptococcal group B by granulocytes incubated with phenylbutazone. Whether these effects occur in vivo in patients given non-steroidal anti-inflammatory drugs remains to be determined.

Our observations suggest that non-steroidal anti-inflammatory drugs should be used cautiously when infection is suspected in a patient with an apparently benign "non-specific" inflammatory lesion of the skin.

We thank Dr Jonathan L. Meakins (McGill University, Montreal) for his advice.

Comment

Necrotising fasciitis is a potentially fatal infection of soft tissue that usually occurs after trauma or surgery. The group A β-haemolytic streptococcus was recovered from cultures of the blisters from areas of necrosis; blood cultures in two cases also yielded this organism. Treatment included intravenous administration of aqueous benzylpenicillin in high doses (12-20 M U/day), fluid replacement, and early surgery. One patient (case 5), with necrotising fasciitis extending to the lateral chest wall, died of septic shock within 24 hours after admission despite immediate surgery and aggressive supportive therapy. The five other patients survived after a stay in hospital that entailed multiple re-examinations of infected areas, excision of necrotic tissue, and eventual skin grafting in four cases.

Smoking, sugar, and inflammatory bowel disease

Previous studies have suggested that an association exists between smoking habit and both ulcerative colitis and Crohn's disease. We reported studies of the diets before illness of patients who developed both types of inflammatory bowel disease: the patients who developed Crohn's disease had a high intake of refined sugar and a low intake of fibre from fruit. We now report the smoking behaviour of these patients and relate it to their dietary habits.

Subjects, methods, and results

We studied 30 consecutive patients with ulcerative colitis and 30 consecutive patients with Crohn's disease. All were interviewed within three months of diagnosis. The two groups of control subjects had recently attended a fracture clinic but were otherwise healthy. They were matched for age (to

Clinical presentation of patients with necrotising fasciitis associated with non-steroidal anti-inflammatory drugs

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Triggering event</th>
<th>Initial diagnosis</th>
<th>Drugs administered</th>
<th>Delay (days)</th>
<th>Extent of necrotising fasciitis</th>
<th>Culture for group A streptococcus (skin/blood)</th>
<th>Complications</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34/F</td>
<td>Male</td>
<td>Heel scrape</td>
<td>Phlebitis</td>
<td>Indomethacin, phenylbutazone</td>
<td>8</td>
<td>Right calf and foot</td>
<td>-/+</td>
<td>Shock</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>55/F</td>
<td>Male</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Diclofenac</td>
<td>6</td>
<td>Left calf and thigh</td>
<td>+/+</td>
<td>Renal failure, thrombocytopenia</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>47/F</td>
<td>Male</td>
<td>Foot scar</td>
<td>Phlebitis</td>
<td>Indomethacin, oxypenbutazone</td>
<td>6</td>
<td>Right calf, foot and thigh</td>
<td>+/+</td>
<td>Renal failure</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>63/F</td>
<td>Male</td>
<td>Rose thorn scratch</td>
<td>Non-specific inflammation</td>
<td>Indomethacin, aspirin, prednisone 30 mg/day</td>
<td>4</td>
<td>Left arm and forearm</td>
<td>+/+</td>
<td>Shock</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>70/M</td>
<td>Male</td>
<td>Unknown</td>
<td>Non-specific inflammation</td>
<td>Indomethacin, aspirin, oxypenbutazone, then methylprednisolone</td>
<td>10</td>
<td>Upper right arm and lateral chest wall</td>
<td>+/+</td>
<td>Shock</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>43/F</td>
<td>Male</td>
<td>Insect bite</td>
<td>Non-specific inflammation</td>
<td>Phenytoxin b, oxypenbutazone, then methylprednisolone</td>
<td>10</td>
<td>Left calf</td>
<td>+/+</td>
<td>Survived</td>
<td></td>
</tr>
</tbody>
</table>

*Delay from triggering event to overt necrotising fasciitis and referral to hospital.

1 Streptococcus aureus also isolated from cultures of skin blisters in this patient.
Intrauterine death during continuous subcutaneous infusion of insulin

Continuous subcutaneous insulin infusion is an established technique for treating diabetics when tight control of blood glucose concentration is required. It has been recommended in the management of diabetes in pregnancy in well motivated patients difficult to control on conventional treatment.

Case report

A 27 year old patient, dependent on insulin for 20 years, attended our prepregnancy clinic. She was on short and intermediate acting insulin (twice daily, 0.5 units/kg), and blood glucose concentrations were often very high, with pronounced fluctuations with glycosylated haemoglobin (HbA1) concentration over 10%. (normal 6-8%) despite her meticulous approach to treatment. She had had recurrent hypoglycaemia but no episodes of ketoacidosis for over 10 years.

She was started on continuous subcutaneous insulin infusion using a syringe pump operated by a battery that was designed to deliver a basal infusion and bolus doses before meals (CFP Betatron 11 Model 9200).

Safety features included two alarms; one to indicate malfunction of the battery, the other to indicate an empty syringe or obstruction. This resulted in high blood glucose concentrations and a few hypoglycaemic episodes. HbA1 concentration decreased although we were unable to get it below 9%.

She conceived, and the pregnancy progressed satisfactorily for 31 weeks. Mid-morning blood glucose concentration was 7 mmol/l (126 mg/100 ml); HbA1 concentration 91%, on a total daily dose of insulin of about 50 units (28 units basal with a bolus of 5-15 units before meals). One evening before going out she noticed that her blood glucose concentration at 6 pm was high (13 mmol/l (234 mg/100 ml)) so she gave herself a boost of 15 units of insulin but did not test for ketones. At 7 pm she changed the infusion, relocated the needle—the area round the infusion was still slightly red—refilled the syringe and checked the pump was recording correctly. At midnight she felt well, but, being very tired, omitted to test her blood glucose concentration. At 4 pm she awoke feeling nauseated and vomited repeatedly.

By morning her blood glucose concentration was 13 mmol/l (234 mg/100 ml), and despite advice to test for ketones when her blood glucose was high or if she was unwell, she did not do so. She realised that she had failed to "insulin the pump" when she relocated the needle the night before—thus leaving the dead space in the tubing full of air—and she corrected this and gave herself a boost of insulin (15 units). By 11 am she was feeling well and was normal. She had not, however, felt the baby move since the previous evening and, although she suspected the baby was dead, did not report to hospital until late evening. On admission she appeared well, with no evidence of infection. Blood glucose concentration was 4 mmol/l (72 mg/100 ml) and she had ketonuria. Bicarbonate concentration was normal. 24 hour urinary excretion of ketones was 25 mmol (equivalent of 1 intravenous dose).

Intrauterine death was confirmed, labour was induced, and a stillborn baby boy was delivered weighing 2.28 kg. The baby was slightly macromosaic, but postmortem examination showed no congenital abnormality.

Comment

Although the patient appeared competent in the use of the pump, she omitted to test for acetone and delayed reporting vomiting and lack of fetal movement. She received no basal insulin for 12 hours and effectively no insulin at all for about seven hours because she forgot to prime the pump. This presumably caused ketoadiposis, which although not severe was sufficient to kill the baby. The automatic alarm would not have been activated because the insulin was leaving the syringe without obstruction.

Pickup et al stopped infusion for nine hours to investigate what would happen if accidental failure of continuous subcutaneous infusion of insulin occurred.

The onset of the neonatal ketoadiposis was not as mild as would have been expected if it had been caused simply by the baby consuming unused insulin. After the infusion was restarted the blood glucose concentration returned more rapidly and the ketoadiposis was more pronounced than if the baby had not been born for 24 hours and had been dead, did not report to hospital until late evening. On admission she appeared well, with no evidence of infection. Blood glucose concentration was 4 mmol/l (72 mg/100 ml) and she had ketonuria

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