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Methotrexate- and Upadacitinib-associated drug-induced pneumonitis leading to severe ARDS requiring prone ventilation and pulse-dose methylprednisolone: a case report and review of the literature

Dr Rupak Kundu

rupak.kundu@ouh.nhs.uk

Somerset NHS Foundation Trust

Dr Innes Turral

Somerset NHS Foundation Trust

Dr Muhammad Mujtaba Shaikh

Somerset NHS Foundation Trust

Case Report

Keywords: Methotrexate, upadacitinib, drug-induced pneumonitis, acute respiratory distress syndrome, methylprednisolone

Posted Date: October 4th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10960100/v1

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Additional Declarations: No competing interests reported.

Abstract

Severe drug-induced pneumonitis (DIP) during concurrent methotrexate and upadacitinib treatment is rarely reported and poses a considerable diagnostic and causality challenge. We report a white man in his late 50s with seropositive rheumatoid arthritis, treated with methotrexate and upadacitinib, who presented with progressive dyspnoea and hypoxaemia. He was initially treated for community-acquired pneumonia and subsequently developed severe ARDS despite maximal non-invasive respiratory support. Thoracic HRCT, together with expert opinion from the rheumatology and respiratory teams, indicated drug-induced pneumonitis as the most likely diagnosis, while an extensive infectious work-up, including testing for Pneumocystis jirovecii, was negative. He required invasive mechanical ventilation (IMV) and received intravenous methylprednisolone pulse-dose therapy (IVMP), 1 g once daily for three consecutive days, and five consecutive sessions of prone positioning, each for 18 hours, resulting in progressive, sustained improvement in oxygenation and respiratory mechanics, thereby averting the need for ECMO. He was successfully extubated after 8 days of IMV and subsequently discharged home 10 days post-extubation, without supplemental oxygen, on a tapering course of prednisolone. At the 3-month post-discharge follow-up, pulmonary function testing revealed resolution of the baseline obstructive pattern and a decline in gas transfer while on prednisolone as the sole DMARD. This case highlights the importance of promptly withdrawing suspected causative agents, rigorously excluding infection and other alternative diagnoses, and escalating respiratory support to IMV and corticosteroid therapy to IVMP when severe DIP continues to progress despite initial treatment.

Introduction

Methotrexate (MTX) remains an anchor disease-modifying antirheumatic drug (DMARD) for rheumatoid arthritis (RA). The SELECT-COMPARE and SELECT-NEXT trials support using upadacitinib, a selective JAK1 inhibitor, in combination with MTX to improve clinical and functional outcomes in RA in patients with an inadequate response to MTX [1, 2]. Pulmonary toxicity associated with MTX is well recognised, whereas upadacitinib-associated pneumonitis appears to be exceedingly rare, with the first case reported only recently [3]. MTX pneumonitis is considered an idiosyncratic hypersensitivity reaction, unrelated to cumulative dose, and can occur at any stage of treatment, including after years of stable exposure [4, 5, 6]. A non-specific interstitial pneumonia (NSIP) pattern is the most commonly reported radiological feature of MTX pneumonitis [7]. In contrast, the recently reported case of upadacitinib-associated pneumonitis developed shortly after treatment initiation and showed predominantly apical ground-glass opacities on imaging [3]. Given the very limited evidence available, the typical latency and characteristic radiological pattern of upadacitinib-associated lung injury remain uncertain.

Drug-induced pneumonitis (DIP) remains largely a diagnosis of exclusion, with no single standardised diagnostic test. This is particularly challenging in patients receiving immunosuppressive therapy, where bacterial, viral, fungal, and opportunistic infections must be carefully excluded. RA-associated interstitial lung disease (RA-ILD) represents another important differential diagnosis and can be difficult to distinguish from DIP during an acute presentation. Previous pulmonary function testing (PFT) and

thoracic imaging, when available, can therefore be notably important in identifying pre-existing lung disease and its progression. Bronchoalveolar lavage (BAL) can help, particularly to exclude infection, while lymphocytosis and, less commonly, eosinophilia can support DIP. Lung biopsy may occasionally provide additional diagnostic information; however, bronchoscopy and biopsy become technically challenging and potentially unsafe in critically ill patients with profound hypoxaemia and high ventilatory requirements.

This case illustrates these diagnostic difficulties in a patient receiving both MTX and upadacitinib who developed rapidly progressive pneumonitis despite having been stable on these drugs for months, leading to severe ARDS.

Case presentation

A 57-year-old white man with asthma, eczema and seropositive RA presented with a 2-week history of worsening dyspnoea and a 1-week history of chest tightness and non-productive cough. He was an ex-smoker, having stopped 10 years earlier. His regular medications included methotrexate (MTX) 25 mg once weekly, upadacitinib 15 mg once daily and prednisolone 2.5 mg once daily, with no dose changes over the preceding 6 months. On admission, he was febrile and tachycardic, requiring oxygen at 10 L/min with a PaO_2 of 10.9 kPa. CXR showed bilateral patchy infiltrates. There was no history of relevant antigen exposure or recent travel. Labs showed a white cell count of 12.34 × 10^9/L, neutrophil count of 11.02 × 10^9/L, lymphocyte count of 0.38 × 10^9/L, eosinophil count of 0 × 10^9/L, CRP of 376 mg/L and total IgE of 848 kU/L. Renal and hepatic function were preserved, and bedside echocardiography ruled out systolic heart failure. He was started on treatment for community-acquired pneumonia and an acute asthma exacerbation with co-amoxiclav, doxycycline, prednisolone 40 mg OD, bronchodilators and intravenous magnesium. Despite treatment, his hypoxaemia worsened, and PaO_2 fell to 6.46 kPa, prompting admission to ICU and initiation of HFNO at 60 L/min with an FiO_2 of 0.60. His PaO_2/FiO_2 ratio (PFR) was 14 kPa, and his ROX index was 7.9 on HFNO.

Over the next 48 hours, severe hypoxaemia persisted despite HFNO at 60 L/min with an FiO_2 of 0.55–0.75; the PFR ranged from 9 to 21 kPa and the ROX index from 4 to 11. White cell count and CRP remained elevated, and a repeat CXR showed worsening airspace opacities. Prednisolone 40 mg daily was continued. Doxycycline was stopped, and co-amoxiclav was switched to amoxicillin after respiratory viral and atypical bacterial PCR, sputum culture, and urinary pneumococcal and Legionella antigen tests were negative.

On day 4, HRCT thorax showed findings suggestive of drug-induced pneumonitis, as shown in **Fig. 1 (a) & (b)**. MTX and Upadacitinib had already been discontinued on admission. Severe hypoxaemia persisted despite HFNO at an FiO_2 of 0.70–0.80, with PFR ranging from 13 to 16 kPa and ROX indices between 4.3 and 6.3. Prednisolone was escalated from 40 mg to 60 mg OD. Procalcitonin was 0.23 µg/L, indicating a low likelihood of bacterial infection. Vasculitis and myositis screens were negative.

On days 5 and 6, his type 1 respiratory failure (T1RF) worsened, with HFNO FiO_2 requirements rising to 0.80–1.00, PFR ranging from 7 to 14 kPa, and ROX indices declining to 2.22–3.5. CPAP/BiPAP was intermittently used during HFNO downtime. Despite escalating NIV support, severe hypoxaemia persisted, with a HACOR score of 6 and a HACOR-U score of 11.5, indicating a high risk of NIV failure. Given the elevated serum LDH of 744 U/L, persistently raised inflammatory markers, and refractory hypoxaemia, we considered Pneumocystis jirovecii pneumonia, sent sputum for Pneumocystis jirovecii PCR, and started empirical high-dose co-trimoxazole instead of amoxicillin.

On day 7, severe T1RF persisted despite FiO_2 1.0, with PFR 7–12 kPa, an ROX index of approximately 3, and a HACOR score of 7. Prednisolone was replaced with intravenous hydrocortisone 60 mg four times daily. Inflammatory markers remained elevated, although the infectious work-up was negative, including sputum *Pneumocystis jirovecii* PCR, serum β-D-glucan, and serum and sputum galactomannan, as well as serum and sputum cytomegalovirus PCR.

On day 8, persistent severe hypoxaemia and a new onset of increased work of breathing necessitated endotracheal intubation and initiation of lung-protective mechanical ventilation. Following multidisciplinary review by respiratory and rheumatology teams, DIP leading to severe ARDS was considered the leading diagnosis, and IVMP (1g once daily for three consecutive days) was started. Despite 12 hours of invasive ventilation (PEEP 14–16 cm H2O), severe hypoxaemia persisted, with PFR ranging from 9–12 kPa, accompanied by hypercapnia and respiratory acidosis. We therefore initiated prone ventilation and referred him to the extracorporeal membrane oxygenation (ECMO) team to consider venovenous ECMO support.

After five prone-ventilation sessions, each lasting 18 hours, along with IVMP therapy, we observed sustained improvement in oxygenation and respiratory mechanics. The PFR increased to 25 kPa after the first session, 26 kPa after the second, 28 kPa after the third, and 31 kPa after the fourth and fifth. Static respiratory-system compliance improved from 22 to 42 mL/cm H_2O, while plateau pressure decreased from 27 to 22 cm H_2O. He was subsequently managed in the supine position with PEEP 8–10 cm H2O, and IVMP was switched to hydrocortisone 50 mg QDS for a further seven days before tapering. Inflammatory markers declined rapidly after IVMP, as shown in **Fig. 2**. Repeat respiratory sample culture grew Candida sp., while repeat respiratory PCR for *Pneumocystis jirovecii* remained negative. Co-trimoxazole was stopped after a total of 7 days. Chest Physiotherapy continued. BAL was not attempted due to profound hypoxia and high PEEP requirement.

On day 12, sedation was decreased in preparation for weaning from mechanical ventilation, as PFR remained > 30 kPa during 48 hours of supine ventilation after the final prone session. However, he developed new-onset fever and hypotension. Given his ongoing immunosuppression from high-dose corticosteroids and recent methotrexate and upadacitinib exposure, a hospital-acquired infection was suspected. After obtaining comprehensive cultures and replacing the existing invasive lines, we started empirical meropenem and vancomycin. This occurred despite improving respiratory parameters and downward-trending inflammatory markers. After 48 hours, all cultures remained sterile, prompting the

discontinuation of the antibiotics. Dexmedetomidine was considered the most likely cause and was replaced with melatonin and as-needed intravenous haloperidol. He became afebrile within 6 hours of discontinuation, supporting the diagnosis of dexmedetomidine-induced fever as previously reported in the literature [8].

He was extubated onto HFNO on the eighth day of IMV. POC Lung ultrasonography showed diffuse B-lines, and repeat echocardiography confirmed preserved cardiac function. He was treated with furosemide 40 mg twice daily for three days to facilitate pulmonary decongestion. His respiratory status gradually improved, and he was completely weaned from supplemental oxygen seven days post-extubation, with no oxygen requirement during ambulation.

Follow-Up and Outcome:

Following respiratory and rheumatology review, we instituted a prolonged corticosteroid-tapering regimen, starting with prednisolone 60 mg once daily and reducing by 10 mg each week to 10 mg once daily, followed by reductions of 2.5 mg each week to a maintenance dose of 2.5 mg once daily. Repeat HRCT, performed two weeks after IVMP and 18 days after the initial HRCT, demonstrated a fibrotic NSIP pattern, as evidenced in **Fig. 3 (a) & (b)**.

A CT thorax performed approximately three years before presentation showed no structural pulmonary abnormality. However, pulmonary function testing performed around the same time demonstrated mild airflow obstruction with significant air trapping and mildly reduced gas transfer.

He was discharged home 10 days after extubation, with a CRP of 6.9 mg/L. Methotrexate and upadacitinib were permanently discontinued. At respiratory and rheumatology outpatient review one month later, he remained clinically well, with a further reduction in CRP to 4.3 mg/L while continuing a tapering course of prednisolone. At three months after discharge, PFT demonstrated resolution of the previously observed obstructive pattern and air trapping, but more pronounced gas-transfer impairment, with DLCO declining from 78% to 63% predicted, as shown in **Table 1.** His oxygen saturation was 96% on room air, chest auscultation was clear, and he was not on any DMARD other than prednisolone. He reports adherence to the steroid regimen. Figure 4 simplifies the clinical course for reader understanding.

Discussion

Diagnosing DIP in patients receiving multiple immunomodulatory therapies is challenging, as discontinuing a non-culprit agent may trigger a disease flare. Our case met the modified Searles and McKendry criteria proposed by Kremer et al. for definite MTX-associated lung injury, based on compatible radiological infiltrates, negative microbiological investigations, acute dyspnoea, dry cough, severe hypoxaemia, and a peripheral white-cell count below 15×10^9/L [9]. The absence of previous reports of pneumonitis after 6 months on a stable dose of upadacitinib further supported MTX as the primary culprit. Nevertheless, combined pulmonary toxicity from MTX and upadacitinib cannot be

excluded, and, to our knowledge, this is the first reported case of combined MTX and upadacitinib-induced pneumonitis.

The diagnosis was reached by exclusion after ruling out important differentials, including heart failure, bacterial, viral and opportunistic infections, systemic vasculitis and myositis. Previous thoracic imaging showed no interstitial abnormality, while the acute clinical course made RA-ILD less likely. Although total serum IgE was elevated, acute asthma was unlikely to be the primary cause of T1RF, given the absence of clinical bronchospasm on admission and of airflow obstruction during IMV monitoring. The elevated IgE was non-specific and may have reflected the patient's atopic background.

The cornerstone of DIP management remains prompt withdrawal of the offending medication, initiation of systemic corticosteroid therapy, and respiratory support. In our patient, despite stopping both immunomodulators and completing a seven-day course of escalating prednisolone, T1RF progressed unabated. Consequently, we initiated IVMP, which proved crucial in mitigating the acute hyperinflammatory state.

Concurrently, HFNO and NIV failed to stabilise the progressive hypoxaemia. Prolonged vigorous spontaneous breathing during non-invasive respiratory support may have contributed to patient self-inflicted lung injury (P-SILI), further aggravating the underlying inflammatory alveolar and interstitial damage [10]. The team initially maintained non-invasive respiratory support following multidisciplinary consensus, balancing the anticipated delayed response to corticosteroids with the patient's strong preference to avoid IMV. The published literature reports clinical improvement in DIP within approximately one to two weeks of initiating steroid; however, the expected time to response is not well defined [5, 6]. Ultimately, our case continued to have clinical deterioration necessitating intubation. The ensuing refractory hypoxaemia was successfully managed with five sessions of prone ventilation and pulse-dose steroid, which improved oxygenation and respiratory system compliance.

Conclusion

DIP should be considered in patients receiving methotrexate and upadacitinib who develop unexplained, progressive respiratory failure, irrespective of the dose and duration of exposure to these DMARDs. Prompt withdrawal of the suspected agents, exclusion of alternative causes of T1RF, and timely treatment with IVMP and invasive ventilation, including prone sessions, can be lifesaving in severe ARDS due to DIP.

Declarations

Reporting guideline

This case report was prepared in accordance with the CARE reporting guideline.

Ethics approval and consent to participate

Not applicable

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

All relevant data supporting this case report are included in the manuscript, with anonymisation.

Competing interests

The authors declare no competing interests.

Funding

The authors received no funding for the preparation or publication of this manuscript.

Authors' contributions

Dr R.K. conceptualised the report, collected and interpreted the clinical data, conducted the literature review and drafted the manuscript. Dr R.K., Dr I.T., and Dr M.S. contributed to the patient's clinical management, interpretation of the findings, and critical revision of the manuscript. All authors reviewed and approved the final manuscript.

Acknowledgements

The authors thank the multidisciplinary intensive care, respiratory and rheumatology teams involved in the patient's care.

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Table

Table 1: Comparison of Baseline (Year 2023) and Three-Month (Year 2026) Post-Discharge PFTs, showing resolution of the obstructive pattern but a marked decline in gas transfer

PFT Parameter	Year 2023	Year 2026
FEV_1, L (% predicted)	3.05 (76.8%)	3.29 (85.3%)
FVC, L (% predicted)	4.43 (88.7%)	4.56 (93.3%)
FEV_1/VC, %	68.8%	72.0%
TLC, L (% predicted)	8.10 (104.2%)	6.81 (87.5%)
RV, L (% predicted)	3.46 (**146%**)	2.17 (**88.4%**)
DLCO, mmol/min/kPa (% predicted)	8.44 (**75.8%**)	6.90 (**63.4%**)
KCO, mmol/min/kPa/L (% predicted)	1.23 (86.0%)	1.18 (84.5%)

Figures

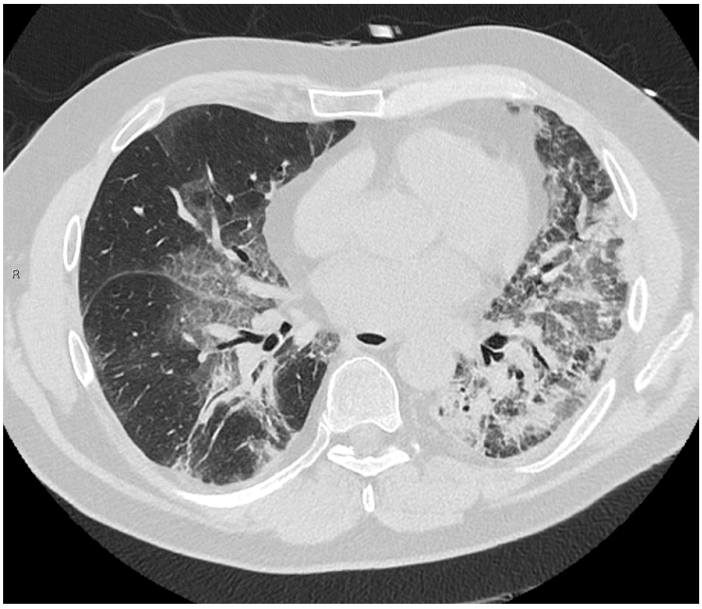

Figure 1 (a): HRCT Thorax (Axial View) four days prior to IVMP, showing extensive bilateral infiltrates

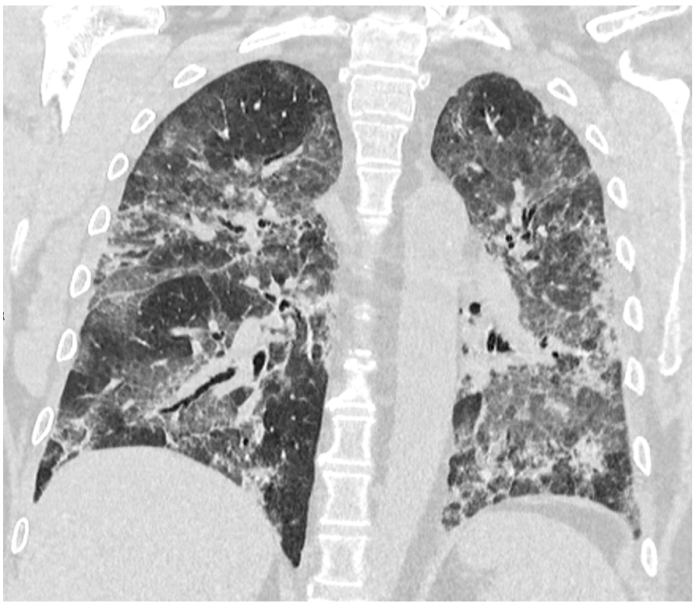

Figure 1 (b): HRCT Thorax (Coronal View) four days prior to IVMP, showing extensive bilateral infiltrates

Figure 1

See image above for figure legend.

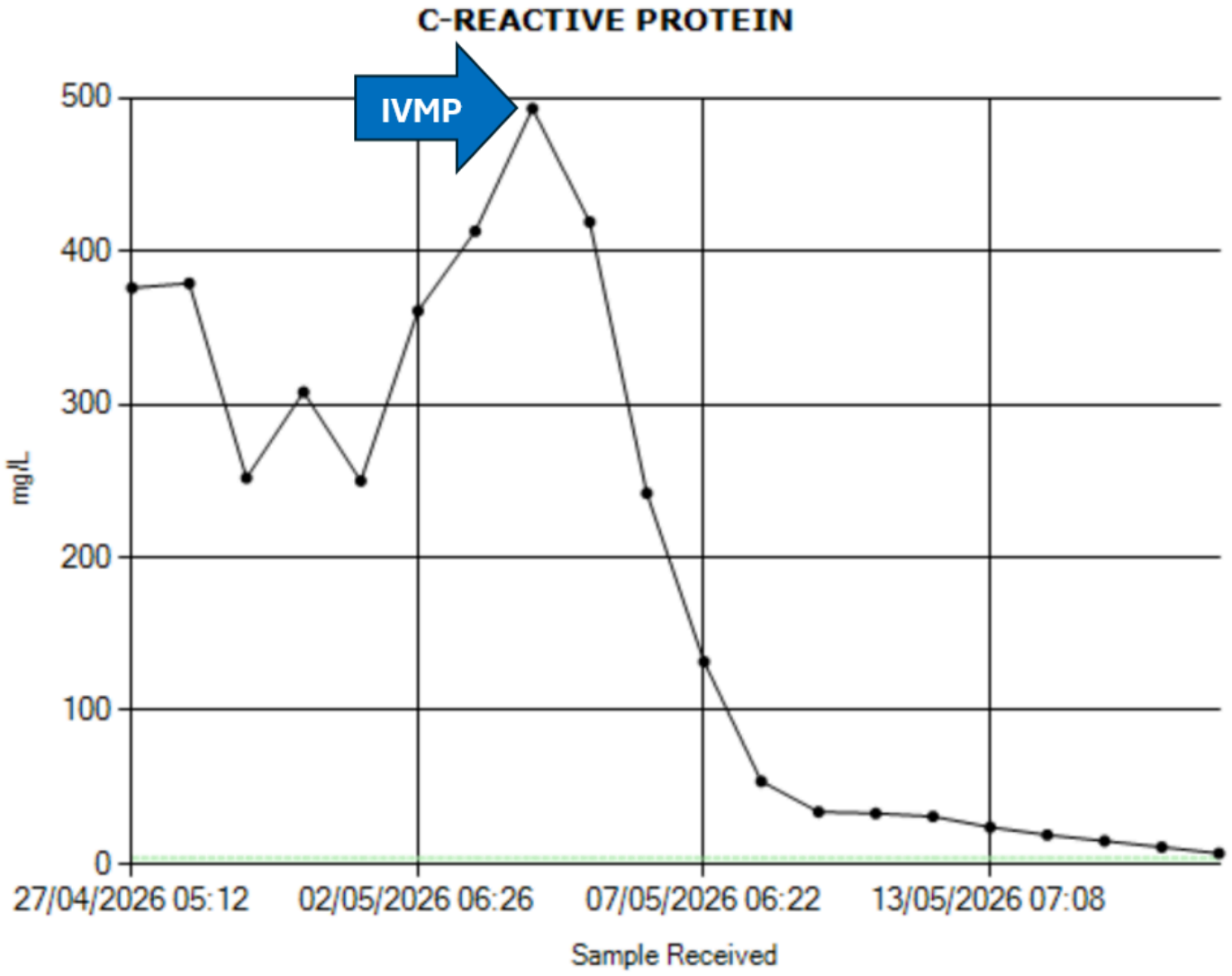

Figure 2

CRP Trend (IVMP = intravenous Methylprednisolone pulse dose therapy, started on day 8 of admission)

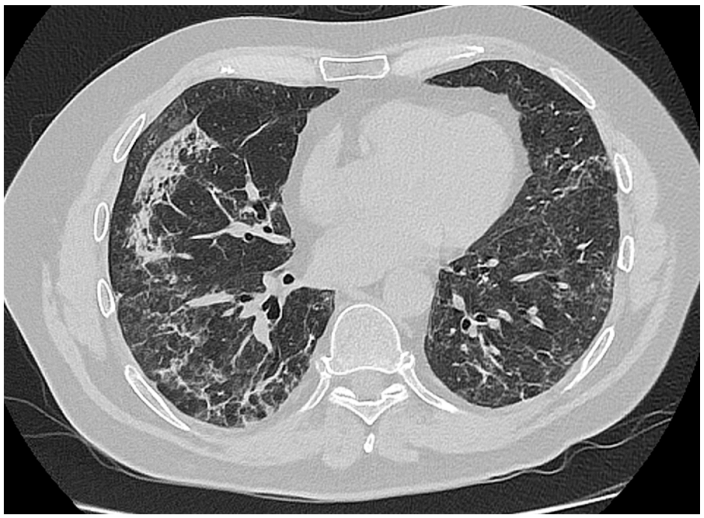

Figure 3 (a): HRCT Thorax (Axial View) two weeks after IVMP, showing significant resolution of bilateral infiltrates

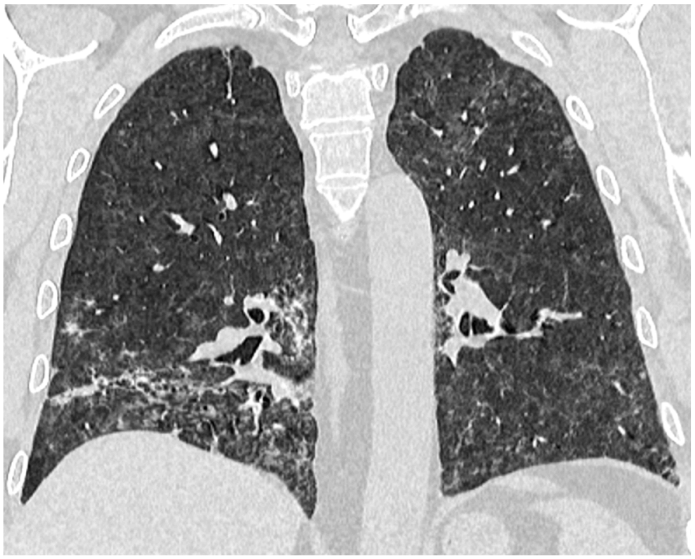

Figure 3 (b): HRCT Thorax (Coronal View) two weeks after IVMP, showing significant resolution of bilateral infiltrates

Figure 3

See image above for figure legend.

Figure 4

Clinical Timeline, showing major events during the clinical course