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SARS-CoV-2 and *Aspergillus* pneumonia in kidney transplantation: More frequent than we think?

Neumonía por SARS-COV-2 y *Aspergillus* en trasplante renal: ¿más frecuente de lo que pensamos?

Dear Editor,

Invasive pulmonary aspergillosis can complicate some viral infections, such as the flu, and we are starting to perceive it as a poor prognostic factor in patients co-infected with SARS-CoV-2 pneumonia.

We report the case of a 67-year-old man with chronic kidney disease secondary to focal segmental glomerulonephritis, that was on haemodialysis. In June 2020, he received a kidney transplant, with induction with basiliximab and treatment with tacrolimus, mycophenolate and steroids. Also received combined prophylaxis with cotrimoxazole and valganciclovir.

Thirty (30) days after transplantation, the patient was diagnosed with SARS-CoV-2. The dose of immunosuppressants was reduced, and azithromycin and hydroxychloroquine were started. On day +14, he was admitted to the hospital due to fever and respiratory failure. Chest X-ray revealed bilateral infiltrates and laboratory tests showed creatinine 1.5 mg/dl, CRP 72 mg/l, Hb 10.6 g/dl, lymphocytes 340/μl, D-dimer 1.021 ng/ml and interleukin-6 31.9 pg/l. On admission, mycophenolate was discontinued and treatment was started with dexamethasone + remdesivir + ceftriaxone + prophylactic heparin. Based on criteria of severity it was decided to administer tocilizumab on the third day after admission and tacrolimus was suspended on the fifth day due to poor clinical course and supratherapeutic levels.

On day +7, he was admitted to the ICU due to reduced level of consciousness and respiratory failure requiring mechanical ventilation. Antibiotics were added, meropenem, amikacin, linezolid and voriconazole, maintaining prophylactic valganciclovir and Soltrim (trimethoprim/sulfamethoxazole). In addition to persistent positive PCR for SARS-CoV-2, *Aspergillus fumigatus* was found in the routine bronchial aspirate and serum galactomannan was 4,5. Given the persistence of high levels of tacrolimus, voriconazole was replaced by intravenous isavuconazole. After 13 days of hospitalisation, the patient's clinical course deteriorated with massive cerebral haemorrhage and he died that same day.

In November 2020, the COVID-19 Registry of the Spanish Society of Nephrology (SEN) reported 2,474 patients on renal replacement therapy, 37% of which were kidney transplants.[1] This population is considered to be at higher risk due to their state of immunosuppression and frequent contact with health centres.[2]

Severely ill COVID-19 patients have higher concentrations of proinflammatory cytokines (IL-1, IL-2, IL-6 and tumour necrosis factor alpha) and anti-inflammatory cytokines (IL-4 and IL-10), with lower expression of interferon gamma, and they have lower numbers of CD4 and CD8 cells.[3] Therefore, the risk of suffering from fungal co-infections is greater.[4] In fact, an incidence of invasive aspergillosis of up to 0.65% has been described within the first year in kidney transplant recipients, with a mortality rate of up to 39% in the first 12 weeks.[5]

Despite the high number of COVID-19 cases reported, its association with invasive aspergillosis has not been well established. The EORTC/MSG European group concludes that the diagnosis of COVID-19-associated pulmonary aspergillosis (CAPA) is a challenge, since the radiological characteristics of the invasive fungal lesion overlap with the pre-existing alterations as a result of viral SARS- CoV-2 pneumonia.[6,7] In addition in COVID-19 patients, the high risk of aerosol generation limits the collection of respiratory samples (bronchial aspirate or bronchoalveolar lavage), so the diagnosis is often based on serum galactomannan antigen, and an index >0.7 is considered positive.[8]

There are many species of *Aspergillus* spp., but *Aspergillus fumigatus complex* is the most common aetiological agent. The

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treatment of choice is voriconazole. In our case, it was changed to isavuconazole because oral administration was not possible, because of its reduced influence on CYP3A4 activity (the patient had levels above the therapeutic concentrations despite having suspended tacrolimus) and because of its greater propensity to cross the blood-brain barrier.[9] However, *Aspergillus fumigatus* azole resistance is increasingly common. Some authors advise against the use of monotherapy in favour of combination treatment with echinocandins or liposomal amphotericin B if there is suspicion of resistance or poor clinical course, and performing molecular identification.[10]

Unfortunately, antifungal susceptibility for *Aspergillus* spp. is not available in all laboratories or it may take a long time, so the rate of azole resistance in Spain may be underestimated.

In conclusion, SARS-CoV-2 and invasive mycoses co-infection in immunosuppressed patients is probably greater than that described in the literature. For this reason, and given the diagnostic limitations, the detection of fungal markers should point to the early establishment of treatment.

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Chronic kidney disease is associated with worse outcomes following SARS-CoV2 infection among 18647 patients: A population-based cohort study

La enfermedad renal crónica se asocia con peores resultados después de la infección por SARS CoV2 entre 18647 pacientes: estudio de cohorte basado en la población

Dear Editor:

The clinical spectrum of COVID-19 ranges from asymptomatic cases to those who develop acute-respiratory distress syndrome and require intensive care unit (ICU) admission.[1,2]

Previous studies have identified chronic kidney disease (CKD) as a risk factor for severe outcomes following SARS-CoV2 infection.[3] This observation derives from data from small cohorts of hospitalized patients mainly from China[4–7] and a UK cross-sectional survey describing 16,749 patients hospitalized with COVID-19.[8] Recently, the largest nationwide

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