Multiple drugs

Various toxicites and off-label use: case report

A 44-year-old man developed iatrogenic acute liver damage during venous thromboembolism prophylaxis with enoxaparin sodium and off-label therapy with lopinavir/ritonavir and hydroxychloroquine for Covid-19. Further, he developed alteration of gut microbiota leading to pneumatosis intestinalis (PI) following empirical therapy with amoxicillin/clavulanic acid and antibacterial therapy with piperacillin/tazobactam and teicoplanin. The treatment with lactulose for acute liver damage also contributed to the development of PI [not all routes, dosages and times to reactions onsets stated].

The man presented to hospital in Italy on 20 March 2020, with complaints of a persistent fever, chest pain and productive cough for 9 days, which persisted after paracetamol and amoxicillin/clavulanic acid [amoxicillin-clavulanate] therapy. Subsequent analyses led to the diagnosis of Covid-19. Hence, he started receiving off-label therapy with lopinavir/ritonavir 400/100mg twice daily and hydroxychloroquine 200mg twice daily. Due to the suspicion of a secondary bacterial infection, he also received piperacillin/ tazobactam 4.5g three times daily and IV teicoplanin 400mg once daily (after a loading dose). In addition, he started receiving SC enoxaparin sodium [enoxaparin] 4000UI once daily for venous thromboembolism prophylaxis. Six days later, his condition improved, and his fever subsided. However, around the same time, his AST and ALT levels increased, and he developed hyperammonaemia, with slightly elevated levels of γ -glutamyl transferase. Iatrogenic acute liver damage secondary to enoxaparin sodium, lopinavir/ritonavir and hydroxychloroquine was suspected.

The man's treatment with lopinavir/ritonavir and hydroxychloroquine was discontinued, and further doses of paracetamol were avoided. Enoxaparin sodium was withheld. Teicoplanin was continued, and he started receiving acetylcysteine. He also received lactulose at an average dose of 25 mL/day over the subsequent 6 days for the liver damage. Repeat laboratory analyses performed 6 days from the earlier ones confirmed normalisation of AST; however, ALT still appeared elevated, and D-dimer levels were found to be remarkably high. Echo-colour-Doppler tests were performed to rule out thromboembolic event, and lung contrast-enhanced CT scans unexpectedly revealed intraperitoneal free bubbles as a collateral finding. Subsequent abdominal contrast-enhanced CT scans revealed the collection of air in dependent and non-dependent portions, involving the caecum and the right colon, consistent with PI. Filling defects were not observed in the lumen of abdominal aorta and its branches; neither portal venous air nor free fluid collection was observed. Due to the complete absence of symptoms, as well as the progressive normalisation of blood tests, he was discharged on 7 April 2020, and a follow-up was scheduled. He was prescribed empirical therapy with ciprofloxacin, metronidazole and enoxaparin sodium 4000UI once daily for 1 week. During follow-up on 24 April 2020, he was asymptomatic; abdominal CT scan revealed complete resolution of all previously observed pathological changes; all laboratory analyses were within the normal limits, apart from only slightly elevated levels of D-dimer, ferritin and ALT. He eventually tested negative for Covid-19. Hence, it was believed that the prolonged administration of antibiotics caused alteration of his gut microbiota, resulting in PI; lactulose was thought to have contributed to the development of the PI.

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