Multiple drugs

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Various toxicities: case report

A 59-year-old man developed Covid-19 pneumonia, *Candida albicans* infection, *Pseudomonas aeruginosa* infection and nosocomial infection during immunosuppressive therapy with mycophenolate and tacrolimus. He had received off-label treatment with interferon-α, umifenovir and lopinavir/ritonavir for Covid-19 pneumonia. Additionally, he exhibited a lack of efficacy during treatment with cefoperazone/sulbactam and caspofungin for nosocomial infection, meropenem and voriconazole for *Pseudomonas aeruginosa* infection, tacrolimus and mycophenolate for transplant rejection prophylaxis, albumin human, plasma for anuric acute kidney injury and immune globulin [*routes and durations of treatments to reactions onsets not stated; not all dosages stated*].

The man was hospitalised in the isolation ward on 01 February 2020 with a 3-day history of cough, fever, fatigue, chills and diarrhoea. Anamneses revealed that, he had a 25-year history of hepatitis-B virus infection and decompensated cirrhosis. In May 2017, he underwent liver transplant due to hepatocellular carcinoma. Post-transplant, he was treated with immunosuppressive therapy with mycophenolate and tacrolimus. He was also receiving entecavir for hepatitis-B virus infection. Upon admission, he denied any history of alcohol consumption or smoking. However, his wife was diagnosed with Covid-19 on the previous day and was in home isolation. Unfortunately, he had close contact with his wife. On day 1 of admission, his examination revealed the following: body temperature 40.0°C, BP 134/86mm Hg, HR 112 beats/min, RR 24 /min. He also had splenomegaly, jaundice and ascites, indicative of chronic rejection. Laboratory test revealed the following: WBC 3.2 $x10^9$/L, lymphocyte count 0.7 $x10^9$/L, CRP 35.1 mg/L, total bilirubin 83.9 µmol/L, ESR 102.0 mm/h, alanine aminotransferase of 60 U/L and γ-glutamyl transpeptidase 1087 U/L. Blood gas analysis revealed the following: partial pressure of oxygen (Pao2) 98mm Hg and partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) 297. The real-time polymerase chain reaction (RT-PCR) assay of a pharyngeal swab was positive for SARS-CoV-2. The chest CT scan showed bilateral ground-glass opacities. He was diagnosed with mild COVID-19 pneumonia.

Hence, the man started receiving off-label treatment with nebulised interferon-α, umifenovir and lopinavir/ritonavir as per Chinese Covid-19 Interim Management Guidance. He also received empirical treatment with piperacillin/tazobactam for increased CRP levels. His dosages of mycophenolate and tacrolimus were halved due to risk of drug-drug interactions with lopinavir/ritonavir. On day 4 of admission, he developed critical respiratory failure. Hence, nasal oxygenation therapy was initiated with standard methylprednisolone. However, his hypoxaemia rapidly worsened with a decrease in PaO_2 and PaO_2/FiO_2 ratio. Hence, he was placed on invasive ventilation. On day 12, he had a pneumothorax and pleural effusion, which was closed to chest drainage. Follow-up chest CT revealed remarkable bilateral lung inflammation worsening. His blood culture showed positive results for *Candida albicans*, while pleural fluid and alveolar lavage showed positive results for *Pseudomonas aeruginosa*. Hence, a diagnosis of nosocomial infection in a transplant recipient was made. Subsequently, pathogen drug sensitivities were performed, and he was initiated on cefoperazone/sulbactam and caspofungin. On day 15, he was placed on extracorporeal membrane oxygenation because of the exacerbation of respiratory failure. Despite treatment, his bilirubin level continued to rise, while magnetic resonance cholangiopancreatography revealed substantial bile duct dilatation. On day 23, endoscopic retrograde cholangiopancreatography was performed, and a large amount of pus was drained, which was positive for *Pseudomonas aeruginosa*. Hence, he was received treatment with voriconazole and meropenem over the next 10 days. Subsequently, he developed anuric acute kidney injury. Hence, continuous renal replacement therapy and plasma exchange was initiated. He also received an infusion of albumin-human [albumin], blood, immune globulin [immunoglobulin] and plasma. On day 33 and 35 of admission, RT-PCR tests showed negative results. However, his condition worsened with fluctuating levels of PaO_2/FiO_2 and multiple organ failure on day 37. In spite of several rescue efforts, his condition rapidly deteriorated, and on day 45 of admission (16 March 2020), he died. His death was attributed to septic shock caused by *Candida albicans* infection, *Pseudomonas aeruginosa* infection and nosocomial infection.

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