Acute severe pulmonary toxicity due to biosimilar infliximab in a Crohn's disease patient☆

Toxicidad pulmonar aguda grave secundaria al uso de infliximab biosimilar en un paciente con enfermedad de Crohn

Infliximab is an anti-tumour necrosis factor alpha (TNF-α) antibody used in the treatment of inflammatory bowel disease (IBD). Its use is associated with infectious and immunological pulmonary complications, including interstitial lung disease.[1]

We present the case of a 54-year-old male, an active smoker (15 pack-years), who has suffered from ileocolic Crohn's disease for 14 years. The patient required maintenance treatment with thiopurines for 46 months, but these were discontinued when he was shown to be in prolonged remission. Over the following nine months, he had a severe flare-up that was initially treated with intravenous methylprednisolone. Inflectra® (infliximab biosimilar), azathioprine and cotrimoxazole were later added for maintenance.

The patient consulted with chest pain and dyspnoea 18 days after receiving the second dose of infliximab. He was afebrile, but had tachycardia and tachypnoea. Arterial blood gases (oxygen via nasal cannula at 4 l/min) showed: $pO_2 = 67$ mmHg, $pCO_2 = 37$ mmHg, bicarbonate = 24 mM/l. The only other relevant findings from blood tests were: C reactive protein = 115 mg/l (normal < 5 mg/l); D-dimer = 900 ng/ml (normal ≤ 500 ng/ml); and rheumatoid factor = 54.1 IU/ml (normal < 40). Computed tomography (CT) angiography of the chest detected filling defects in the segmental pulmonary arteries and diffuse, bilateral, symmetrical lung involvement in a mosaic pattern (Fig. 1A). The echocardiogram and Doppler ultrasound of the lower limbs were normal. The patient was started on low molecular weight heparin (LMWH) 1 mg/kg body weight every 12 h. However, despite this, he suffered a severe deterioration of respiratory function and had to be transferred to Intensive Care. Repeat CT angiography showed radiological deterioration, with ground glass opacities and areas of septal thickening (Fig. 1B). Bronchoscopy study was negative for mycobacteria, *Pneumocystis jirovecii*, *Mycoplasma pneumoniae* and *Aspergillus*. With the diagnosis of suspected interstitial pneumonitis, piperacillin/tazobactam, cotrimoxazole and methylprednisolone were administered intravenously.

The patient gradually improved and was discharged with oral methylprednisolone, azathioprine, cotrimoxazole, LMWH and oxygen therapy. The infliximab biosimilar was discontinued and vedolizumab (anti-alpha-4 beta-7-integrin antibody) was prescribed to avoid the use of other anti-TNF-α drugs. Six months after discharge, oxygen therapy was discontinued and the peri-bronchial consolidation disappeared, but a non-specific mosaic pattern and minimal bronchiectasis persisted (Fig. 1C).

None of the other medications to which the patient was exposed during this period have been linked to the development of interstitial lung disease. Therefore, given that re-exposure would be both dangerous and unethical, we attribute the adverse event to the infliximab biosimilar.

In patients with IBD, the most common lung complications derive from the development of pulmonary thromboembolism1, as the extraintestinal manifestations of IBD rarely affect the respiratory system. Other complications, such as drug-related pulmonary toxicity (mesalazine, methotrexate, etc.), are less common.[1]

Among the non-infectious complications of infliximab is interstitial pneumonia. Although the incidence thereof is not known, in some registries it is estimated at around 2.9%.[2] It is more common in males, older people and individuals with a previous history of lung disease or glucocorticoid use.[3]

There are few reported cases of patients with IBD and interstitial pneumonitis secondary to infliximab[4] and we are yet to find one associated with an infliximab biosimilar.

A series of 122 patients with diffuse interstitial lung disease (DILD) associated with anti-TNF-α treatment was reported in Spain. Most of the patients were being treated for rheumatoid arthritis, with almost half receiving infliximab.5 DILD developed an average of 26 weeks after

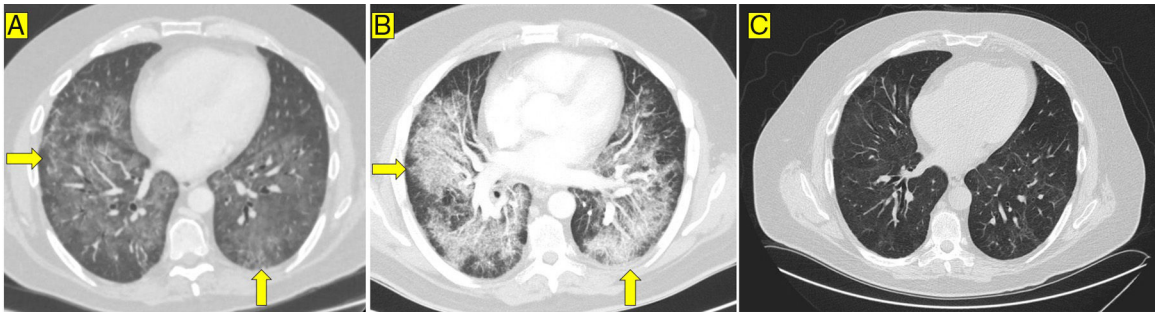

Figure 1 Chest CT scan. Radiological images of interstitial lung disease.

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administration with symptoms of dyspnoea, fever and cough.[5] Most patients were treated with corticosteroids, sometimes given in combination with other immunosuppressants, and the mortality rate was 29%.5

In our case, the patient made a good recovery from the lung disorder with corticosteroid treatment, and is now asymptomatic.

In conclusion, despite the fact that the most common complications are infectious, inflammatory lung involvement related to anti-TNF-α drugs should be suspected in case of respiratory symptoms or impaired gas exchange. This complication has been described with the reference drug infliximab and can also occur with the infliximab biosimilar. In order to ensure early diagnosis and management of this complication, it is important to stress that patients receiving anti-TNF-α drugs can develop DILD, particularly if they have risk factors.

The authors notified the SEFV (*Sistema Español de Farmacovigilancia* [Spanish Pharmacovigilance System]) about this case.

References

1. Harbord M, Annese V, Vavricka SR, Allez M, Barreiro-de Acosta M, Boberg KM, et al. The first european evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. J Crohns Colitis. 2016;10:239–54.
2. Dixon WG, Hyrich KL, Watson KD, Lunt M, Symmons DP. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2010;69:1086–91.
3. Curtis JR, Sarsour K, Napalkov P, Costa LA, Schulman KL. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor α agents, a retrospective cohort study. Arthritis Res Ther. 2015;17:319.
4. Sen S, Peltz C, Jordan K, Boes TJ. Infliximab-induced nonspecific interstitial pneumonia. Am J Med Sci. 2012;344:75–8.
5. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. Semin Arthritis Rheum. 2011;41:256–64.

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Pancreaticopleural fistula associated with choledocholithiasis: An infrequent complication of acute pancreatitis☆

Fístula pancreatopleural en relación con coledocolitiasis: una complicación infrecuente en la pancreatitis aguda

Pancreaticopleural fistula is an uncommon but potentially serious complication of pancreatitis, with an incidence of around 0.4–4.5% of patients with chronic pancreatitis.[1] It is more common in the alcoholic aetiology and when pseudocysts appear.[2] It is caused by disruption in the posterior aspect of the pancreatic duct, either directly or more often through the rupture of a pseudocyst[3] or necrotic collection, with pancreatic secretions leaking into the pleural space through the aortic or oesophageal hiatus or more rarely through the diaphragm.[2] The most common clinical presentation is dyspnoea secondary to pleural effusion, predominantly on the left side, which develops in 75% of cases.[4]

We present the case of a 72-year-old male with a history of acute necrotising pancreatitis in April 2013 which required admission to the ICU due to sepsis secondary to infected necrosis. The patient developed spontaneous intestinal fistulisation of the collection, with thrombosis of the splenic vein and superior mesenteric vein, and development of left segmental portal hypertension with splenomegaly and collateral circulation. Subsequently, he had to be admitted in October 2015 and September 2016 for fever secondary to a necrotic collection treated conservatively with antibiotic therapy due to the presence of intestinal fistulisation. Clinically, he made good progress and did not require an invasive approach, so he was discharged to undergo follow-up as an outpatient. In January 2017 he was admitted for dyspnoea secondary to left pleural effusion, requiring pleural drainage, which showed fluid compatible with exudate. In light of elevated pleural amylase (9317 U/l), CT of the chest/abdomen was requested, showing the spread of the necrotic collection from the tail of the pancreas to the head towards the subphrenic region, with fistulisation through the diaphragm to the left pleural space. Juxtapapillary choledocholithiasis not seen in previous explorations was also observed, and confirmed by magnetic resonance (MR) cholangiography. Given the stability of the patient, treatment with octreotide (100 μg/8 h) was started, achieving clinical improvement, although the pleural effusion persisted. Because of the distal location of the pancreatic duct rupture associated with the necrotic collection, after considering an endoscopic approach to the fistula, the decision was finally made to use a combined approach with endoscopic retrograde cholangiography (ERCP) to extract

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