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Cephradine-induced interstitial nephritis

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SUMMARY

A patient developed acute interstitial nephritis following cephradine administration. The clinical illness preceding the interstitial nephritis and the eosinophilia in peripheral blood suggested an allergic reaction. Immunological studies demonstrated an allergy to cephradine and penicillins which was IgG2-mediated. It is probable, therefore, that allergy to cephradine caused the renal lesion from which there was full clinical and biochemical recovery.

INTRODUCTION

Many anti-microbial agents are nephrotoxic and acute renal failure in association with cephalosporin therapy has been well described (Appel & Neu, 1977). We now report a case of acute renal failure due to interstitial nephritis following therapy with cephradine, one of the newer cephalosporins. Data are presented suggesting that this was caused by allergy to cephradine.

METHODS AND RESULTS

Case report

A 23 year old Caucasian female who had bilateral congenital dislocation and subluxation of the hips was admitted to hospital for a routine left Chiari pelvic osteotomy. She had had a shelf acetabuloplasty at the age of 9. There was no past history of renal disease. Before operation the patient was normotensive, had a plasma urea of 6·0 mmol/l and her urine contained no protein, sugar or blood.

She had an uneventful operation under general anaesthesia, but on the first post-operative day she developed retention of urine and required bladder catheterization for 4 days. Cephradine 500 mg q.d.s. was given orally for 7 days although there was no bacteriologically proven urinary tract infection. After removal of the catheter she passed normal volumes of urine without difficulty. Two weeks after the end of the course of cephradine she developed fever, generalized aches, a sore throat and an erythematous macular rash. A white blood count (WBC) was $4{\cdot}0 \times 10^9$/l with 7% eosinophils. Blood, throat swab and urine cultures were sterile and a Paul–Bunnell test for glandular fever was negative. The rash and fever persisted over the next two weeks. At this stage a guide wire from the hip operation was removed under local anaesthesia. Two days later (5 weeks after the course of cephradine) she became oliguric.

Physical examination revealed a widespread erythematous rash with some exfoliation. There was a pyrexia (38·5°C), the pulse was 90/min and the blood pressure 120/80 mm Hg. There were no cardiac murmurs. A trace of sacral and ankle oedema was noted. The optic fundi were normal.

A urine specimen showed a trace of protein, a few red cells, an osmolality of 268 mOsm/l and was sterile on culture. The haemoglobin was 10·7 g/dl with normal red cells on the film; the WBC was $9{\cdot}0 \times 10^9$/l with 20% eosinophils and the erythrocyte sedimentation rate 84 mm in 1 hr. Platelet count and clotting studies were normal and the Coombs test was negative. The plasma urea rose rapidly to 37·0

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mmol/l and creatinine to 1007 μmol/l. A high dose intravenous urogram showed symmetrical kidneys of normal size without evidence of obstruction. Further blood cultures were sterile; a throat swab grew streptococcus faecalis but the anti-streptolysin titre was less than 200 u/ml. Circulating antinuclear factor was absent. Serum complement levels were normal and circulating immune complexes were not detected. A percutaneous renal biopsy was obtained from the left kidney on the third oliguric day (pathology described below).

She was treated with fluid, protein and potassium restriction and received oral Calcium Resonium for slight hyperkalaemia. Oliguria persisted for 4 days and was followed by polyuria. The rash, fever and eosinophilia resolved within a few days. Subsequently renal function improved steadily. One month following the onset of oliguria, plasma urea was 4·1 mmol/l and creatinine 71 μmol/l and 6 months later were still within the normal range.

A review of all medication administered before the onset of acute renal failure showed that apart from cephradine the patient had also received the following: thiopentone, pethidine, d-tubocurarine, suxamethonium, halothane and nitrous oxide at the time of her operation; quinine regularly for nocturnal muscle cramps; soluble aspirin for a brief period related to sore throat and fever; dichloralphenazone occasionally for night sedation; distalgesic (dextropropoxyphene/paracetamol), diazepam and dioctyl sodium succinate intermittently; lignocaine at the time of her local anaesthetic; and a single oral dose of 500 mg phenoxymethylpenicillin was administered after the onset of oliguria had been noted.

Pathology

The needle biopsy of kidney showed changes consistent with a typical interstitial nephritis (Heptinstall, 1976). The renal tubules were separated by an oedematous interstitium diffusely infiltrated by inflammatory cells, including eosinophil and neutrophil polymorphs, lymphocytes and histiocytes. Plasma cells were present but scanty. The neutrophils and eosinophils were particularly aggregated around tubular basement membranes, which were disrupted in places, with hyaline cast extrusion. Elsewhere, tubules showed varying degrees of degeneration, some being lined with regenerating epithelium. Glomeruli were mostly normal, although a few showed a minor degree of mesangial hypercellularity. There was no evidence of arteritis. Immunofluorescent microscopy using appropriate antisera did not show any immunoglobulins, complement components or fibrinogen.

In vitro studies of drug allergy

(i) *Total IgE.* Total serum immunoglobulin E (IgE) was estimated on several occasions during the illness by the paper radioimmunoabsorbent test (PRIST, Pharmacia). Values ranged from 0·5–20 iu/ml (normal < 200 iu/ml).

(ii) *Allergen-specific IgE.* Serum IgE antibodies specific to the major penicillin haptenic determinant (the penicilloyl group), and two minor determinants (penicillenate and penicillamine) were measured by the radio-allergosorbent test (RAST) (Wide, Bennich & Johannson, 1967). A 'cephalosporoyl' determinant prepared from cephaloridine as described by Assem & Vickers (1974) was also used. The procedures employed were as follows: the four determinants were first conjugated to bovine gammaglobulin (BGG), as described by Assem & Vickers (1975), and then the protein conjugates were coupled to cyanogen bromide-activated 'Sephadex'. The particulate antigen conjugates prepared in this way were incubated with the patient's serum, washed with buffered saline, incubated with ^{125}I-labelled anti-IgE, washed again, and then counted in a gamma counter. The patient's serum was compared with serum from a normal (non-allergic) subject.

Penicilloyl-specific IgE antibodies could be detected by this technique (Table 1), providing evidence for immediate-type allergy to penicillin. Allergy to the cephalosporoyl derivatives could not be demonstrated on this test.

(iii) *Allergen-induced histamine release from leucocytes.* This test is an *in vitro* correlate of immediate-type allergy whether mediated by IgE or IgG antibodies. Leucocytes were isolated from peripheral venous blood and then incubated *in vitro* with antigen preparations (Assem *et al.*, 1971). The antigens used include the four described above in (ii) and other conjugates (see Table 2), prepared as described

TABLE 1. Radioallergosorbent test (RAST) for allergen specific IgE

Allergen in solid phase (allergosorbent)	Uptake of ^{125}I-labelled* anti-IgE by allergosorbent after incubation with 0·1 ml serum (ct/min)	
	Patient's serum	Control serum
Penicilloyl—BGG	36·5	0·9
Penicillenate—BGG	0	0
Penicillamine—BGG	0	0
Cephaloridine—BGG	0	0
BGG (protein carrier alone)	0	0

* Total radioisotope added 4501 ct/min (1·0 ng anti-IgE).

previously. Benzylpenicilloyl-polylysine was obtained from Sigma Chemical Co. Ltd., London. Histamine release from leucocytes was measured by two different techniques. Firstly, an automated spectrofluorometric procedure (Technicon) was used which has a drawback due to the fluorescence of some cephalosporin and penicillin derivatives. Secondly, a bioassay technique was performed utilizing isolated guinea-pig ileum (Assem & Schild, 1968).

These tests provided evidence of allergy to penicillin and cephalosporin derivatives (Table 2). This was shown by the high level of histamine release when leucocytes from the patient were challenged with protein conjugates of either cephradine or penicillin derivatives, whereas the unconjugated drugs (the hapten alone) did not produce significant release.

(iv) *Detection of cytophilic antibody class by reversed leucocyte anaphylaxis.* In order to detect the class (whether IgE or one of the four subclasses of IgG) of leucocyte sensitizing antibodies, these cells were challenged with specific antisera against these immunoglobulins and the histamine thus released was measured (Assem & Turner-Warwick, 1976). The antibodies in this patient appeared to be mainly of the IgG2 subclass rather than IgE (Table 3).

TABLE 2. Allergen-induced histamine release from leucocytes

Antigen preparation (molar concentration of haptenic group)	Histamine release (percentage of total cell content)	
	Individual replicates	Mean
Control (tyzodes solution)	13·8, 21·1, 6·5, 14·3	13·9
Ampicillin ($2·5 \times 10^{-4}$M)	7·7, 38·3	23·0
Benzylpenicillin ($2·5 \times 10^{-4}$M)	7·3, 5·7	6·5
Cephradine ($2·5 \times 10^{-4}$M)	23·9, 17·8	20·9
Cephaloridine ($2·5 \times 10^{-4}$M)	8·1, 13·9	11·0
Benzylpenicilloyl-polylysine ($0·8 \times 10^{-5}$M)	15·0, 6·2	10·6
Benzylpenicilloyl-polylysine ($2·5 \times 10^{-5}$M)	48·0, 49·3	48·7
Benzylpenicillenic-bovine gammaglobulin ($2·5 \times 10^{-5}$M)	29·5, 36·8	33·2
Penicillamine-bovine gamma-globulin ($2·5 \times 10^{-5}$M)	34·0, 47·8	40·9
Cephradine-human gamma globulin ($1·0 \times 10^{-6}$M)	64·5, 70·3	67·4
Cephaloridine-bovine gamma globulin ($1·0 \times 10^{-6}$M)	6·1, 12·0	9·1

TABLE 3. Reversed leucocyte anaphylaxis test

Antisera	Histamine release (percentage of total cell content)
Control (tyzodes solution)	2·3
Anti-IgE	12·8
Anti-IgG1	7·8
Anti-IgG2	35·9
Anti-IgG3	6·6
Anti-IgG4	8·9

(v) *Lymphocyte transformation test.* The previous tests were *in vitro* correlates of immediate-type allergy (anaphylaxis). Lymphocyte transformation tests were also performed as an index of delayed-type (cell-mediated) allergy. The technique used was that of Girard *et al.* (1967). The uptake of ^{3}H-thymidine was measured in a liquid scintillation counter. Tests were carried out on two occasions. There was a small but insignificant response on exposure to cephradine, and no response with other test allergens.

(vi) *Skin tests.* These were carried out by the intradermal injection of 0·03 ml of the following allergen preparations: cephradine ($2{\cdot}9 \times 10^{-4}$ M), cephradine-human serum albumin and cephaloridine-human serum albumin ($2{\cdot}5 \times 10^{-5}$ M haptenic determinant. The results of these tests were inconclusive.

DISCUSSION

Two weeks after a course of cephradine this patient developed fever, skin rash and eosinophilia, all of which persisted until the onset of acute renal failure 3 weeks later. Renal biopsy demonstrated acute interstitial nephritis. Such a history is itself suggestive of an allergic drug reaction. However, we have also been able to demonstrate allergy to cephradine (and penicillin) on the basis of allergen-induced histamine release from the patient's leucocytes. The antibody mediating this allergy was probably of the IgG2 subclass.

Some further observations can be made from the results of the leucocyte histamine release test. The allergy to penicillin was due to the major determinant (Table 2) (the penicilloyl group) and at least two minor determinants (the penicillenate and penicillamine groups), all three of which are breakdown products of the penicillin nucleus. These groupings apart, there may also have been a side chain specificity which is suggested by one of the replicate responses to ampicillin (α-aminobenzyl penicillin) which was considerably greater than that to benzyl penicillin (Table 2). The possible importance of the side chain specificity (Fig. 1) is reflected by the response to cephradine, which has a side chain closely related to that ampicillin (a difference of one double bond in the ring of the side chain), but not to cephaloridine. Cephradine conjugate gave a bigger and more reproducible response than cephaloridine conjugate. Similarities of structure between cephalosporins and penicillins may explain the immunological cross reaction between them (Assem & Vickers, 1974) and it is less surprising, therefore, that a reaction to a cephalosporin should have occurred in a patient in whom one could also demonstrate penicillin allergy.

Acute interstitial nephritis occurs fairly commonly as part of an allergic reaction to drugs. This type of lesion has been described with sulphonamides, phenindione, phenazone, penicillins (including penicillin G, ampicillin and methicillin), as well as other drugs. Our patient had intermittently been prescribed dichloralphenazone for night sedation and had also been given a single oral dose of penicillin V although only after the onset of oliguria. In some cases of methicillin- and penicillin-induced acute interstitial nephritis immunofluorescent deposits of IgG or complement components have been demonstrated, sometimes associated with the tubular basement membrane (Baldwin *et al.*, 1968; Colvin *et al.*, 1974). We were unable to demonstrate such deposits and therefore lack direct evidence linking the allergy demonstrated in peripheral blood with the renal lesion.

It may be difficult to establish whether a cephalosporin-induced renal lesion is due to an allergic or

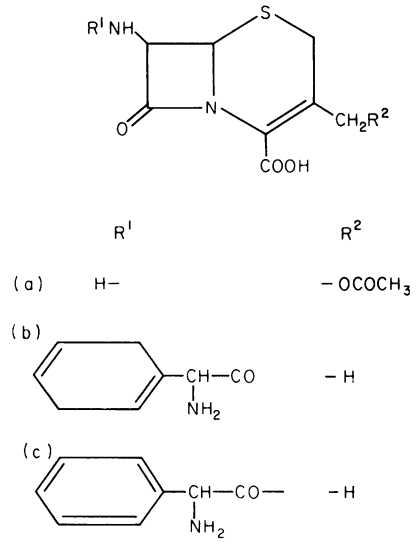

FIG. 1. Structural formulae of various cephalosporins. The top figure shows the cephalosporin mucleus. The side chains R^1 and R^2 shown below correspond to: (a) 7 aminocephalosporanic acid, (b) cephradine and (c) cephalexin. The R^1 side chain of ampicillin is identical to that of cephalexin and differs only slightly from that of cephradine.

toxic mechanism. Certain cephalosporins such as cephaloridine and cephalothin are nephrotoxic, whereas others such as cephalexin are said not to be (Linton, Bailey & Turnbull, 1972). Cephradine, which has only slight structural differences from cephalexin, is probably free of nephrotoxicity (Hassert *et al.*, 1973). If cephradine caused the renal lesion in our patient an allergic reaction is the most probable mechanism because of the associated clinical features, the evidence of allergy demonstrated in peripheral blood, and the fact that the drug had been stopped 5 weeks before the onset of renal failure—this latter making direct nephrotoxicity particularly unlikely.

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