



EXCEPTIONAL CASE

Severe tubulointerstitial nephritis: tracking tuberculosis even in the absence of renal granuloma

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Abstract

Extra-pulmonary tuberculosis is frequently located in the kidneys and, in such cases, could be associated with a granulomatous interstitial nephritis. Granulomas are not always detected, especially in human immunodeficiency virus (HIV)-positive patients. We report here a case of tubulointerstitial nephritis without granulomas in an HIV-negative patient. Since all laboratory tests failed to isolate *Mycobacterium tuberculosis* in the kidney, a targeted biopsy guided by positron emission tomography-computed tomography was performed on a mediastinal node, revealing a positive culture. After 6 months of treatment, no recovery of the renal injury has been observed.

Key words: chronic kidney disease, granuloma, positron emission tomography-computed tomography, QuantiFERON, tuberculosis, tubulointerstitial nephritis

Background

Urogenital tract is the second most common site for extra-pulmonary tuberculosis (TB), accounting for one-quarter of such cases [1]. According to the European Dialysis and Transplant Association, only 0.65% of patients admitted for dialysis have TB as primary renal diagnosis [2]. Renal injury is generally due to urinary tract scarring, and less commonly to glomerulonephritis or secondary amyloidosis, but granulomatous interstitial nephritis could be the sole manifestation. We report here a case of tubulointerstitial nephritis (TIN) without granulomas in a human immunodeficiency virus (HIV)-negative patient, which led to the diagnosis of disseminated TB.

Case report

A 41-year-old Congolese woman, living in France for 5 years, was hospitalized for kidney injury. She had no medical history except for six uncomplicated pregnancies. Two months after her last delivery, she noticed general sickness, loss of weight and nocturnal fever. Physical examination was unremarkable. Laboratory results were as follows: white cell $7 \times 10^9/L$, with lymphopenia $0.8 \times 10^9/L$; microcytic anaemia 80 g/L; C-reactive protein 68.5 mg/L; serum creatinine (SCr) 457 $\mu\text{mol/L}$; estimated glomerular filtration rate (eGFR) by chronic kidney disease-epidemiology collaboration (CKD-EPI) formula 10 mL/min/1.73 m². Renal ultrasonography was normal. Urinalysis revealed low tubular proteinuria (0.6 g/g creatinine), sterile leucocyturia

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(250/mm³) and no haematuria. Renal biopsy showed diffuse active interstitial inflammation without granulomas (Figure 1).

The first aetiological assessment was inconclusive: no drug abuse (including over-the-counter medications), negative hepatitis B, hepatitis C and human immunodeficiency viruses serologies, negative blood and urine cultures, normal chest X-ray, cardiac ultrasound and no immunologic antibodies (antineutrophil cytoplasmic antibody, antinuclear antibody, anti-RO/SSa and anti-La/SSb were negative). Complement was not activated. Serum angiotensin-converting enzyme was normal.

The patient was initially treated with IV methylprednisolone (500 mg/day for 3 days), followed by oral prednisolone (1 mg/kg/day), which was gradually tapered off. A first interferon gamma release assay (IGRA), using QuantiFERON-TB Gold in Tube (QFT-TB) testing (Qiagen), was performed and considered indeterminate due to no reactivity in the mitogen control positive well. Due to a high suspicion of TB, antitubercular treatment was introduced 3 weeks later.

As the fever persisted, investigations were intensified: 'Ziehl-Neelsen' staining, polymerase chain reaction (PCR) and

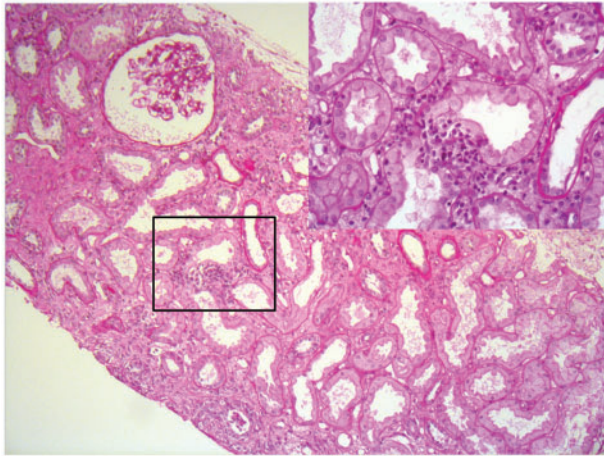


Fig. 1. Periodic acid-Schiff (PAS) staining ($\times 100$ magnification): active interstitial inflammation with lymphocytes, histiocytes and polymorphonuclear leucocytes. Inset shows PAS staining ($\times 400$ magnification): acute tubulitis without basement membrane thickening.

culture on renal biopsy; two early morning urine cultures were performed and gave negative results for *Mycobacterium tuberculosis* (MTb). Positron emission tomography-computed tomography (PET/CT) showed uptakes in stomach, ileocecal valve and two mediastinal lymph nodes (Figure 2). A transbronchial biopsy of one mediastinal node showed granuloma formations with central necrosis, whereas PCR was negative for MTb. Finally, after 4 weeks, MTb grew in lymph node. Once corticotherapy was decreased, a second QFT-TB assay was performed and the result was then positive. Six months later, fever and biological inflammation reduced, while renal function remained at Stage 5 chronic kidney disease (CKD) (SCr 508 $\mu\text{mol/L}$, eGFR 8 mL/min/1.73 m²). A second kidney biopsy confirmed chronic lesions with atrophic tubules (Figure 3).

Discussion

TIN during TB infection is rare, but is characterized by the presence of interstitial granulomas. To the authors' best knowledge, this is the first reported case of TB-associated TIN without granulomas in an HIV-negative patient; as for HIV-positive patients, inhibition of cell-mediated immunity during the post-partum period could explain the high risk of TB, and the lack of granulomas [3, 4].

In the face of ongoing migration, TB is probably an underdiagnosed cause of TIN, since MTb is rarely isolated. Urine cultures, 'Ziehl-Neelsen' staining and culture on renal biopsy mostly provide negative results [1]. Additionally, PCR has also shown poor sensitivity in paraffin-embedded extra-pulmonary samples (32% positive), probably associated with a low burden of mycobacteria [1, 5].

In extra-pulmonary TB cases, PET/CT can help perform targeted biopsies [6], as in the case of our patient. As previously published, an indeterminate IGRA test may be explained by high doses of glucocorticoids [7] or CKD [8]. Once the use of immunosuppressive drugs is reduced, the test result may turn positive, as noticed in our case. Therefore, the difficult diagnosis of TB entails many aetiologies for TIN, such as drug reaction, infections and autoimmune diseases.

Even in developed countries and in the absence of granuloma on renal biopsy, TB should be tracked in high-risk

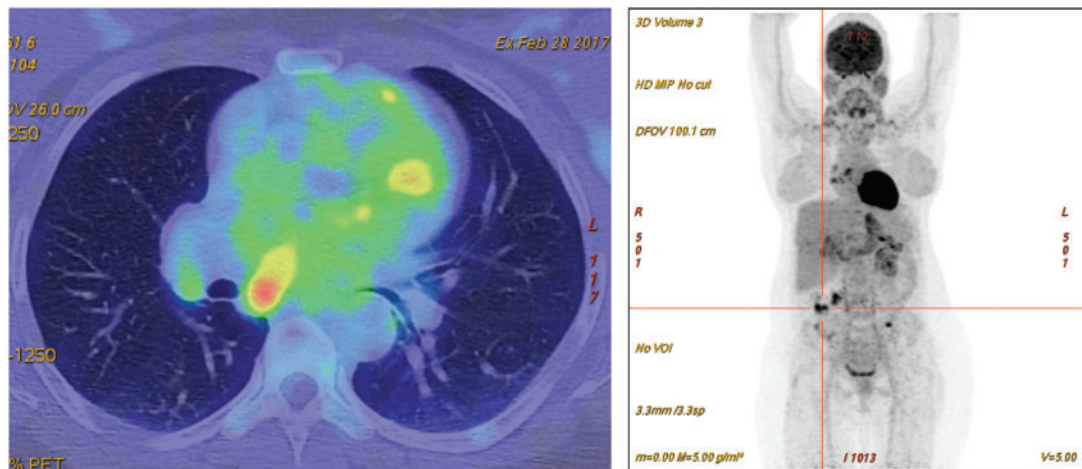


Fig. 2. PET/CT. Axial image: hypermetabolic activity within subcarinal lymph node. Coronal image: hypermetabolic activity on ileocecal valve and two mediastinal lymph nodes.

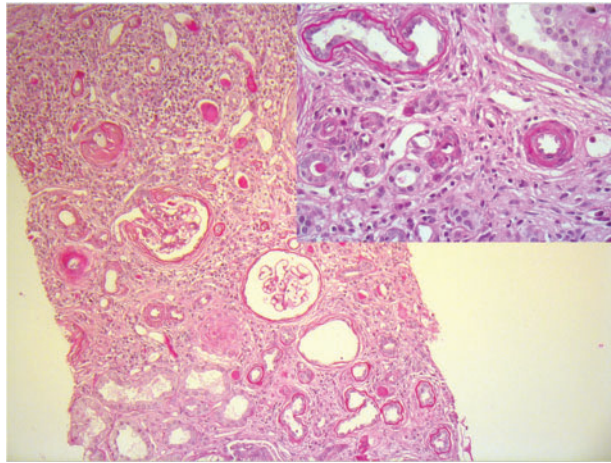


Fig. 3. Periodic acid-Schiff (PAS) staining ($\times 100$ magnification) chronic lesion with atrophic tubules, ischaemic glomeruli and arteriolar thickening. Inset shows PAS staining ($\times 400$ magnification) mild lymphocytic tubulitis.

populations, including immunosuppressed patients in the post-partum period or with severe CKD.

Treatment of TIN caused by TB is based on a standard 6-month antibiotic treatment, without ethambutol to avoid optic neuritis [1]. Currently, the pathogenesis of TB-associated TIN is unknown. TIN might not be directly to bacterial invasion, but to indirect immunological mechanisms, and therefore the use of corticosteroids could reduce interstitial fibrosis [9]. Shribman *et al.* report a case of miliary TB complicated by an immune complex nephritis, which could be in favour of an immunological process in TB-associated renal injury [10].

Due to the poor renal prognosis, diagnosis must be done as early as possible, preferably when eGFR is >15 mL/min. Indeed, two-thirds of patients presenting with an eGFR <15 mL/min need to start a renal replacement therapy within 12 months after diagnosis [1].

Conclusion

TB remains an underdiagnosed cause of severe TIN, especially in the lack of granulomas on renal biopsy, leading to a delay of specific treatment and a poor renal outcome. Physicians should be advised to hunt down TB in high-risk populations or in cases where there is a lack of corticotherapy response. When there is no evidence of pulmonary disease, PET/CT imaging could help in making the diagnosis.

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Conflict of interest statement

None declared.

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