CASE REPORTS

Haematuria during methicillin therapy

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HAEMATURIA has been reported as a rare complication of treatment with benzylpenicillin and methicillin (Baldwin *et al.*, 1968). This following example provided a difficult exercise in differential diagnosis.

Case report

A 15-year-old boy (P.S. 110521) with a ventricular septal defect was admitted as an emergency 6 days after falling and bruising his knee. After this he had gradually developed an increasing pyrexia, tachycardia and loose stools. He denied dental treatment within the last 6 months. A ventricular septal defect had been diagnosed clinically at the age of 1 year and was shown by catheterization at the age of 7 years to be small (left to right shunt of 0.8 l/min; Dr H. A. Flemming). He had never had effort intolerance. On admission he had a non-productive cough, pleuritic pain bilaterally, increasing dyspnoea and generalized abdominal pain. He was confused.

On examination his temperature was 103.6°F (39.8°C), his pulse 120, regular and blood pressure 100/80 mmHg. He had the characteristic signs of a ventricular septal defect but no specific clinical signs of septicaemia. He was grossly dyspnoeic with shallow grunting respiration at a rate of 46/min. He had generalized abdominal tenderness. There were no abnormalities in the teeth of gums and both knees were normal on examination.

Investigations. On admission, haemoglobin 12.5 g%, WBC 8400 mm³ with a normal differential count, ESR (Westergren) 32 mm in 1 hour, MSU protein 1+ no RBC. Throat swab commensals only. Chest X-ray showed some cardiomegaly with pulmonary plethora. IVP (on recovery) within normal limits. Blood culture: *Staphylococcus pyogenes* 1300 colonies/ml of blood resistant to penicillin, ampicillin and colomycin, and sensitive to cloxacillin, methicillin, erythromycin, cephaloridine, Septrin and fusidic acid.

Treatment was started with methicillin (21g/day) and erythromycin (1.5 g day) given by continuous intravenous infusion. Probenecid (2g/day orally)

was also given. Methicillin was given in preference to cloxacillin because a low proportion of it is bound to protein in the plasma. Since L-forms of staphylococci are especially likely with penicillin therapy, erythromycin was also given. The minimum bactericidal concentration of methicillin to this staphylococcus was > 3.12 < 6.25 µg/ml. The minimum serum level of methicillin while given at a dose of 12 g/day was 25 µg/ml. Intravenous fusidic acid (2g/day) was substituted for erythromycin on the tenth day. On the eighteenth day, the dose of methicillin was halved to 8 g/day, the fusidic acid was given orally, and Septrin four tablets daily (trimethoprim 320 mg and sulphamethoxazole 1.6 g) was added.

Course. The main features are demonstrated in Fig. 1. Blood cultures were consistently negative from the seventh day. He developed a morbilliform rash maximal over the torso from the seventh day, gradually fading over the following 5 days. He had macroscopic haematuria of varying degree from the seventh day after admission. A microscopic haematuria persisted at discharge from hospital but had ceased by the follow-up 1 month later. There were no pus cells in the urine. He was discharged 6½ weeks after admission and at out-patient follow-up has remained well 3 months after discharge.

FIG. 1. Temp, oral temperature (°F); Eos, blood eosinophils/mm³; blood urea (mg/100 ml). **Drug therapy.** Er, erythromycin; Me, methicillin; Pr, probenecid; Fu, fusidic; Se, Septrin. Closed bars, oral; cross-hatched bars, intravenous.

Discussion

This case history is of interest because of the diagnostic problems presented by the onset of haematuria during the course of severe staphylococcal septicaemia treated with massive doses of penicillin, since it may be a complication both of the disease and of the therapy. Haematuria may arise during the course of staphylococcal septicaemia but in this patient the onset was later than the height of the infection, and haematuria resulting from infection is usually associated with pus cells in the urine. There are on record two cases of haematuria during probenecid therapy (Boger & Strickland, 1954) where it was ascribed directly to the uricosuria rather than to drug sensitivity, but in our case the dose was low and the duration of treatment short. When the probenecid was discontinued the haematuria diminished. However, it again increased when the daily intravenous dose of methicillin was raised from 12 g to 16 g. The persistence of the haematuria coupled with the continued fever despite clinical recovery suggested a methicillin sensitivity. Following reduction of the intravenous methicillin to 8 g/day, the haematuria again temporarily decreased and gradually stopped after the drug was discontinued. It seems likely that the temporary fall in the degree of haematuria after stopping the probenecid was due to a fall in the blood levels of methicillin at that time.

Baldwin *et al.*, (1968) described the syndrome of hypersensitivity as characterized by fever, evanescent morbilliform rash, haematuria, azotaemia and eosinophilia. Our patient showed all these features.

Of their seven patients four were on doses of methicillin ranging from 7 to 24 g/day and demonstrated some or all of these features. All recovered after discontinuing penicillin therapy. Two of their patients had renal biopsies which showed an interstitial nephritis with tubular damage but no evidence of glomerular lesion or arteritis. This hypersensitivity only appears to develop in patients given high doses of methicillin over prolonged periods and the allergen has been postulated as a penicillin hapten/renal protein. The delayed hypersensitivity skin test (Redmond & Levine, 1968) appears to have little diagnostic usefulness since it is present in 21% of patients who have no recent exposure to penicillin and who can tolerate penicillin without allergic reactions.

It may be of interest to note that no difficulties or side-effects were noted while doses of fusidic acid were given in the form of a new preparation in the maximum doses (2 g/day).

Acknowledgments

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Osteogenesis imperfecta in a child presenting with neurological features

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Summary

A case of osteogenesis imperfecta presenting with a rare neurological complication (spastic paraplegia) is presented. The aetiology of the neurological lesion is discussed.

OSTEOGENESIS imperfecta is a systemic disease of the mesenchymal tissues of the body, which is inherited

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as an autosomal dominant characteristic with a variable degree of expression. The condition usually presents in childhood with pathological fractures, bony deformities and blue sclerae. There is a wide spectrum of severity. Clinical features less commonly seen include dislocated joints, opalescent teeth with defective dento-enamel junctions, (dentinogenesis imperfecta), otosclerosis and deafness. (Heys, Blattner & Robinson, 1960). Neurological complications are rare. Single cases of osteogenesis imperfecta with neurological abnormalities have been reported