Cryptococcal granulomatous interstitial nephritis and dissemination in a patient with untreated lupus nephritis

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Abstract
Infection is a significant cause of mortality and morbidity in systemic lupus erythematosus (SLE). There are many reports of cryptococcal infection in patients with SLE, on immunosuppression. However, untreated lupus with cryptococcal infection and dissemination is rare. CD4 lymphopaenia is not reported in such patients. We describe a patient with untreated SLE to be having cryptococcal granulomatous interstitial nephritis and dissemination with CD4 lymphopaenia.

Keywords: cryptococcus; dissemination; interstitial nephritis

Introduction
Patients with systemic lupus erythematosus (SLE) have an increased risk for infections with common pathogens as well as with opportunistic organisms. Disseminated cryptococcal infection can not only mimic but also coexist with active untreated lupus and present with cryptococcal granulomatous interstitial nephritis (GIN).

Case report
A 38-year-old man presented with fever, anasarca and acute renal failure for 2 months. He was not known to be a hypertensive or diabetic. There was no history of previous treatment or past history of nephritic or nephrotic illnesses, headache, arthritis, rash or myalgia. He was normotensive. There was fever (102°F), pedal oedema and pallor, but meningismus was absent and neurological examination was unremarkable.

Laboratory examination revealed anemia (Hb: 84 g/L), white cell count of 5600/mm3, neutrophilia (neutrophil 96 and lymphocytes 4), renal failure (serum creatinine: 212.16 µmol and serum urea: 76.75 mmol), urine (RBC: 25–30, WBC: 2–4) and proteinuria with severe hypoalbuminaemia (UP/UC: 1.71, serum albumin: 13 g/L). He had hyponatraemia (Sr Na: 117 mmol/L), hypothyroidism (TSH: 185 µIU/ml) and transaminase elevation (AST: 259 IU, ALT: 84 IU). Immunological markers were positive for SLE: [elevated dsDNA: 94 Au/ml (normal: <30)], ANA: positive-nucleolar pattern and hypocomplementaemia, C3: 0.25 g/L (normal: 0.94–1.8 g/L) and C4: 0.06 g/L (normal: 0.1–0.4 g/L). The C-reactive protein was elevated: 88.6 mg/L (normal: <6 mg/L). Direct Coombs test was positive.

The cerebrospinal fluid (CSF) analysis suggested chronic meningitis (glucose: 25 mg%, protein 125 mg% with presence of 20 cells in the CSF with 80% of lymphocytes) and the latex agglutination test (Remel Inc., Lenexa, KS, USA) was positive for the cryptococcal antigen.

Cultures of the CSF, blood, bone marrow aspirate and urine after an expressed prostatic massage grew mucoid cream colonies of Cryptococcus neoformans on Sabouraud dextrose agar and brown colonies on birdseed agar. These
were serotyped on canavanine–glycine–bromthymol blue (CGB) agar and shown to be Cryptococcus neoformans var neoformans serotype A/D. The bone marrow biopsy showed necrotizing granulomatous inflammation. There was no evidence of diabetes, hepatitis B, C or human immune deficiency virus infection.

The patient had profound CD4 lymphopaenia with a low CD4/CD3 ratio (CD4+ cells: 30 cells/µL and CD3+ cells: 63 cells/µL; mean counts in south Indian healthy adults by flow cytometry: 799 CD4 cells; Guava® EasyCD4™ System with Cytosoft® software, version 2.2).

A renal biopsy showed class IV lupus nephritis with concomitant cryptococcal granulomatous interstitial nephritis. Figure 1 shows renal interstitium with a granulomatous infiltrate and numerous cryptococci.

The patient required haemodialysis and blood products in the first week but subsequently became dialysis independent. He was treated with amphotericin B (1.5 mg/kg), empiric anti-tubercular drugs, along with empirical carbapenems and vancomycin for 2 weeks. 5-Flucytosine was not used in view of transaminase elevation. With treatment, he became afebrile and consciousness improved.

During the third week of admission, he became febrile again probably due to a line sepsis. The blood culture grew β hemolytic streptococcus Group G, associated with pancytopenia; Hb: 93 g/L (post-transfusion) WBC: 2800/mm³, platelets: 22000/mm³. He was treated for 7 days with intravenous crystalline penicillin 20000 units every 6 h, but continued to deteriorate.

The patient died on the 30th day after admission, having received 2 weeks of amphotericin B and 3 weeks of antibiotics. Postmortem examination showed the presence of numerous variably sized and shaped yeast like organisms with the capsule highlighted with mucicarmine stain in lung, spleen, kidney, bone marrow and mediastinal lymph nodes along with extensive necrosis.

Discussion

Infections are associated with granulomatous interstitial nephritis in 6.7% of cases [1,2]. Patients with disseminated cryptococcus have shown renal involvement of 26–45.5% [3].

Our patient presented with lupus nephritis and cryptococcal granulomatous interstitial nephritis with dissemination with no prior immunosuppression. A case report, and a review of 44 SLE patients on immunosuppression, showed 77% of the fungal infection to be cryptococcus either in isolation or with another fungus, manifesting as meningitis in the majority [4]. Chen et al. discussed two patients without prior immunosuppression having cryptococcal meningitis [5].

Our patient had CD4 lymphopaenia that predisposes patients to severe infections. In idiopathic CD4+ lymphopaenia, defective production of IFN-γ and TNF-α has been documented [6].

Suarez-Rivera et al. in their case report discussed the role of cell-mediated immune response in a patient with crescentic glomerular nephritis, cutaneous anergy, cryptococcal mediastinalitis with no evidence of dissemination and a relative CD4 lymphopaenia [7]. Patients with steroid-sensitive nephrotic syndrome have an absolute or relative decline in CD4+ lymphocytes (helper cells) with an increase in CD8 lymphocytes (cytotoxic/suppressor cells) not only in relapse but even in a state of remission, related to a predominance of Th1 cytokines, IL2, in nephrotic syndrome. The lymphokine soluble immune response suppressor factor (SIRS) produced predominantly by CD8 lymphocytes inhibits antibody production and delayed-type hypersensitivity responses in nephrotic syndrome [8].

Cryptococcaemia has a poor prognosis and can present with a sepsis syndrome without obvious neurological involvement. The deteriorating clinical manifestations culminating in death after an initial response to appropriate anti-fungal and anti-bacterial therapy could be an immune reconstitution syndrome [6]. This results from enhanced but partially reconstituted pathogen-specific, cell-mediated immunity and induction of proinflammatory cytokines, leading to an exaggerated inflammatory reaction. Antifungal therapy causes a reversal in the Th2 to a Th1 cytokine profile leading to a pro-inflammatory response.

Renal involvement with cryptococcosis has been reported as causing pyelonephritis, papillary necrosis with microabscesses in four diabetics [9], and as acute renal failure with cryptococcal granulomatous interstitial nephritis in histology in a renal transplant recipient [3] and in a previously normal individual [10].

This is an instructive report of a patient with untreated SLE, profound CD4 lymphopaenia presenting with cryptococcal granulomatous interstitial nephritis and dissemination.

Conflict of interest statement. None declared.

References

A confusional state associated with use of lanthanum carbonate in a dialysis patient: a case report

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Abstract

A 75-year-old woman was admitted with febrile confusion and abdominal pain. She was taking medications that included lanthanum carbonate. Examination, biology, a cerebral scan, and a review of her medications could not explain the confusion. The plain film of the abdomen revealed multiple diffuse calcium-like deposits throughout the digestive tract. The plasma levels of lanthanum were higher than normal. The confusion resolved after discontinuation of the lanthanum carbonate.

This case raises the problem of the potential role played by lanthanum tablet residue in the genesis or aggravation of diverticular flare-up and the problem of the potential permeability of the blood–brain barrier with lanthanum use in case of its digestive accumulation, leading to increased serum concentrations.

Keywords: adverse event; confusion; therapeutic

A 75-year-old woman undergoing haemodialysis was admitted to our Nephrology Unit on 7th May 2007 with febrile confusion and abdominal pain. She had become febrile for a few days prior to admission. Upon arrival, her body temperature was 38.5°C. She complained of dizziness associated with falls but had not experienced loss of consciousness. Neurological examination revealed confusion with no focal abnormality, the osteotendinous reflexes were quick, but there was no sign of localization or motor deficiency. Abdominal examination revealed diffuse abdominal pain but no vomiting or diarrhoea.

Predialytic blood tests showed normal blood count, serum sodium 141 mmol/L, serum potassium 5.7 mmol/L, blood urea nitrogen 45.6 mmol/L and serum creatinine 733 µmol/L. Liver tests and serum glucose were normal.

C-reactive protein was 74 mg/L. Rare colonies of Candida tropicalis were found in stool cultures. A brain CT scan showed cerebral atrophy without any recent lesion.

The ECG showed sinus rhythm with no repolarization or conduction abnormality. The plain film of the abdomen (Figure 1) revealed multiple diffuse calcium-like deposits throughout the digestive tract, especially in the rectosigmoid region. Repeated radiographs showed that these deposits continued to migrate through the digestive tract after withdrawal of the lanthanum carbonate. The abdominal CT scan (Figure 2) showed no mesenteric vascular abnormalities, but rectosigmoid distension with perirectal fat infiltration. Rectosigmoidoscopy revealed diverticular sigmoiditis with bowel mucous membrane inflammation, and the presence of off-white foreign bodies on the bowel wall. Upon analysis these were found to be lanthanum carbonate tablet residues.