Rituximab-associated colitis☆

Colitis asociada a rituximab

Rituximab (RTX) is an anti-CD20 monoclonal antibody that is used as biological therapy in B-cell chronic lymphoproliferative disorders. Most adverse reactions reported are caused by infusion of the medicine and comprise haematological disorders, fever, nausea, asthenia, hypotension and headache. However, the rare cases of rituximab-associated colitis reported in the literature also deserve special mention.[1–3]

The case of a 55-year-old male diagnosed with advanced stage IV-A mantle cell lymphoma (non-Hodgkin lymphoma) is presented. He received treatment with intensified chemotherapy, autologous haematopoietic stem cell transplantation and conditioning therapy. He then presented with slow progression and relapse, so a new treatment cycle was administered (gemcitabine, oxaliplatin + rituximab for eight cycles), and maintenance therapy with 12 doses of RTX bimonthly for two years, achieving complete response. He subsequently experienced chronic watery diarrhoea without rectorrhagia or abdominal pain and with negative stool cultures. A colonoscopy was performed that revealed erythematous mucosa of the colon from the rectum to the caecum, with oedema and exudation, as well as erythematous terminal ileum with five isolated ulcerations, the biopsies of which revealed chronic non-specific active colitis with preservation of the glandular architecture, and chronic non-specific ileitis with granulation tissue. Symptomatic treatment with loperamide was prescribed. A colonoscopy was performed 4–5 months after RTX suspension, which still showed segmental colitis, with the caecum and ileocaecal valve showing mucosal ulcers with fibrous stenosis, facilitating the examination of the distal ileum, which was endoscopically normal (Fig. 1). Biopsies of the distal ileum were consistent with mildly-active chronic colitis and necrotic fibrinous-leukocytic fragments suggestive of drug (RTX) induced colitis. With this confirmed diagnosis and given the persistent diarrhoea, albeit to a lesser extent, treatment with mesalazine was initiated, with the patient showing clinical improvement.

This case highlights a rare but potentially serious paradoxical reaction to RTX, which can be particularly acute in immunosuppressed patients. RTX is often used as a potential treatment for patients with ulcerative colitis (UC) who are unresponsive to treatment with corticosteroids. The first clinical trial conducted, which was limited by its small sample size, showed a possible short-term, unsustained response, with no significant effect on the onset of remission in moderately-active UC.[4]

A review has also been published of the few reported cases of UC onset following treatment with RTX. The symptom described is watery or bloody diarrhoea, with onset several days or even several weeks after starting RTX.[5] Treatment consists of withdrawing RTX, standard UC treatment or even surgery.[1,3,5]

Recently, numerous paradoxical adverse effects consistent with colitis have been reported in patients undergoing treatment with new immunological therapies (immunotherapy) for various conditions, including lung cancer, colon cancer and melanoma, which may represent the negative repercussions of manipulating the immune system with these agents.[6] The aetiopathogenesis of these paradoxical processes caused by biological medicinal products like RTX could be because the administration of RTX induces CD20+ B cell depletion. B and T lymphocytes interact in the intestinal wall and are responsible for mucosal immunoregulation, which increases immune tolerance. The histopathological findings suggest that the exacerbation of colitis may be caused by complete CD20+ B cell depletion and the high infiltration of T lymphocytes in the intestinal mucosa.[4,5]

In conclusion, the purpose of this case study is to highlight this condition that is so rarely reported in the medical literature, encouraging doctors to suspect this complication when colitis-like symptoms manifest in a patient receiving RTX and to promptly administer the appropriate therapeutic measures. RTX-induced colitis is described as a rare RTX-associated complication. It is characterised by symptoms of chronic bloody diarrhoea that causes ulcerations in the colonic mucosa, similar to UC, and which responds favourably after suspending RTX and treating with 5-aminosalicylic acid and/or corticosteroids.[1–3]

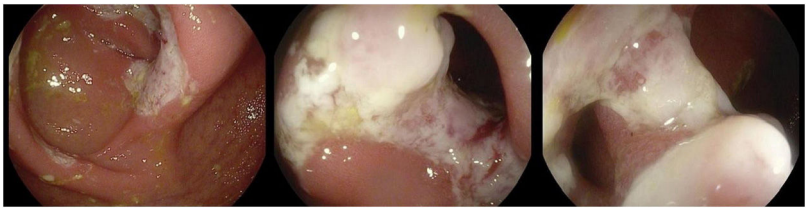

Figure 1 Caecum and ileocaecal valve with mucosal ulcers and fibrous stenosis, facilitating examination of the normal distal ileum.

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Inappropriate use of the term of acute liver failure in a tertiary hospital☆

Utilización no apropiada del término de insuficiencia hepática aguda en un hospital de tercer nivel

Acute liver failure is characterised by the acute loss of liver function in a subject with no prior history of liver disease.[1–3] However, this term should not be used in certain specific situations, such as in the event of prior liver disease, liver resection, liver injury secondary to trauma and where liver damage is caused by a systemic process such as shock or multiple organ failure with an aetiology other than primary liver failure.[2] We conducted a retrospective, descriptive, observational study in a tertiary hospital to understand how this term is used as a diagnosis in patient discharge reports, both in cases where its use is appropriate, as well as in situations where its use is specifically not recommended.

Patients aged ≥18 years diagnosed with liver failure or acute liver damage and who were admitted between 1 January 2007 and 30 September 2017 were included, irrespective of their other diagnoses. Patients were identified by searching the diagnoses specified on all the hospital's discharge reports. The study was approved by the corresponding Independent Ethics Committee. The diagnosis was considered appropriate if it met the criteria established by the European Association for the Study of the Liver's Clinical Practice Guidelines on the management of acute (fulminant) liver failure.[2] Acute liver damage was defined as elevated transaminase levels associated with coagulopathy, severe acute liver damage as an INR ≥1.5 and acute liver failure as the onset of hepatic encephalopathy (neurological impairment with hyperammonaemia). In cases with inappropriate diagnoses, the main diagnosis that caused the liver damage was considered in those cases in which there was secondary damage, where there was prior liver disease or in the absence of liver damage criteria. During the study period, acute liver failure or acute liver damage was diagnosed in 444 patients. The results of the descriptive analysis are shown in Table 1.

Although other authors have already observed the inappropriate use of this term in a variety of situations, [2] no studies have been conducted to date to quantify the current extent of this misuse. The findings of this study highlight the fact that this is not an isolated problem. The primary reason for the inappropriate use of these terms in our hospital is the onset of true liver damage secondary to another primary cause that gives rise to shock or multiple organ failure. We believe that there are two fundamental explanations for this finding: a lack of specific terminology in these situations and of consideration that these diagnoses may be the prior cause of acute liver failure, particularly in critical patients.[1,4] Use of these terms in connection with liver transplant was only found in a small number of cases, probably due to the use of more specific terminology. A significant percentage of diagnoses (12.8%) concerned patients with prior liver disease, despite the fact that the very definition of acute liver failure excludes this comorbidity,[1–3] even going back to its original description.[5] Finally, another diagnosis deemed to be inappropriate was the finding of acute hepatitis with no signs of acute liver damage. The lack of a clear cut-off point to define the presence of coagulopathy may be an influential factor in this scenario.

The primary limitations of our study stem from its retrospective nature at a single site. The diagnoses were established by the doctors responsible for each patient, which implies a degree of variability between the healthcare professionals involved, and the recommended terms were taken from guidelines published after the study period. In addition, the low incidence of this entity could be related to a possible overestimation of inappropriate diagnoses, due to the higher incidence of the other scenarios. Finally, because the objective of the study was to identify those situations in

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