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Subacute interstitial pneumonitis due to *Mycobacterium bovis* after intravesical bacillus Calmette-Guérin instillation in a renal transplant patient☆

Neumonitis intersticial subaguda por *Mycobacterium bovis* tras instilaciones vesicales de bacilo de Calmette-Guérin en un trasplante renal

Dear Editor,

The estimated incidence rate of urothelial bladder carcinoma is 1.4–2.2% in kidney transplant (KT) patients.[1] However, the clinical course may be more aggressive than in the general population, with higher rates of progression and relapse.[2]

Intravesical administration of bacillus Calmette-Guérin (BCG), an attenuated live strain of *Mycobacterium bovis*, is one of the main adjuvant therapies for managing non-invasive bladder cancer. BCG instillation produces a massive local immune reaction with antitumour activity.[3] However, both local and systemic infectious complications have been reported in relation to this treatment, especially in immunocompromised patients. Disseminated infection as a result of the systemic absorption of BCG may occur in 0.4% of cases and it is usually manifested as fever, weight loss, night sweats or dyspnoea, and even multiple organ failure in severe cases.[4,5] Interstitial pulmonary involvement is a rare complication.

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We report for the first time a case of interstitial pneumonitis caused by *M. bovis* after bladder instillations of BCG in a KT patient.

This case involves an 81-year-old woman with a history of chronic kidney disease secondary to polycystic kidney disease, who underwent kidney transplantation 11 years earlier with a normally functioning graft, in maintenance therapy with tacrolimus and everolimus. Ten years after transplantation, she was diagnosed with urothelial bladder carcinoma without muscle invasion and, after transurethral resection of the tumour, she began treatment with intravesical BCG.

Thirty days after the first instillation she began suffering from asthenia, weight loss, sweating and fever mainly at night, and cough without expectoration, which lasted for 2 months. After receiving 2 cycles of empirical antibiotic therapy with amoxicillin–clavulanic acid and levofloxacin without improvement, the patient returned to the emergency department.

On admission she had a temperature of 38 °C and 98% oxygen saturation, with no other noticeable findings. The results of laboratory tests and viral serologies revealed only anaemia of chronic disease and elevated C-reactive protein. Broad-spectrum antibiotic therapy with meropenem was initiated, fever and symptoms persisted during the following days.

All bacterial and viral microbiological studies were negative. A CT scan of the chest, abdomen and pelvis was performed, which showed a lung pattern with diffuse bilateral involvement and poorly defined nodules with a centrilobular distribution, suggestive of infection caused by atypical microorganisms or mycobacteria. The study was completed with a bronchoscopy for microbiological sampling, although direct microscopy showed no acid-alcohol resistant bacilli and cultures of mycobacteria obtained from bronchoalveolar lavage were negative at 8 weeks. The study using the polymerase chain reaction technique for *Mycobacterium tuberculosis complex* sequences in the bronchoalveolar lavage was also negative. No transbronchial biopsy was performed because it was considered a high-risk procedure for the patient.

With the diagnostic suspicion of systemic lung infection caused by *M. bovis*, treatment with isoniazid, rifampicin and ethambutol was prescribed for 6 months. Fever and associated symptoms gradually disappeared, while acute-phase reactants decreased. A subsequent control CT scan showed that the impairments described had been resolved.

This clinical case demonstrates the risk of developing systemic complications in KT patients treated with bladder instillations of BCG.

The pathophysiology of pulmonary manifestations after intravesical BCG treatment is still controversial. Some authors believe it is a hypersensitivity reaction, based on the histological finding of granulomas without microbiological isolation and a favourable response to corticosteroids.[6] Other authors, however, have reported mycobacterial isolation in different tissues,[7] which would demonstrate a haematogenous dissemination of the bacillus. It has therefore been pointed out that the low sensitivity of microbiological studies would be a result of the rapid control of bacillary replication by the host immune system and the attenuated virulence of BCG, which, however, would not prevent the formation of granulomatous lesions.[8] Therefore, the diagnosis is made by the presence compatible clinical symptoms and the early response to tuberculostatic treatment.

Some authors argue that intravesical instillation of BCG is safe in immunocompromised patients, however there are no conclusive studies in KT patients.[1,4,9] To that effect, concomitant prophylactic administration of isoniazid alone or in combination with rifampicin has been tested, with favourable results in some cases, although not without adverse effects.[1] On the other hand, other authors argue that it should be contraindicated due to an increased risk of systemic dissemination together with a lower local immune response.[10]

In conclusion, bladder instillations of BCG in kidney transplantation can produce disseminated mycobacterial infection, with a long-term clinical course with few symptoms. Therefore, a high index of suspicion is necessary to begin treatment at an early stage.

Conflicts of interest

The authors declare no conflicts of interest related to the publication of this article.

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Caution with the use of the new direct acting antivirals in the hepatitis C virus related renal disease☆

Precaución con el uso de los nuevos antivirales de acción directa para el tratamiento del virus de la hepatitis C en pacientes con enfermedad renal asociada

Dear Editor,

Hepatitis C virus (HCV) and chronic kidney disease (CKD) are often linked prompting a significant increase in morbimortality. New direct acting antivirals (DAA) against HCV achieve rapid response in short period of time.[1] However, their use in HCV related renal disease (HCVRRD) is pretty scarce. We present 5 patients with CKD and HCV treated with them (Table 1). All subjects were males (52–57 years old) with impaired renal function and different degrees of proteinuria and microhematuria. Renal biopsy was performed in 1 patient (membranoproliferative glomerulonephritis secondary to cryoglobulinemic vasculitis) being avoided in others due to high risk of bleeding (thrombocytopenia and antiplatelet therapy). Four subjects started on sofosbuvir (SOF) and daclastavir (DAC) and one received DAC with simeprevir (SIM). While HCV viral load achieved negativization (14–30 days), a decline in renal function and a dramatic increase in proteinuria were observed in those SOF with DAC. The only biopsied patient received corticosteroids and Rituximab (375 mg/m^2, 4 doses) 4 weeks after starting therapy with renal recovery and proteinuria decrease. Patient receiving DAC and SIM finally died of gastrointestinal bleeding 3 months later. Three individuals were admitted during antiviral therapy: severe cellulitis in one case; 2 heart failure episodes in other; last subject required different admissions and finally started chronic hemodialysis.

In our patients, CKD is related with HCV infection, confirmed at least in one case and high suspicion in the others. Treatment of HCV becomes the mainstay 1–2, not only for the infection itself but also for the kidney. In our experience, new DAA achieved a rapid decrease in viral load with an important increase of microhematuria, proteinuria and a notable worsening of renal function in 4 of these 5 patients, one of them finally requiring hemodialysis. The explanation for this disturbing phenomenon could be either an emergent acute intersticial nephritis, but the rapid increase and the amount of proteinuria and microhematuria did not support this possibility, or the exacerbation of HCVRRD, most firmly supported for the same reasons. As suggested by the favorable outcome of the only confirmed HCVRRD patient treated according to published recommendations,[2] this situation could be due to an amplification of the immunological processes involved. The lack of diagnostic confirmation made us to avoid using rituximab in the others.

In our experience, the new DAA are very potent and effective drugs, but with a paradoxical worsening of the HCVRRD, mainly when sofosbuvir is used, an aspect that should be studied.

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