Reumatismo - The Italian Journal of Rheumatology

Reumatismo 2026; 78:1947
doi:10.4081/reumatismo.2026.1947

Acute lung injury timely associated with the administration of tocilizumab

Alojzija Hočevar,[1,2] Anja Srpčič,[1] Katja Lakota,[1] Miša Fister[3]

[1]Department of Rheumatology, University Medical Centre Ljubljana; [2]Faculty of Medicine, University of Ljubljana; [3]Centre for Intensive Internal Medicine, University Medical Centre Ljubljana, Slovenia

Key words: tocilizumab, adverse drug reaction, acute lung injury.

Correspondence: Alojzija Hočevar, Department of Rheumatology, University Medical Centre, Vodnikova cesta 62, 1000 Ljubljana, Slovenia.
Tel.: +38615221353. E-mail: alojzija.hocevar@gmail.com

Dear editor,

The interleukin-6 (IL-6) receptor inhibitor tocilizumab has been successfully used to treat various autoimmune diseases and has an acceptable, well-established safety profile (1). Tocilizumab-induced lung injury has been rarely reported in the literature (2, 3).

We describe a case of acute lung injury developing after the reintroduction of tocilizumab following its temporary interruption in a patient with an autoinflammatory syndrome.

A 59-year-old female was diagnosed in 2019 with an undifferentiated autoinflammatory disease after repeated episodes of fever up to 39°C and predominantly large-joint arthritis. The diagnosis was made after an extensive diagnostic work-up, including positron emission tomography/computed tomography (CT) and immunoserological testing, which resulted negative.

She had previously failed multiple synthetic and biologic disease-modifying antirheumatic drugs (DMARDs) (methotrexate monotherapy, leflunomide monotherapy, methotrexate in combination with biologic DMARDs, including adalimumab, etanercept, and anakinra), all used alongside high-dose glucocorticoids. Following an episode of macrophage activating syndrome in July 2022, treatment was switched to intravenous tocilizumab (8 mg/kg every 4 weeks), with continued methotrexate (10 mg weekly) and glucocorticoids. The disease remitted, and the patient remained clinically stable until October 2024, when she received her last regular tocilizumab infusion.

In November 2024 and January 2025, the patient sustained leg injuries. Tocilizumab infusions were temporarily discontinued due to the development of two slowly healing leg ulcers. In February 2025, she was admitted to our department due to a relapse of autoinflammation, despite an already increased dose of glucocorticoids (from 5 mg to 30 mg prednisolone equivalent) and methotrexate (from 10 to 15 mg) initiated at an outpatient visit in January. Laboratory results at admission are presented in Table 1. Chest X-ray at admission is shown in Figure 1A.

After excluding infection, we decided to reintroduce intravenous tocilizumab (8 mg/kg). The infusion of medication was uneventful. However, within 24 hours, the patient developed severe dyspnea with hypoxemia (requiring O_2 supplementation *via* a 40% Venturi mask) along with mild arterial hypotension (90/65 mmHg). The patient remained afebrile and had no skin eruptions. On auscultation, fine inspiratory crackles were heard in the lungs. Repeated chest X-ray revealed extensive diffuse bilateral infiltrates (Figure 1B).

The patient was transferred to the intensive care unit (ICU), where she received non-invasive ventilatory support and low-dose noradrenaline for hemodynamic instability over the next 2 days. Acute renal injury was treated with dialysis. As a potential infection was suspected, a broad antimicrobial therapy was prescribed (piperacillin tazobactam, clindamycin, and anidulafungin). However, extensive microbiological investigations, including blood cultures, urinary culture, urine pneumococcal and legionella antigen tests, nasopharyngeal polymerase chain reaction (PCR) test for respiratory viruses, mycoplasma and chlamydia infection, tracheal aspirate culture, and *Pneumocystis jirovecii* PCR of tracheal aspirate, PCR for cytomegalovirus, serology for HBV, HCV, HIV, swab of skin ulcers, were all negative.

Thoracic CT showed diffuse bilateral consolidations and ground-glass opacifications (Figure 1C). Bronchoscopy was not performed due to severe dyspnea, to avoid unnecessary intubation, which would further jeopardize the patient's state, and the rapid clinical improvement with immunomodulatory treatment. Because of acute lung injury, we also considered the possibility of other inflammatory rheumatic diseases and performed additional laboratory tests, including urinalysis, which showed no changes suspicious for glomerulonephritis, creatine kinase, immunoserological tests such as antinuclear antibodies, anti-extractable nuclear antigen antibodies, antineutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibodies, and myositis antibody panel, which included anti-melanoma differentiation-associated gene 5 and several anti-synthetase antibodies, all resulting negative. A stable complete blood count, without a new development of cytopenia, and normal liver transaminases pointed against a possible macrophage activation syndrome.

The patient was treated with high-dose glucocorticoids (1 mg/kg prednisolone) and underwent plasma exchange (3 sessions; day 3-5 after tocilizumab). Clinical improvement was rapid: by day 8, she no longer required supplemental oxygenation or vasoactive support, and renal function slowly recovered. A chest X-ray image taken 10 days after the tocilizumab infusion is presented in Figure 1D. Table 1 shows the key laboratory results during her acute illness.

In the presented case, we suspected tocilizumab-induced acute lung injury. This serious adverse event that required treatment in

the ICU was unexpected, especially as the patient had been receiving regular treatment with tocilizumab for 2 years. We hypothesized the development of anti-drug antibodies during the 4-month pause, leading to acute lung injury due to immune complex deposition. However, our working hypothesis was not confirmed by anti-drug antibody testing. In addition, a reporter gene assay, which could be used to measure IL-6 functional activity in serum samples, showed an inhibition of IL-6 signaling by tocilizumab administration, also arguing against the presence of anti-drug antibodies. Nonetheless, fluctuating serum concentrations of IL-6 after tocilizumab infusion may have contributed to the lung injury. Elevated blood IL-6 levels are recognized as a potential biomarker of lung injury and multi-organ dysfunction in critically ill patients with sepsis. Yet, the exact role of IL-6 remains unclear: it is not known whether it is preventive or detrimental to organ damage or just a paraphenomenon. Animal models report both the proinflammatory and anti-inflammatory roles of IL-6 on lung injury (4). We treated our patient with plasma exchange and an increased dose of glucocorticoids. The rationale for plasma exchange was to rapidly remove harmful cytokines and other pro-inflammatory molecules, as well as free tocilizumab molecules and circulating immune complexes. Although the rapid patient's improvement after plasma exchange and glucocorticoid supports an adverse immune mechanism, an interpretation of IL-6 and other cytokine levels is not easy due to the patient's treatment with plasma exchange and dialysis.

Our patient was taking methotrexate; nevertheless, we believe the latter was unlikely to be the cause of acute lung injury. Methotrexate therapy was chronic, and methotrexate pneumonitis is a rather early complication, manifesting in the first weeks or months of treatment.

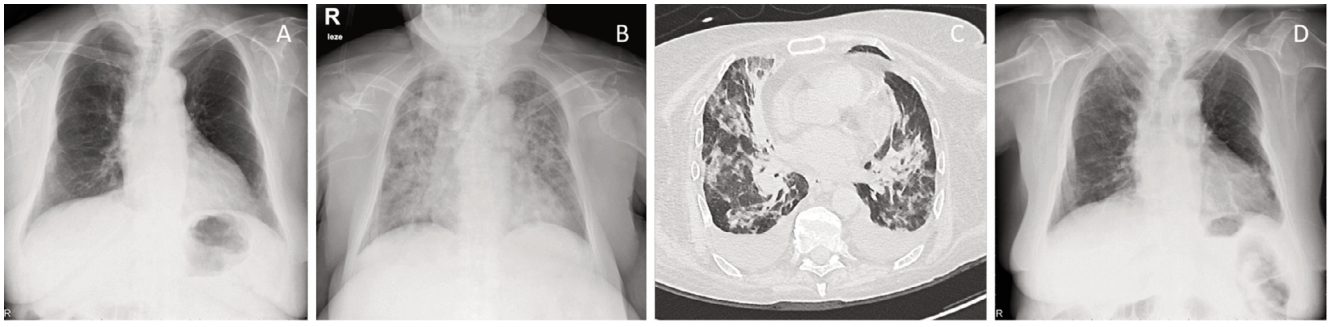

Figure 1. Chest X-ray and computed tomography (CT): radiograph before tocilizumab infusion (**A**); radiograph 1 day after tocilizumab (**B**); CT 3 days after tocilizumab (**C**); radiograph 10 days after tocilizumab (**D**).

Table 1. Laboratory results in our case.

Laboratory test	Before tocilizumab infusion	Day 1 and 2 after tocilizumab	Day 8 after tocilizumab	Day 10 after tocilizumab
C reactive protein (mg/L; ref. <5)	245	156	6	<5
Procalcitonin (mcg/L; ref. <0.24)	0.67	0.70	0.23	ND
WBC (×10⁹/L)/Hb (g/L)/Plt (×10⁹/L)	12.6/90/396	9.2/89/389	14.7/98/254	16.9/90/284
AST (µkat/L)/ALT (µkat/L)	0.38/0.16	0.43/0.10	0.43/0.20	ND
Ferritin (mcg/L; ref. 5-204)	6534	2085	1821	1244
IL-18 (pg/mL)*,$	>9880	>9880	>9880	ND
CXCL9 (pg/mL)*,#	1865	8090	1728	ND
IL-6 (ng/L; ref. <7.0)	1415	2471	1123	197
Serum tocilizumab (ng/mL)	Not detected	118.4	14.5	ND
Anti-tocilizumab antibodies	Not detected	Not detected	Not detected	ND
Soluble IL-6 receptor (ng/mL; ref. 14-46)	21	73	187	171
Reporter gene assay (normalised luciferase activity)**	1.618	0.254	0.261	ND
Creatinine (µmol/L)	68	113	295	294

WBC, white blood cells; Hb, haemoglobin; Plt, platelets; AST, aspartate aminotransferase; ALT, alanine transaminase; IL, interleukin; ND not determined; *Luminex assay; $the mean value of IL-18 in nine healthy blood donors was 378 pg/mL; #the mean value of CXCL9 in nine healthy blood donors was 472 pg/mL; **reporter gene assay – the functional activity of IL-6 in serum samples was measured using iLite IL-6 assay cells (Svar, Sweden). These cells are engineered to express Firefly luciferase under the control of an IL-6-responsive promoter. The cells also contain Renila luciferase reporter gene under the control of a constitutive promoter to normalize for cell number variation. The result is expressed as the ratio between the two signals and represents the sum of all factors (IL-6, IL-6R, tocilizumab, inhibitory antibodies) affecting IL-6 signaling in assayed samples.

Infections should always be considered as a differential diagnostic possibility. The results of extensive microbiological investigations before and after tocilizumab infusion were negative, and the patient's state improved after immunomodulatory therapy, which is not expected in case of an infection.

Repeated immunoserological testing and additional examinations also failed to confirm the development of other inflammatory rheumatic diseases, including systemic small vessel vasculitis, inflammatory myopathy, and macrophage activation syndrome. In summary, based on this case, we report an exceedingly rare but potentially life-threatening complication timely associated with tocilizumab treatment.

References

1. Kastrati K, Aletaha D, Burmester GR, Chwala E, Dejaco C, Dougados M, et al. A systematic literature review informing the consensus statement on efficacy and safety of pharmacological treatment with interleukin-6 pathway inhibition with biological DMARDs in immune-mediated inflammatory diseases. RMD Open 2022; 8: e002359.
2. Sugihara K, Wakiya R, Shimada H, Kato M, Kameda T, Nakashima S, et al. Interstitial lung disease occurring shortly after tocilizumab infusion in a patient with polyarticular juvenile idiopathic arthritis: a case report. Allergy Asthma Clin Immunol 2021; 17: 90.
3. Sangüesa Gómez C, Flores Robles BJ, Jara Chinarro B, Espinosa Malpartida M, Barbadillo Mateos C. Acute pneumonitis in a patient with adult-onset disease after toclizumab treatment with good response to anakinra. Reumatol Clin 2016; 12: 345-7.
4. Liu Y, Chen L. Impact of interleukin 6 levels on acute lung injury risk and disease severity in critically ill sepsis patients.

Received: 29 September 2025; Accepted: 19 January 2026; Early view: 29 January 2026.

Contributions: all authors meet the authorship requirements and have read and approved the manuscript for submission.

Conflict of interest: the authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics approval and consent to participate: the authors did not seek the consent of the ethics committee for submitting this paper.

Patient consent for publication: the patient read the Slovenian translation of the manuscript and gave her written consent for the submission/publication of her case.

Availability of data and materials: data are available upon reasonable request.