

Elevated drug level, Covid 19 and reactivation of Herpes Zoster: 2 case reports

In a case report, two men aged 36 year and 56 year developed Covid -19 or reactivation of *Herpes Zoster* infection during immunosuppressant therapy with mycophenolate mofetil, prednisolone and tacrolimus. A 36-year-old man additionally developed elevated tacrolimus level due to concomitant administration of lopinavir/ritonavir with tacrolimus [routes and duration of treatments to reaction onsets not stated].

Case 1: The 36-year-old man was hospitalised with cough, fever, diarrhoea, rhinorrhoea and decreased urine output. He had a history of end stage renal disease and he had undergone kidney transplant in April 2016. Following transplant, he started receiving immunosuppressant therapy with long acting tacrolimus 2mg every 24 hrs, prednisolone 10mg once a day and mycophenolate mofetil 500mg every 12 hours. At current presentation, it was observed that on 12 March 2020, he developed febrile sensation, rhinorrhoea and coughing, and after 2 days, he developed diarrhoea with decreased urinary output. On 16 March 2020, he underwent testing and the next day, he tested positive for Covid-19. Subsequently, he was hospitalised. He had mild fever and the laboratory tests showed increased CRP, decreased lymphocyte count, elevated serum creatinine level with increased protein to creatinine ratio. A chest radiograph demonstrated subsegmental atelectasis on both lower lung field and peri-bronchial infiltration in the left upper lobe. On day 2 of hospitalisation, fever spiked. Thus, his mycophenolate mofetil was stopped and off label treatment for Covid 19 was started with lopinavir/ritonavir 400/100mg twice a day. After 2 days, clinical tests showed abruptly increased tacrolimus level (16.5 ng/mL). This sudden increase in the tacrolimus level was attributed to the concomitant administration of lopinavir/ritonavir with tacrolimus. Therefore, tacrolimus was withdrawn and prednisolone was switched to methylprednisolone. Gradually tacrolimus levels decreased and reached to therapeutic range within 10 days. Due to recurrence of diarrhoea and fever, he was further treated with hydroxychloroquine. Subsequently, kidney function stabilised. On day 13, lopinavir/ritonavir was stopped. The next day, methylprednisolone was again changed to prednisolone. Tacrolimus was resumed on day 18 at the dose of 0.5mg every 24 hours and on day 23, hydroxychloroquine was stopped. His chest lesion also improved and kidney function also stabilised. Thereafter, he tested negative for Covid 19 in two subsequent tests.

Case 2: The 56-year-old man was transferred from a local hospital due to cough and sputum. He had a history of end stage renal disease and type 2 diabetes mellitus. He underwent kidney transplant in October 2004 and then again in December 2011. One year post transplant, he developed acute antibody mediated rejection, treated with steroid pulse therapy and rituximab. Subsequently, he started receiving maintenance immunosuppressive therapy with long acting tacrolimus 4mg every 24 hours, mycophenolate mofetil 500mg every 12 hours and prednisolone 10mg once a day. On 1 March 2020, he visited for testing of Covid 19, as he had a contact history of confirmed Covid 19 patient. He was initially asymptomatic, but tested positive for Covid 19. During hospitalisation, he experienced flank pain and was diagnosed with reactivation of *Herpes Zoster* infection. Thus, he was treated with famciclovir. After discontinuation of famciclovir, he had cough and sputum. Additionally, a chest CT showed ground-glass opacity in the lung and laboratory tests showed elevated CRP levels. Therefore, he was transferred to the current hospital from a local hospital. At current hospital admission, mycophenolate mofetil was stopped and tacrolimus was continued with prednisolone. On the same day, he was given off label treatment with hydroxychloroquine 400mg once a day for Covid 19. On day 9, there was no cough, his vitals were stable, but the chest lesion was slightly aggravated and he was still positive for Covid 19. Thus, azithromycin was added as a supportive therapy to hydroxychloroquine. Finally, the chest radiograph showed improvement in the lung lesion and respiratory symptoms were also alleviated. On hospital days 17 and 18, RT-PCR showed negative results for Covid 19.