Multiple drugs

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Various toxicities: case report

A 55-year-old woman developed invasive pulmonary aspergillosis (IPA) during immunosuppressive treatment with antithymocyte globulin, prednisone, mycophenolate mofetil and tacrolimus, and off-label tocilizumab for COVID-19. She also developed acute kidney injury and had graft loss secondary to drug toxicity during treatment with tacrolimus. Additionally, she received off-label treatment with hydroxychloroquine, ceftriaxone, azithromycin, immune globulin and tocilizumab for COVID-19 [*not all dosages and routes stated*].

The woman with end-stage kidney disease secondary to unilateral renal agenesis underwent kidney transplantation (KT) with induction immunosuppressive agent antithymocyte globulin [Grafalon]. Later, she received maintenance immunosuppressive therapy with prednisone (0.5 mg/kg/day for 1 month with a subsequent gradual reduction until reaching a dose of 5–10 mg/day), mycophenolate mofetil and tacrolimus. She had a family history of chronic kidney disease (CKD) in her first-degree relatives. On 16 March 2020, she was discharged from hospital with a serum creatinine (SCr) of 3.7 mg/dL. Her anti-infective prophylaxis therapy included cotrimoxazole and valganciclovir. On 17 April 2020, she was re-admitted for a 7 days history of severe asthenia associated with fever. Upon admission, RT-PCR on nasopharyngeal swab tested positive for SARS-CoV-2. Therefore, she started receiving off-label treatment with hydroxychloroquine, ceftriaxone and azithromycin. Also, prophylactic anticoagulation with unspecified low-molecular weight heparins and supplemental oxygen therapy were also started. Additionally, treatment with mycophenolate mofetil was discontinued, tacrolimus dosage was reduced, and prednisone dose was maintained at baseline (she was taking 15mg daily at the time of admission). Later, she was administered with IV off-label immune globulin 0.5 g/kg daily for 5 days. On day 2 of admission, she received a single dose of off-label tocilizumab 600mg. In the subsequent days, she became afebrile, although hypoxaemia persisted and productive cough appeared on day 7 of admission. At this time, a sputum culture yielded numerous colonies of *Aspergillus fumigatus*. On day 12, a chest CT scan revealed diffuse areas of ground-glass opacity, traction bronchiectasis with thickening of bronchial walls, and a "tree-in-bud" pattern in the distal airway. Based on these findings diagnosis of IPA attributed to immunosuppressive treatment was made.

Therefore, the woman started receiving treatment with isavuconazole on day 13 of admission. Eventually, after 20 days from the initial nasopharyngeal swabbing, her RT-PCR tested negative for SARS-CoV-2. Her respiratory condition improved. Thus, supplemental oxygen therapy was discontinued on day 18. However, A fumigatus was newly recovered from a second sputum culture. On day 32, a CT scan showed improvement of the ground-glass opacities but the emergence of a cavitary lung nodule of 5cm in diameter in the middle lobe with thick irregular wall and outlet of bronchial structures into the cavity. A similar nodule of 2.5cm was also identified in the lower left lobe. These findings were suggestive of IPA progression. Thus, amphotericin B liposomal was added to isavuconazole therapy. Moreover, prednisone was stopped and tacrolimus dosage was again reduced to a target trough level of 5 ng/mL. She remained afebrile and asymptomatic over the following days. A new CT scan performed after 3 weeks of amphotericin B liposomal and isavuconazole therapy revealed a significant reduction in the size of both nodules. On day 53, she was discharged from hospital, and continued to receive amphotericin B liposomal and isavuconazole therapy. At 12 week follow-up, CT scan revealed the complete resolution of the nodule in the lower left lobe. Meanwhile, she had acute kidney injury with a SCr of 4.5 mg/dL, which was considered as secondary to tacrolimus toxicity. Thus, tacrolimus dosage was reduced, and treatment with IV fluids and unspecified supportive measures was started. However, her condition progressively worsened. Therefore, on day 16, renal replacement therapy was started. A kidney biopsy revealed arteriosclerosis and moderate-intense arteriolar hyalinization attributable to donor lesions, tubular vacuolization probably related to tacrolimus toxicity, mild acute tubular damage and isolated calcium oxalate deposits in tubular lumen. Primary hyperoxaluria was suspected given the family history of CKD and the presence of calcium oxalate deposits. In the absence of kidney function improvement, a second biopsy repeated 3 weeks apart revealed no significant changes compared to the previous histopathological assessment. At the time of discharge, she returned to dialysis. It was concluded that she had graft loss secondary to tacrolimus toxicity.

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