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Legionella infection with acute renal failure and thrombocytopenia mimicking allograft rejection

A pitfall in post-transplantation diagnosis

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Abstract. A patient is described who developed cavitary *Legionella* pneumonia 2 weeks after kidney transplantation. The initial pulmonary symptoms were followed by severe thrombocytopenia and acute renal failure. Although acute irreversible graft rejection was suspected, this was not supported by the pathology findings in the resected kidney, which were compatible with tubular damage. We presume that the extrapulmonary symptoms were caused by Legionellosis.

Key words: Kidney transplantation - *Legionella* pneumonia - Acute rejection - Acute renal failure - Thrombocytopenia - Lung abscess.

Legionnaires' disease is a systemic affection, although pneumonia is usually the principal clinical finding. It was first described in 1977 [5] and is caused by a previously unrecognized gram-negative, aerobic bacillus *Legionella pneumophila*, which has been isolated from sputum, blood, pleural fluid, and extrathoracic sites of infected individuals [17].

The infection can be both community-acquired and nosocomial. Hospital outbreaks of the disease have been linked with contamination of water storage and distribution systems [9], and immune compromised hosts are known to be at risk for developing nosocomial Legionellosis.

The patient reported here developed a *Legionella* infection 2 weeks after renal cadaveric transplantation. Since there was acute renal failure together with a decreasing number of platelets, the kidney was removed under the assumption of irreversible acute allograft rejection.

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Case report

A 53-year-old woman with polycystic kidney disease and liver cysts, who had been treated with chronic intermittent hemodialysis, received a cadaveric kidney transplant on 29 July 1987. Immunosuppression was given with prednisone, 20 mg/24 h, and cyclosporin A (CsA), monitored by trough levels in whole blood (starting dosage 12 mg/kg body wt. per 24 h). The initial clinical course was characterized by gradual improvement of renal function (endogenous creatinine clearance 20 ml/min) without major clinical problems. On the 16th day the patient had pleuritic pain on the right side. There was no fever or hemoptysis. A pleural friction rub could be heard on auscultation. Arterial blood gas analysis showed hypocapnia (pCO_2 3.0 kPa), and the chest X-ray film revealed a basal consolidation in the right lower lobe. Pulmonary embolism was clinically suspected, and although ventilation-perfusion scintigraphy gave only a low probability of thromboembolism, treatment was started with intravenous heparin and acenocoumarol.

The complaints persisted over the following days. Moreover, the patient had bloody sputum, from which no significant pathogens could be cultured by routine techniques. Because of fever and leukocyturia, cefamandole was administered. Cultures of blood and urine later proved to be negative.

A rise in serum creatinine was presumed to be caused by acute rejection. A biopsy was not performed because of the anticoagulant therapy. Antirejection treatment was started with methylprednisolone intravenously, but because of the onset of anuria the treatment was switched to rabbit antithymocyte globulin (RATG; see Fig. 1).

Both radiographically and clinically a progressive infiltration of the right lower lobe was observed. Infected pulmonary infarction as well as *Legionella* pneumonia were considered as possible diagnosis. A dubiously positive direct immunofluorescence assay (DFA) with antiserum to *L. pneumophila* serogroup 4 was obtained from sputum of the patient, and because of the possibility of Legionnaires' disease, erythromycin was added to the antibiotic treatment.

Severe thrombocytopenia (5×10^9/ml) was found, without evidence of disseminated intravascular coagulation. A diethylene

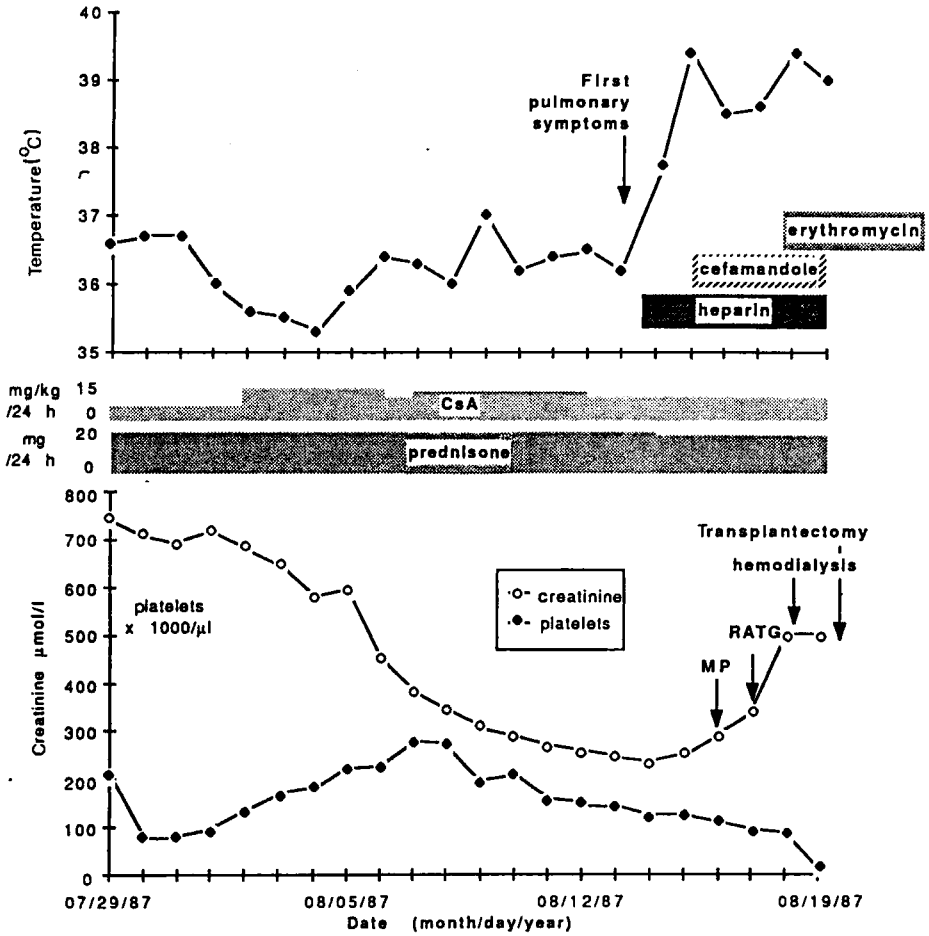

Fig. 1. The clinical course of patient in case report until transplantectomy

triaminepenta-acetic acid (DTPA) kidney scintigraph showed poor perfusion with a possible leak of radiopharmacon into the iliac fossa. It was decided to perform transplantectomy after infusion of platelets and administration of protamine. Immunosuppression was withdrawn and the patient was again treated with hemodialysis.

After the transplantectomy, the diagnosis of *Legionella* pneumonia was confirmed by culture of *L. pneumophila* on a buffered charcoal yeast extract on an agar plate and by a rise in the serum antibody titer against *L. pneumophila* serogroup 4 from 1:128 to 1:>2048 in the indirect immunofluorescence assay. DFA staining of consecutive sputum specimens was positive for 4 weeks. The chest roentgenogram showed irregular air spaces, indicating cavitation of the lobar infiltrate. Antibiotic treatment was continued with erythromycin (4 × 500 mg) and later also rifampicin (2 × 600 mg), which led to full recovery from the pulmonary symptoms.

Macroscopically, the removed kidney showed no changes. In particular, no discoloration was seen characteristic of focal inflammation, hemorrhage, and necrosis due to rejection. Microscopically, however, small foci of lymphocytic infiltration were present, predominantly perivascularly, without invasion of tubular epithelium or vascular obstruction. Glomeruli showed normal cellularity. Proximal tubules were dilated and lined with flattened epithelium (Fig. 2a) bearing little or no brush border. At a more distal site, mainly in the medulla and the papilla, the tubules showed cell degeneration and necrosis, and tubular lumina were filled with debris and granular casts (Fig. 2b). Immunofluorescence microscopy with fluorescein-isothiocyanate-labeled anti-*Legionella* antisera did not reveal any immunoreactive bacterial antigens in renal structures.

Discussion

The occurrence of *Legionella* pneumonia in renal transplant patients has been well documented since its first description in 1977 [1]. In this population the infection usually is hospital acquired and sometimes occurs in clusters as was recently described [18]. Infection as early as 2 weeks after transplantation suggests nosocomial hazard due to environmental contamination with *Legionella* [13]; to date, however, there have been no further occurrences of *Legionella* pneumonia in our ward. Cultures of the water supply system were negative for *Legionella*.

Although a wide spectrum of prodromal symptoms including general malaise, myalgia, diarrhea, and headache may occur, pulmonary symptoms and fever are predominant. Pulmonary infiltrates and chest pain occur in nearly all patients. Renal complications of the disease are often confined to transient and mild azotemia, hematuria, proteinuria, pyuria, and cylindruria, but acute renal failure may also occur [15].

Laboratory findings include leukocytosis with a shift to the left, hypoxia and hypocapnia. In some cases a marked thrombocytopenia has been de-

scribed [8], and mild abnormalities of liver function can develop.

The chest X-ray film may show unilateral or bilateral nonspecific 'patchy' opacities, which subsequently form a dense lobar or multilobar consolidation. Pleural effusion is common but cavitation is rare in previously healthy individuals. In patients with disturbed cellular immunity, however, the incidence of cavitary *Legionella* pneumonia is high [7].

The actual presence of the micro-organism in renal tissue was first demonstrated in a patient with evidence of pyelonephritis [3]. In a pathology report on the disease in 23 fatal cases the micro-organism was isolated from extrathoracic sites in 27% of the patients [17]. Although the renal findings were unremarkable in most cases, in one of the patients the bacteria were present as free and intracellular forms, predominantly within the lumina of moderate-sized renal arteries. The involvement of the spleen (25%), bone marrow (13%), liver, myocardium, and brain also suggests that hematogenous spread is not uncommon.

It is conceivable that in certain organs the outgrowth of Legionellae is responsible for the local manifestations; the cause of renal failure, however, is not quite clear but it is probably associated with the tubular abnormalities observed. Direct cellular toxicity may be present. Acute tubular necrosis is described, usually without a previous phase of shock [4]. Tubulointerstitial nephritis is incidentally reported [12]. Rhabdomyolysis and myoglobinuria have been found [6] but the renal lesions were not demonstrated. There is one report of rapidly progressive glomerulonephritis coinciding with Legionnaires' disease [16]. Nephrotoxicity of the administered drugs must be considered in some patients. Because the formerly mentioned factors were not present in all patients with acute renal failure, the presence of circulating endotoxin has been postulated [17].

The patient in our case report was treated for suspected Legionnaires' disease but we presumed acute rejection as the cause of renal failure because of the accompanying thrombocytopenia and because in the absence of other obvious causes rejection is the most frequent diagnosis in this period. Confirmation by biopsy was not performed, however, because of the anticoagulant therapy and the progressive thrombocytopenia. The DTPA scintigraph was also compatible with the diagnosis of acute irreversible rejection. The previous heparin and cefamandole medication was considered a less likely cause of the thrombocytopenia, while the possibility of Legionellosis as a causal factor was overlooked.

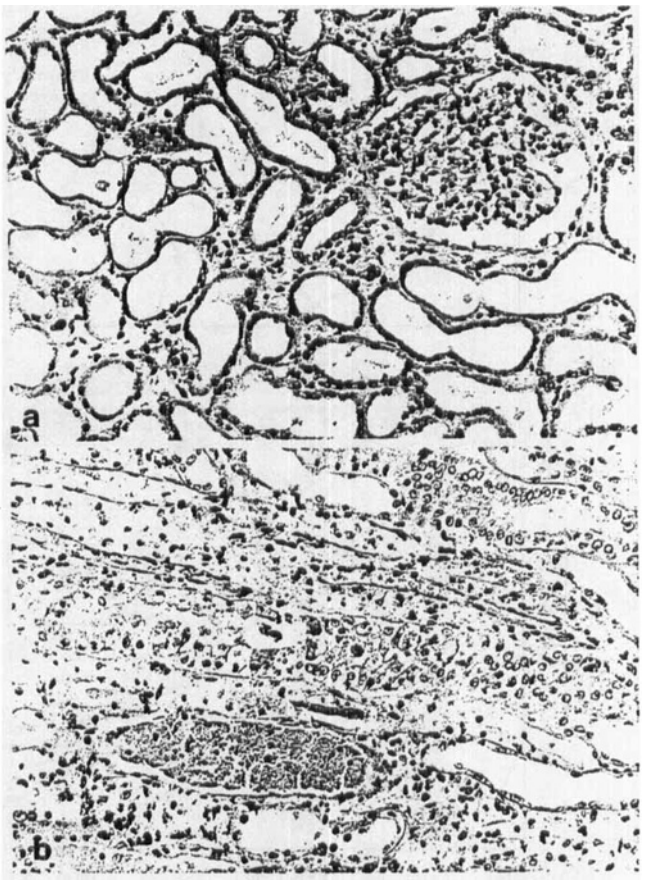

Fig. 2. **a** Renal cortex with a normal glomerulus and marked dilation of proximal and distal tubules, lined with flattened epithelium. H & E, ×28. **b** Medullary region showing tubules with cellular degeneration and debris. PAS, ×70

During both acute and hyperacute rejection, platelets are sequestered in the kidney in association with vascular injury (arterial thrombosis) and fibrin deposition [2, 14]. The associated drop in platelet count can be corrected by nephrectomy, which is the recommended treatment in such cases [11].

Cyclosporin A levels were never in the toxic range and no histological clues of toxicity, such as giant mitochondria, isometric vacuolization, microcalcifications, or arteriolopathy [10], were seen. Since no evidence of rejection could be found in this case and no hypotension or urinary tract obstruction was present, it seems reasonable to ascribe both the renal failure and the thrombocytopenia to Legionnaires' disease associated with tubular cell damage. This may also explain the sterile leukocyturia. *Legionella* bacteria could not be identified in the resected kidney and histological changes were compatible with tubular damage. Tubular necrosis, as was mentioned before, has repeatedly been reported to occur during *Legionella* infection

[4], supporting the likelihood of Legionellosis-related acute renal insufficiency in this patient.

We have shown that in renal transplant patients with a pulmonary infiltrate, thrombocytopenia, and acute renal failure, Legionnaires' disease should be suspected. An unnecessary transplantectomy can be prevented through observation of the macroscopic aspect of the graft together with a peroperative biopsy.

References

1. Bock BV, Edelstein PH, Snyder KM, Hatayama CM, Lewis RP, Kirby BD, George WL, Owens ML, Haley CE, Meyer RD, Finegold SM (1977) Legionnaires' disease in renal-transplant recipients. Lancet II: 410-413
2. Busch GJ, Reynolds ES, Galvanek EG, Braun WE, Dammin GJ (1971) Human renal allografts; the role of vascular injury in early graft failure. Medicine 50: 29-98
3. Dorman SA, Hardin NJ, Winn WC (1980) Pyelonephritis associated with *Legionella pneumophila*, serogroup 4. Ann Intern Med 93: 835-837
4. Fenves A (1985) Legionnaires' disease associated with acute renal failure: a report of two cases and review of the literature. Clin Nephrol 23: 96-100
5. Fraser DW, Tsai TR, Orenstein W, Parking WE, Beecham HJ, Sharrar RG, Harris J, Mallison GF, Martin SM, McDade JE, Shepard CC, Brachman PS, and the Field Investigation Team (1977) Legionnaires' disease: description of an epidemic pneumonia. N Engl J Med 297: 1189-1197
6. Hall S, Wasserman M, Dall L, Schubert T (1983) Acute renal failure secondary to myoglobinuria associated with Legionnaires' disease. Chest 83: 633-635
7. Meenhorst PL, Mulder JD (1983) The chest X-ray in *Legionella* pneumonia (Legionnaires' disease). Eur J Radiol 3: 180-186
8. Meenhorst PL, Meer JWM van der, Borst J (1979) Sporadic cases of Legionnaires' disease in the Netherlands. Ann Intern Med 90: 529-532
9. Meenhorst PL, Reingold AL, Groothuis DG, Gorman GW, Wilkinson HW, McKinney RM, Feeley JC, Brenner DJ, Furth R van (1985) Water-related nosocomial pneumonia caused by *Legionella pneumophila* serogroups 1 and 10. J Infect Dis 152: 356-364
10. Mihatsch MJ, Thiel G, Basler V, Ryffel B, Landmann J, Overbeck J von, Zollinger HU (1985) Morphological patterns in cyclosporine-treated renal transplant recipients. Transplant Proc 17: 101-116
11. Morris PJ (1979) Kidney transplantation, principles and practice. Academic Press, London New York, pp 203-223
12. Relman AS (1978) Case records of the Massachusetts General Hospital (case 17-1978). N Engl J Med 298: 1014-1021
13. Rubin RH, Wolfson JS, Cosimi AB, Tolkoff-Rubin NE (1981) Infection in the renal transplant recipient. Am J Med 70: 405-411
14. Starzl TE, Boehmig HJ, Amemiya H, Wilson CB, Dixon FJ, Giles GR, Simpson KM, Halgrimson CG (1970) Clotting changes, including disseminated intravascular coagulation, during rapid renal-homograft rejection. N Engl J Med 283: 383-390
15. Tsai TF, Finn DR, Plikaytis BD, McCauley W, Martin SM, Fraser DW (1979) Legionnaires' disease: clinical features of the epidemic in Philadelphia. Ann Intern Med 90: 509-517
16. Wegmüller E, Weidmann P, Hess T, Reubi F (1985) Rapidly progressive glomerulonephritis accompanying Legionnaires' disease. Arch Intern Med 145: 1711-1713
17. Weinburger DD, Helms CM, Renner ED (1981) Sporadic Legionnaires' disease. A pathologic study of 23 fatal cases. Arch Pathol Lab Med 105: 130-137
18. Wilczek H, Kallings I, Nyström B, Hoffner S (1987) Nosocomial Legionnaires' disease following renal transplantation. Transplantation 43: 847-851