

Respiratory failure in a tofacitinib treated patient with ulcerative colitis

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Abstract

Tofacitinib is an oral Janus Kinase (JAK) inhibitor recently approved for the management of moderate to severe ulcerative colitis (UC). Safety data on tofacitinib has suggested a moderately increased risk for venous thromboembolism (VTE) as well as non-opportunistic infections and non-infectious drug-related lung disease. We faced a diagnostic dilemma between an infectious and non-infectious cause of acute respiratory insufficiency in a patient on recent tofacitinib therapy. A lung CT scan showed bilateral interstitial pneumonic infiltrates and a PCR on bronchoalveolar lavage fluid was positive for cytomegalovirus (CMV). The patient's condition improved after discontinuation of tofacitinib and treatment with anti-viral drugs and high dose corticosteroids. A CMV primary infection was suspected, however a drug-induced interstitial lung disease cannot be excluded in the differential diagnosis of patients with autoimmune disorders under tofacitinib therapy who present with fever, hypoxia and pulmonary infiltrates. (*Acta gastroenterol. belg.*, 2024, 87, 336-339).

Keywords: Tofacitinib, cytomegalovirus, interstitial lung disease, case report, hypoxemia, respiratory failure.

Introduction

Janus Kinase (JAK) inhibitors such as tofacitinib have been approved for the treatment of moderate to severe UC (1). According to a recent meta-analysis tofacitinib increases the risk of non-opportunistic respiratory infections when compared to placebo or other biological therapies (2). Several reports have also linked tofacitinib with opportunistic respiratory infections such as *Pneumocystis jirovecii* pneumonia, varicella pneumonia or latent tuberculosis reactivation (3-5). Others have raised concerns that tofacitinib might be linked to venous thromboembolism (VTE) (6) and drug-induced interstitial lung disease (ILD) (7), yet no significant association was detected in a recent meta-analysis (2). Nonetheless, pulmonary disease remains a rare extra-intestinal manifestation of inflammatory bowel disease (IBD) and is often related to drugs or infection (8).

Case description

A 55-year-old man was admitted in February 2021 because of respiratory failure and high fever. He was diagnosed with UC in 2012 and had a refractory disease course since 2018, with insufficient response to thiopurines, infliximab, vedolizumab, and ustekinumab. Two months earlier, the patient had been admitted to the intensive care unit (ICU) with respiratory failure due to severe COVID-19 pneumonia. During that episode,

a computed tomography (CT) scan revealed extended ground glass opacities in both lungs with mediastinal and bilateral hilar adenopathy reflective of severe COVID-19 pneumonia (Fig 1A). The patient was treated with oxygen, dexamethasone and remdesivir, and ten days later he was discharged in good general condition.

After this episode, the patient had no respiratory complaints until one week before the current hospitalization, when severe fatigue developed. The day before admission he developed high fever (40.0°C) with shivering, night sweating, dry cough and dyspnoea at rest. He still had symptoms of active UC, with ongoing diarrhoea and abdominal pain. In this context, tofacitinib 10 mg BID was initiated 9 days earlier. On clinical examination, he appeared uncomfortable with laboured breathing. His temperature was 36.3°C, blood pressure 103/78 mmHg, heart rate 103 beats per minute, respiratory rate 30 breaths per minute, and his oxygen saturation 93% while breathing ambient air. An arterial blood gas analysis revealed mild respiratory alkalosis with a pH of 7.458, a pCO₂ of 25.9 mmHg and mild hypoxemia with a pO₂ of 75.9 mmHg. The HCO₃ was 17.9 mmol/l (lower limit of normal: 21 mmol/l) and the anion gap (AG) was borderline normal (i.e. 11 mmol/l) indicating secondary metabolic acidosis, probably in the context of chronic diarrhoea and metabolic compensation. The white-cell count was 17860/μL (reference range 4300 to 9640) with neutrophilia and monocytosis. C-reactive protein was 34.4 mg/L (reference range < 5.0). Nucleic acid testing of a nasopharyngeal swab for influenza viruses, respiratory syncytial virus and SARS-CoV-2 was negative. A urine test for legionella and pneumococcal antigen was negative. Cultures of stool and blood samples remained negative. Faecal calprotectin was 254 mg/kg. On a CT pulmonary angiography there was no evidence of pulmonary embolism, however extensive peri-bronchovascular ground glass opacities and crazy paving with subpleural sparing were observed (Fig 1B).

The patient was admitted to the ICU, received high flow nasal oxygen therapy and was empirically treated with piperacillin/tazobactam and clarithromycin for a

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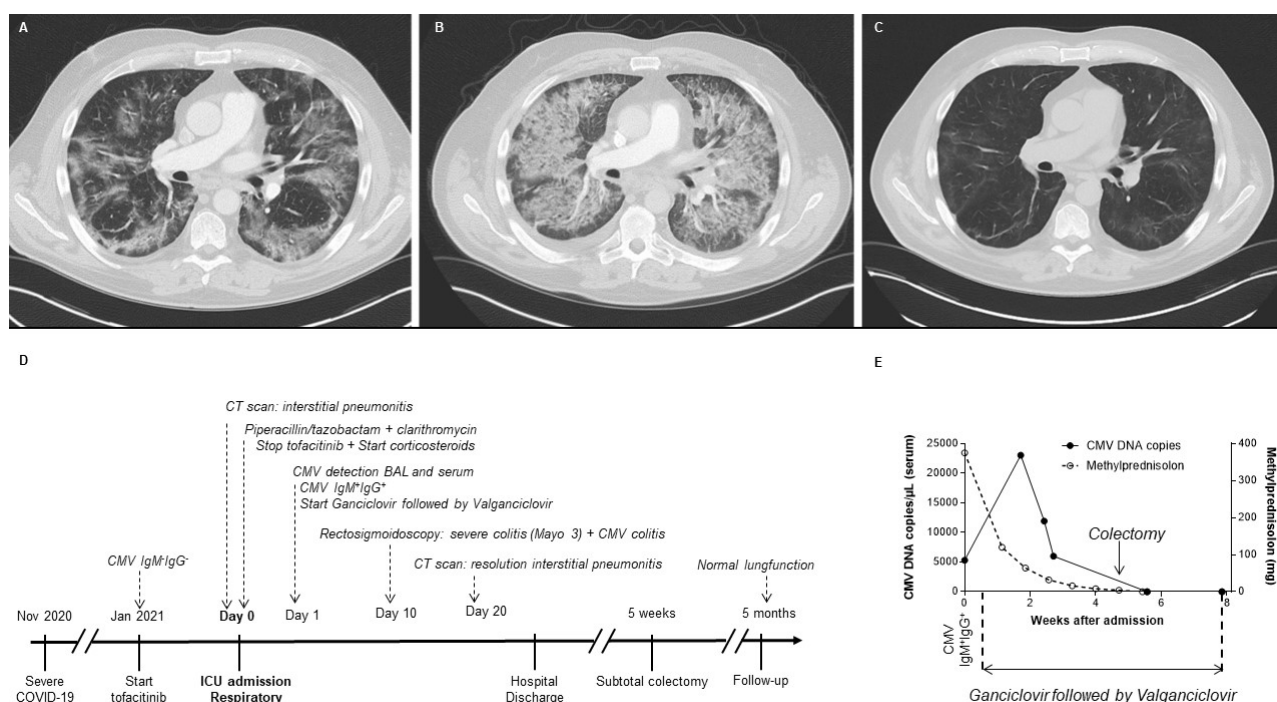


Figure 1. — Evolution throughout the hospitalisation. An axial CT image (A), obtained with intra-venous contrast enhancement during hospitalization at the COVID-19 ICU two months before the current presentation, shows extended crazy paving and ground glass opacities mainly in the periphery in both lungs. An axial CT image (B), obtained with intra-venous contrast enhancement during the emergency department presentation, shows extensive central peri-bronchovascular ground glass opacities and crazy paving with subpleural sparing. A high resolution axial CT image (C) obtained without intra-venous contrast enhancement 20 days after the current presentation (cfr. B) and approximately 3 months after the severe COVID-19 pneumonia (cfr. A), shows significant reduction in ground glass opacities in both lungs. Timeline (D) illustrating course of patients medical history and hospitalization. Graph (Panel E) shows kinetics of CMV DNA copies in serum and corticosteroid tapering over time. The patient was treated with ganciclovir followed by valganciclovir until CMV DNA was undetectable for 2 consecutive times in serum. Five weeks after admission a total colectomy was performed.

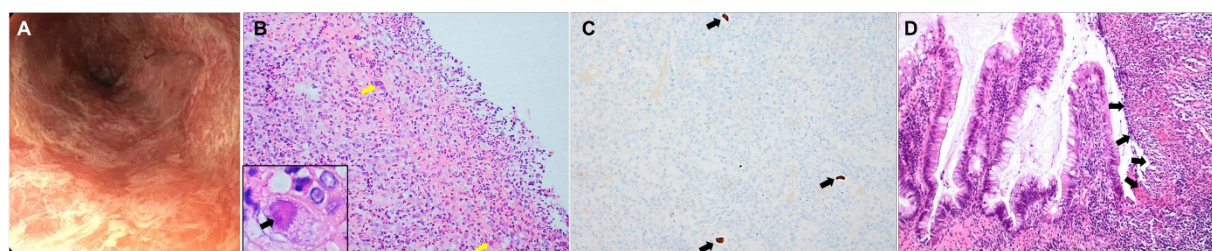


Figure 2. — CMV colitis. Rectosigmoidoscopy (A) shows Mayo 3 UC with ulcerations, erosions and absent vascular pattern. A haematoxylin and eosin (H&E) stained section of the colon biopsy (B) showing an ulceration and granulation tissue. Several cells are large with prominent eosinophilic nuclei, indicating viral infection (yellow arrows). The inset shows a close-up of such a cell with a basophilic nuclear inclusion (black arrow), suggestive for CMV infection. CMV immunohistochemistry (C) performed on the biopsy showing several positive nuclei (black arrows). H&E section from the colon resection (D), showing a chronic colitis with villous mucosa and ulceration (black arrows). Magnification in Panel B: 200x (inset 1000x), Panel C: 200x, Panel D: 100x.

type IV community-acquired pneumonia. At the same time tofacitinib was ceased and a high dose corticosteroid regimen was initiated because of suspected drug-induced ILD. Oxygen supplementation was tapered and stopped after 1 week. Corticosteroids were gradually tapered over 5 weeks.

The day after admission, a bronchoalveolar lavage (BAL) was performed. A screening multiplex for respiratory pathogens, an ELISA for galactomannan and

a PCR for varicella zoster and *Pneumocystis jirovecii* DNA performed on the BAL fluid were all negative. Cytomegalovirus (CMV) DNA was detected at 2425 copies/μL BAL fluid, and 5315 copies/μL serum. Although serological analysis for CMV was negative 10 days before the current admission, both anti-CMV IgM and IgG were detected at admission, indicating a CMV primo-infection. Treatment with ganciclovir (5 mg/kg bid) was initiated followed by valganciclovir (900 mg bid)

until CMV viral loads were undetectable in the serum in at least 2 consecutive samples (Fig 1D-E). Ten days after admission, a rectosigmoidoscopy was performed because of abdominal cramps and diarrhoea, which demonstrated severe colitis (Mayo 3) (Fig 2A). Immunohistochemical (IHC) analysis of colon biopsies revealed CMV colitis superposed on the refractory UC (Fig 2B-C) and the diagnosis of CMV colitis was made. Because of refractory UC, the patient underwent a subtotal colectomy (stage 1 of a 3-stage ileal pouch-anal anastomosis procedure) five weeks after admission, when he was still treated with valganciclovir and low dose corticosteroids (Fig. 1E). Anatomopathological examination of the resected colon confirmed active chronic colitis consistent with UC (Fig 2D). CMV immunohistochemistry on the surgical specimen was negative.

Twenty days after admission, a high-resolution CT scan showed nearly complete resolution of ground glass opacities in both lungs (Fig 1C). At a follow-up visit 5 months after the current admission, the patient is doing well and has no abdominal complaints with his stoma in place. A lung function test was performed and showed normal spirometry values, lung volumes and diffusion capacity.

Discussion

We report the case of a 55-year-old patient with refractory UC who developed respiratory insufficiency shortly after initiation of tofacitinib treatment. CT-imaging revealed extensive bilateral ground glass opacities and CMV DNA was detected in the BAL fluid. Immunomodulatory drugs for IBD can potentially have a direct toxic effect on the lung (and induce ILD) as well as immunosuppressive effects that increase the risk of lung infection (2,7,9). Thus, the challenge faced in this case was to differentiate between drug-induced ILD and an infectious cause (namely CMV pneumonitis). The timing of the symptoms relative to tofacitinib initiation and prompt recovery after tofacitinib discontinuation and systemic corticosteroid treatment could be suggestive of a drug-induced ILD. However, previously tofacitinib has not been related to an increased risk of ILD (2), on the contrary, recent evidence suggests that targeting the JAK/STAT pathway can be beneficial in lung diseases such as ILD or SARS-Cov-2 induced excessive pulmonary inflammation or fibrotic lung disease (10,11). On the other hand, patients on tofacitinib treatment are vulnerable to infections that relate to impaired T-cell function, such as viral pneumonia. CMV can induce a variety of syndromes in immunocompromised hosts, including pneumonitis and colitis (12). Thus, tofacitinib could have predisposed this patient to the CMV infection.

The diagnosis of CMV pneumonitis in this case was suspected by a combination of recent CMV seroconversion and the detection of CMV DNA in serum and BAL samples. Even though detection of CMV DNA in BAL cannot fully differentiate between CMV pneumonitis and

viral shedding in the alveoli it has been shown that the level of CMV DNA in BAL of immunocompromised patients correlates with true CMV pneumonitis (13-15). Disease likelihood and viral replication levels are generally higher after primary infection and more likely to be clinically important rather than after reactivation. In addition, our patient's CMV disease was accompanied by a CMV colitis demonstrated by IHC and the presence of CMV DNA in the colonic mucosa. The diagnosis of CMV colitis has been described in UC refractory to the treatment and has been associated with an increased risk of colectomy (16,17). In most cases, CMV colitis in UC patients results from reactivation of latent CMV infection. However, CMV colitis is less frequently seen in the context of CMV primary infection, such as in our patient. Currently, there is no consensus on how to manage patients with UC diagnosed with an active CMV infection. Regarding the risk of CMV colitis in patients receiving tofacitinib, only a single UC patient in the OCTAVE study, receiving tofacitinib 10 mg twice daily, had developed CMV colitis (1).

Two months before tofacitinib was initiated our patient suffered from a severe COVID-19 pneumonia, however, our patient was completely recovered prior to initiation of tofacitinib. Whether COVID-19 and/or its treatment might have acted as a predisposing factor for severe drug-induced ILD and/or CMV pneumonitis remains unclear in our case.

In conclusion, we reported a case of a patient with refractory UC who developed respiratory insufficiency shortly after initiation of tofacitinib treatment. It remains critical to be aware of the safety profile of novel drug compounds as it might take years before rare adverse effects such as drug-induced lung injury and opportunistic infections become apparent.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. SANDBORN W.J., SU C., SANDS B.E., D'HAENS G.R., VERMEIRE S., SCHREIBER S., et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *New Engl. J. Med.*, 2017; 376(18): 1723-1736.
2. KHOO J.K., BARNES H., KEY S., GLASPOLE I.N., ÖSTÖR A.J. Pulmonary adverse events of small molecule JAK inhibitors in autoimmune disease: systematic review and meta-analysis. *Rheumatology*, 2020; 59(9): 2217-2225.
3. GRIGOROPOULOS I., THOMAS K., CHRISTOFOROU P., FANIDI I., PAPAVIDI M., KYRIAKOU F., et al. Pneumocystis jirovecii pneumonia after initiation of tofacitinib therapy in rheumatoid arthritis: case-based review. *Mediterr. J. Rheumatol.*, 2019; 30(3): 167-170.
4. ABE N., KUDO T., JODO S. Elderly-Onset Varicella Pneumonia in a Patient With Rheumatoid Arthritis Treated With Tofacitinib. *Arthritis Rheumatol.*, 2018; 70(8): 1233.
5. WINTHROP K.L., PARK S., GUL A., CARDIEL M., GOMEZ-REINO J., TANAKA Y., et al. Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. *Ann. rheum. dis.*, 2016; 75(6): 1133-1138.
6. MEASE P., CHARLES-SCHOEMAN C., COHEN S., FALLON L., WOOLCOTT J., YUN H., et al. Incidence of venous and arterial thrombo-

- embolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. *Ann. rheum. dis.*, 2020; 79(11): 1400-1413.
7. ELIADOU E., MOLEIRO J., RIBALDONE D.G., ASTEGIANO M., ROTHFUSS K., TAXONERA C., et al. Interstitial and granulomatous lung disease in inflammatory bowel disease patients. *J. Crohns Colitis*, 2020; 14(4): 480-489.
 8. HARBORD M., ANNESE V., VAVRICKA S.R., ALLEZ M., BARREIRO-DE ACOSTA M., BOBERG K.M., et al. The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. *J. Crohns Colitis*, 2016; 10(3): 239-254.
 9. SCHLEIERMACHER D., HOFFMANN J.C. Pulmonary abnormalities in inflammatory bowel disease. *J. Crohns Colitis*, 2007; 1(2): 61-69.
 10. MONTERO P., MILARA J., ROGER I., CORTIJO J. Role of JAK/STAT in interstitial lung diseases; molecular and cellular mechanisms. *Int. J. mol. sci.*, 2021; 22(12): 6211.
 11. JAIN N.K., TAILANG M., JAIN H.K., CHANDRASEKARAN B., SAHOO B.M., SUBRAMANIAN A., et al. Therapeutic implications of current Janus kinase inhibitors as anti-COVID agents: A review. *Front. Pharmacol.*, 2023; 14.
 12. KHAN T.V., TOMS C. Cytomegalovirus Colitis and Subsequent New Diagnosis of Inflammatory Bowel Disease in an Immunocompetent Host: A Case Study and Literature Review. *Am. J. Case Rep.*, 2016; 17: 538-543.
 13. KOTTON C.N., KUMAR D., CALIENDO A.M., HUPRIKAR S., CHOU S., DANZIGER-ISAKOV L., et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation*, 2018; 102(6): 900-931.
 14. LODDING I.P., SCHULTZ H.H., JENSEN J.-U., KIRKBY N., PERCH M., ANDERSEN C., et al. Cytomegalovirus viral load in bronchoalveolar lavage to diagnose lung transplant associated CMV pneumonia. *Transplantation*, 2018; 102(2): 326-332.
 15. PIÑANA J.L., GIMÉNEZ E., GÓMEZ M.D., PÉREZ A., GONZÁLEZ E.M., VINUESA V., et al. Pulmonary cytomegalovirus (CMV) DNA shedding in allogeneic hematopoietic stem cell transplant recipients: implications for the diagnosis of CMV pneumonia. *J. Infection*, 2019; 78(5): 393-401.
 16. LV Y.L., HAN F.F., JIA Y.J., WAN Z.R., GONG L.L., LIU H., et al. Is cytomegalovirus infection related to inflammatory bowel disease, especially steroid-resistant inflammatory bowel disease? A meta-analysis. *Infect. drug resist.*, 2017; 511-519.
 17. MOURAD F.H., HASHASH J.G., KARIYAWASAM V.C., LEONG R.W. Ulcerative colitis and cytomegalovirus infection: from A to Z. *J. Crohns Colitis*, 2020; 14(8): 1162-1171.