Multiple drugs

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Pneumatosis intestinalis, thrombocytopenia and off-label use: 4 case reports

In a single centre case series, 4 men aged 61–65 years old were described who developed pneumatosis intestinalis (PI) during treatment with off-label tocilizumab, off-label methylprednisolone or lactulose. Further, a 64-year-old man developed thrombocytopenia during treatment with heparin for potential non-ST-segment elevation myocardial infarction (NSTEMI) [*not all dosages, routes, times to reaction onsets and outcomes stated*].

Case 1: A 65-year-old man developed PI during treatment with lactulose and off-label tocilizumab. The man was admitted and was diagnosed with cytokine release-like syndrome associated with COVID-19 infection. He started receiving off-label treatment with hydroxychloroquine, ascorbic acid, thiamine, tocilizumab and enoxaparin-sodium [enoxaparin] prophylaxis along with salbutamol [albuterol] and meropenem. He was then intubated due to acute respiratory distress syndrome (ARDS). His prophylactic enoxaparin-sodium was switched to heparin and he started receiving off-label treatment with anakinra. Further, he received norepinephrine for vasoplegic shock and received lactulose, metoclopramide and sodium-chloride [saline] due to no bowel movements. He experienced progressive abdominal distension and a CT scan revealed extensive colon and small bowel pneumatosis with mesenteric and portal venous gas, suggestive of bowel ischaemia. The laxative regimen was enhanced with polyethylene glycol and Senna-alexandrina [senna]. Intra-abdominal pressure was found to be ranged from 13–19mm Hg, which was suggestive of abdominal compartment syndrome. Six days after initiating mechanical ventilation, he developed acute tubular necrosis (ATN) from haemodynamic instability and non-oliguric acute kidney injury (AKI) likely secondary to COVID-19 sepsis. His propofol therapy was switched to ketamine, and received piperacillin/tazobactam for enteric bacteria. After 12 days, the CT scan was consistent with bowel ischaemia and peritonitis, which was complicated by bowel perforation, small bowel obstruction (SBO), pneumoperitoneum, enterocutaneous fistulas and abscess formation. A diagnosis of PI secondary to tocilizumab and lactulose was made. Thereafter, he developed haematochezia and melena, requiring aggressive resuscitation along with multiple blood and frozen plasma transfusions and repeated drainage procedures for intra-abdominal collections. He gradually and progressively recovered and was finally discharged for rehabilitation, 90 days after admission. He underwent a right colectomy, and was in good condition. It was stated that lactulose might have contributed in the development of PI.

Case 2: A 61-year-old man developed PI during off-label treatment with tocilizumab and methylprednisolone for COVID-19 infection. The man presented with dyspnoea, tachypnoea, worsening cough (productive, non-bloody), fever, myalgias, chills, hypoxia, hyporexia and chest pain, and was admitted. He received off-label treatment with a course of azithromycin and oseltamivir for suspected COVID-19 infection. Further, COVID-19 PCR test was found to be positive. During the first night of admission, he was noted to be severely hypoxic, and improvement in SpO2 was evident after aggressive resuscitation with IV methylprednisolone 100mg, furosemide, oxygen and pronation. On day 2 of admission, he was transferred to the ICU. He received one dose of off-label tocilizumab, and was started receiving off-label IV methylprednisolone 50mg twice daily, off-label prophylactic enoxaparin-sodium [enoxaparin] along with furosemide, salbutamol [albuterol] and non-invasive ventilation. On day 2 of ICU admission, he received off-label treatment with convalescent-anti-SARS-CoV-2-plasma [convalescent plasma]. One week after admission, worsening hypoxia and haemodynamic instability was noticed and he required endotracheal intubation for mechanical ventilation and received vasopressin and norepinephrine. He experienced two episodes of arterial thrombosis despite proper anticoagulation with argatroban. Five days after initiating mechanical ventilation, physical examination showed a protuberant abdomen and dark output from the nasogastric tube (NGT). Laboratory investigations revealed increased lactate and leucocytosis, increased creatinine, hyperkalaemia and oliguria. Abdominal CT scan showed gas in the portal vein and superior mesenteric artery and cecal and small bowel pneumatosis, indicative of PI. Due to multiorgan failure surgery was not performed and he received treatment with metronidazole, vancomycin, pantoprazole, renal replacement therapy [continuous veno-venous hemofiltration (CVVH)], metabolic support and fluid optimisation. On day 10 of ICU admission, he developed refractory cardiopulmonary arrest associated with metabolic acidosis and lactate levels of 24 mmol/L, leading to death. It was stated that the PI was secondary to tocilizumab and methylprednisolone.

Case 3: A 64-year-old man developed PI during off-label treatment with tocilizumab and methylprednisolone for COVID-19 infection. The man was diagnosed with COVID-19 pneumonia and started receiving off-label treatment with oral hydroxychloroquine 200mg twice daily, IV methylprednisolone 50mg twice daily, SC anakinra 100mg every 6h and SC prophylactic enoxaparin-sodium [enoxaparin] 40mg daily along with salbutamol [albuterol]. Neutrophilia, respiratory alkalosis, lymphopenia, transaminitis and hypoalbuminaemia were noted. Despite initial improvement, 5 days after admission, he presented with a nocturnal crisis of hypoxia, which improved after pronation. After 4 hours, he developed intermittent episodes of delirium, altered mental status and agitation, which was treated with haloperidol. Subsequently, due to worsening hypoxia, he underwent sedation, endotracheal intubation and mechanical ventilation. He was transferred to another ICU and was found to have an unsecure airway, raising concern for potential aspiration. Therefore, he started receiving piperacillin/tazobactam and vancomycin. Nine days after initial hospital admission, he developed septic shock and prerenal acute kidney injury, which required haemodynamic support with a norepinephrine. His enoxaparin-sodium therapy was switched to IV sodium heparin due to a D-dimer of 987 ng/mL. Additionally, he received a single dose of tocilizumab. Three days after tocilizumab administration, physical examination revealed abdominal distension and tympanism with digital percussion. Abdominal X-ray features were compatible with colonic ileus or pseudoobstruction. CT scan revealed diffuse small and large bowel pneumatosis. A diagnosis of PI secondary to tocilizumab and methylprednisolone was made. This was found in the setting of worsening kidney and liver function, increased ventilation requirements, leukocytosis and acidosis. Due to broad multiorgan failure, surgery was not performed. CXR showed additional bilateral consolidations in the lower lobes along with worsening respiratory status, suggestive of superimposed pneumonia. Thereafter, he received comfort care and was withdrawn from mechanical ventilation however, after 4 minutes, he developed a cardiopulmonary arrest leading to death.

Case 4: A 64-year-old man developed PI during treatment with lactulose and off-label treatment with tocilizumab and methylprednisolone. Further, he developed thrombocytopenia during treatment with heparin for non-ST-segment elevation myocardial infarction (NSTEMI). The man was diagnosed with COVID-19 infection. His history was significant for NSTEMI in the setting of uncontrolled hypertension and he had been receiving heparin drip, aspirin, and clopidogrel. He started receiving off-label treatment with hydroxychloroquine along with remdesivir for COVID-19 infection, and received ceftriaxone and doxycycline for potential bacterial pneumonia. These medications were discontinued due to worsening kidney function parameters. One week after admission, he received a single dose of off-label tocilizumab and off-label IV methylprednisolone 40mg every 8h. On hospital day 10, despite non-invasive ventilation (BiPAP), the progressive worsening of the respiratory status was noted, requiring intubation and mechanical ventilation. He was then transferred to another hospital, and hypotension with oliguria, mixed acidosis, hyperkalaemia, hypertriglyceridaemia, hypoalbuminaemia, hyperglycaemia and uraemia were evident, requiring continuous renal

replacement therapy. Intensive resuscitation with albumin-human [albumin], insulin, bicarbonate, norepinephrine and vancomycin was initiated. Propofol therapy was switched to dexmedetomidine. He was treated with lactulose, pantoprazole, polyethylene glycol, methylnaltrexone-bromide [methylnaltrexone] and Senna-alexandrina [senna]. Subsequently, he developed fever, leuckocytosis and low platelets, which were indicative of potential heparin-induced thrombocytopenia. Therefore, heparin therapy was discontinued and was switched to argatroban. Despite intensive supportive care, he required vasopressin treatment, Increase in leucocytes count and lactate were noted. One week after the hospital transfer, physical examination showed abdominal distension and CT scan revealed gas in the portal vein and mesentery as well as extensive intestinal pneumatosis, suggestive of PI. A diagnosis of PI secondary to lactulose, tocilizumab and methylprednisolone was made. Further, he developed refractory septic shock and, 1 day later, he developed cardiopulmonary arrest leading to death.

Miyara SJ, et al. Pneumatosis Intestinalis in the Setting of COVID-19: A Single Center Case Series From New York. Frontiers in Medicine 8: 638075, 4 Jun 2021. Available from: URL: http://journal.frontiersin.org/journal/medicine 803603458