Brucellosis with nephrotic syndrome, nephritis and IgA nephropathy

Nava Siegelmann¹, Abraham S. Abraham¹, Bernard Rudensky² and Ovadia Shemesh¹

¹Department of Internal Medicine B and ²Clinical Laboratory of Bacteriology and Immunology, Shaare Zedek Medical Center, POB 3235, Jerusalem 91031, Israel

Summary: A patient with systemic brucellosis due to *Brucella melitensis* had severe renal involvement. Clinical features included hypertension, macroscopic haematuria, massive proteinuria of 10 g per 24 hours and azotaemia. Following treatment with antibiotics, the azotaemia resolved and proteinuria decreased to less than 0.5 g per 24 hours, but microscopic haematuria and hypertension persisted. Renal biopsy during recovery revealed IgA nephropathy with minimal mesangial changes, suggesting a causal relation between brucellosis and IgA nephropathy with a reversible nephrotic syndrome.

Introduction

Brucellosis is a zoonotic disease, affecting more than 500,000 people in the world annually. During various stages of the disease 4–50% of patients secrete the organism in their urine.^{1–4} However, it is uncommon for patients to present with clinical symptoms and signs of renal disease. Renal brucellosis was documented first by Bruce⁵ in 1889: 'Albumin is found in the urine in the most severe cases, but this appears to be a rare occurrence'. Dunea⁶ classified renal involvement into three clinical types: (1) chronic brucellosis with renal involvement resembling renal tuberculosis or chronic non-specific pyelonephritis;^{7–13} (2) renal involvement associated with brucella endocarditis;^{14–16} and (3) acute nephritis or acute pyelonephritis-like features seen during the acute stage of brucellosis. These features are usually transient.^{17,18}

Massive proteinuria during acute infection with persistent renal involvement after recovery has been rarely described. Dunea *et al.*⁶ described two patients with acute *Brucella suis* infection and massive proteinuria of 6.0–13.0 g/day. During recovery, these patients developed hypertension and suffered persistent proteinuria. Morphological studies revealed a diffuse interstitial nephritis with focal and local glomerular sclerosis. Nunan *et al.*¹⁹ described a patient with an acute *Brucella melitensis* biotype 3 infection and proteinuria of 2.8 g/day. Renal biopsy showed a focal and segmental glomerulonephritis with widespread mesangial changes

and minimal interstitial inflammation. Immunofluorescence microscopy showed heavy mesangial deposits of IgA, which persisted 3 months after complete recovery.

We present a case of acute brucellosis with nephrotic syndrome and IgA nephropathy.

Case report

A 43 year old Arab female first consulted her doctor a month before admission for influenza-like symptoms with generalized weakness and a dry cough. She was found to have a blood pressure of 180/100 mmHg and a haemoglobin of 9.0 g/dl. She was treated with amoxycillin and ferrous sulphate tablets. One month later, she was admitted to our department because of remittent fever up to 39°C with profound perspiration and rigors, weight loss of 11 kg, vomiting, constipation and diffuse abdominal pain, low back pain radiating to the right leg, amenorrhoea and macroscopic haematuria without dysuria.

Physical examination revealed a pale woman with a temperature of 38°C and a blood pressure of 160/100 mmHg. The cervical lymph nodes were moderately enlarged and there was low back tenderness.

Laboratory tests showed urine sediment with 4+ albumin, 10–15 white blood cells per high power field (HPF), multiple dysmorphic red blood cells (RBCs) and a few granular casts. Total urine protein excretion was 10.5 g/day. The haemoglobin was 7.2 g/dl with an MCV of 71 fl. The white

blood count was $9.8 \times 10^9/l$ and the blood sedimentation rate was 133 mm/h. Blood urea nitrogen (BUN) was 12 mmol/l (urea 25.7 mmol/l), serum creatinine 229 $\mu\text{mol/l}$ and creatinine clearance 45 ml/min/1.73 m². Serum albumin was 2.9 g/dl with a total protein of 61 g/l. The lactic dehydrogenase (LDH) was 310 U (normal: 110–220 U). Anti nuclear factor was 2+. Serum complement levels were normal, and tests for rheumatoid factor, anti DNA antibodies and cryoglobulins were negative. Serum levels of immunoglobulin IgA, IgG and IgM were normal.

The electrocardiogram was within normal limits, as were X-rays of the chest, abdomen and sacroiliac joints. Abdominal ultrasound was normal. Echo of the heart was normal, and no vegetations were seen.

During the first 10 days of hospitalization, the patient was febrile, continued to vomit and lost a further 11 kg in weight. Her low back pain radiating to the right leg was so severe that she could not walk on that leg. She was treated with intravenous fluids and two units of packed cells, paracetamol and captopril. Brucella agglutinins were present at a titre of 1:1600 and two blood cultures were positive for *B. melitensis* biotype 1. The patient was treated with doxycycline 200 mg/day and rifampicin 900 mg/day orally for 6 weeks. The fever abated and the low back pain resolved after 3 days of antibiotic treatment. The patient was discharged on the tenth day with a BUN of 6.7 mmol/l (urea 13.3 mmol/l), serum creatinine of 123 $\mu\text{mol/l}$ and a total urine protein excretion of 2 g/day.

Four weeks after the antibiotic treatment was completed, the patient had regained 15 kg in weight. Her blood pressure was 160/100 mmHg and the rest of the physical examination was normal. The haemoglobin level, BUN, serum creatinine, LDH and albumin were all normal. Creatinine clearance was 100 ml/min/1.73 m². Urinalysis revealed 10 RBCs per HPF and total urine protein excretion was 0.48 g/day. On kidney biopsy performed during the recovery phase (light microscopy) most glomeruli appeared normal, although some showed minimal mesangial changes. The interstitium was normal and there was intimal hypertrophy of the arterioles compatible with hypertension.

Immunofluorescence staining revealed granular deposits in the mesangium of IgA, IgG and, to a lesser degree, of C3, compatible with IgA nephropathy.

Sixteen months later the patient has normal kidney function tests. Urinalysis examination

revealed no cellular elements and in 24 hour urine collection no protein was found. The creatinine clearance was 112 ml/min/1.73 m².

Discussion

A case of nephrotic syndrome during acute brucella infection, that responded to treatment with antibiotics, is described. The association of the nephrotic syndrome with bacterial infections has been described with syphilis, leprosy, tuberculosis²⁰ and rarely with brucellosis.⁶ Bacterial endocarditis, as well as postinfectious glomerulonephritis (PGN), has also been associated with nephrotic syndrome. The clinical features and the echocardiographic findings in our case were not compatible with brucella endocarditis. The normal serum complement levels and the lack of cryoglobulins in the serum did not support the diagnosis of PGN. Renal biopsy during recovery from PGN usually shows prominence of the axial zones and, at times, may show some diffuse or segmental mesangial proliferation.²⁰ The immunofluorescence staining typically shows deposits of IgG and C3, and rarely minimal deposits of IgA and IgM. The renal biopsy in our patient, performed during the recovery phase, revealed the features of IgA nephropathy.

IgA nephropathy is the most common primary glomerular disease.²¹ Extensive mesangial IgA deposits may also be seen in a variety of multi-system diseases (coeliac disease, dermatitis herpetiformis, Crohn's disease and seronegative arthropathy), neoplastic diseases, infections with leprosy or toxoplasmosis and in alcoholic liver disease.²⁰ The association of IgA nephropathy with brucellosis has been described by Nunan¹⁹ in one case. The nephrotic syndrome occurs in up to 70% of cases of primary IgA nephropathy and is not reversible, except for the rare occurrence of steroid sensitive relapsing cases.²⁰ The reversibility of the nephrotic syndrome with antibiotic treatment in our case does not support a diagnosis of primary IgA nephropathy. This case, as well as the case described by Nunan,¹⁹ suggests that IgA nephropathy with massive proteinuria may be secondary to brucellosis. The proteinuria may respond, at least partially, to treatment with antibiotics.

In conclusion, a case of IgA nephropathy with nephrotic syndrome during acute brucellosis is described. The nephrotic syndrome responded to treatment with antibiotics. Brucellosis should be considered as a case of secondary IgA nephropathy.

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