



(CASE REPORT)



## Rituximab-induced diffuse ischemic colitis: A case report

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### Abstract

In the present manuscript a case of a 61 years old man with a form of unclear colitis is reported. The patient presented to our hospital with history of prolonged diarrhea and consequent profound dehydration after treatment with an immunotherapeutic cycle with Rituximab for a B cell lymphoma. An endoscopic pan-colonic examination was performed and some intestinal randomized biopsies were done as to confirm the clinic hypothesis of a colitis, as to define its etiopathogenesis. Histopathological picture of the colon biopsy fragments suggested a diffuse colitis with ischemic aspects. Herein the involvement of rituximab in determining pancolitis is discussed.

**Keywords:** Rituximab; Pancolitis; Colon biopsy; Mucosal ischemia; Adverse reaction

### 1. Introduction

Diffuse large B cell lymphoma (DLBCL) is a lymphoid malignancy involving malignant transformation of a B-cell clone. It accounts for all 20% of non-Hodgkin lymphoma of adults and elderly worldwide. DLBCL shows a diffuse pattern of growth and tissue invasion [1]. Etiopathogenesis of DLBCL is not fully understood. Common pathways of B-cell malignant transformation include gain of function mutation, chromosomal translocation or gene amplification of oncogenes [2]. BCL-6, BCL-2 and Myc genes are frequently involved in the cancerogenesis of DLBCL. BCL6 encodes for a transcription repressor trans-located (t(3;Var)(q27;Var)) or hyper-mutated in DLBCL. BCL-6 is a proto-oncogene involved in cell maturation, proliferation and survival, constitutively activated in some lymphomas.

BCL-2 encodes for a protein of BCL-2 family regulating apoptosis pathways. In particular, its product is an anti-apoptotic protein that inhibits the pro-apoptotic factors BAX and BAK1. For this reason BCL-2 acts as an oncogene in B-cell oncogenesis[3]. Myc is a transcription factor constitutively activated by gain of function mutation in DLBCL [4]. 70% of all DLBCL have a nodal involvement. Groin, arm, neck, mesenteric and thoracic lymphnodes can be equally involved during the neoplasm. Consequently a skin painless lump, site of node enlargement, is the typical symptom of DLBCL [5]. Generic gastro-intestinal symptoms (constipation, diarrhea, bleeding) or respiratory symptoms (dyspnea) are common for a stage III DLBCL and based on organ involvement. In particular, stage III DLBCL implies a lymphoma's spread to both sides of diaphragm extending to extra-nodal sites, such as stage VI DLBCL indicates a disseminated disease with interest of more extra-lymphatic organs and consequent related systemic symptoms [6].

Final diagnosis of DLBCL has been made on microscopic evaluation of excised lesions through morphological and immunohistochemical characterization of neoplastic lymphocytes [5]. Assessing expression of PDL-1 or PDL-2 markers on histological samples can suggest clinicians the sensitivity of the tumor to an anti-PD1/PDL-1 immunotherapy [7]. First line treatment for every DLBCL stage include an R-CHOP regimen. It consists of rituximab, a monoclonal antibody targeting CD20 in association to prednisone, cyclophosphamide and vincristina [8]. This regimen achieves a progression-free survival 3 years from diagnosis in 60-70% of the patients [9].

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Rituximab is a chimeric monoclonal antibody targeting CD20, a differentiation marker primarily expressed in pre-B cell and mature B-lymphocytes. Rituximab indistinctly targets CD20 on normal and neoplastic B-cells. It targets B-lymphocytes through CD20 molecule recognition and through recruitment of Natural Killer (NK) cells. NK cells interact with Rituximab-capped CD20 mediating the antibody-dependent cellular cytotoxicity. Rituximab can also mediate B-lymphocytes elimination via complement dependent cytotoxicity. In particular Rituximab efficacy is directly related to the B-cell expression level of CD20, so it's very efficient in targeting neoplastic B-lymphocyte clones, that express high levels of this marker [10] [11] [12][13].

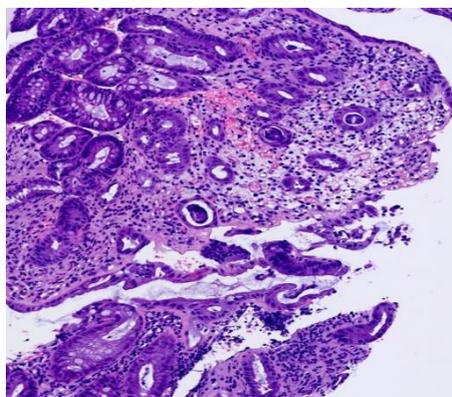
Severe adverse reaction caused by rituximab infusion include: cardiac arrest; cytokine release syndrome; pulmonary toxicity; colitis with bowel obstruction and perforation. Rituximab can also cause re-exacerbation of infection by latent virus like HBV an JC virus [14] [15] [16].

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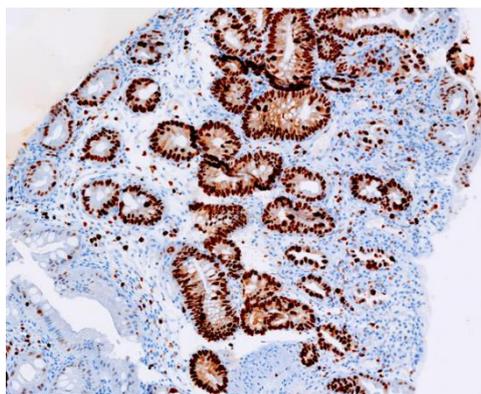
## 2. Case report

In October 2020 a 61 years old male was admitted to the emergency room of our hospital for profuse diarrhea and rectal bleeding causing dehydration. Clinical history of the patient showed that he was under an immunotherapy regimen with Rituximab for treatment of a non-Hodgkin large B cell lymphoma. A colonoscopy and randomized biopsies were made in order to have histological picture.

Microscopic evaluation of colonic tissue revealed features suggestive for ischemic colitis (figure 1). Histologic picture on hematoxylin and eosin stain showed multifocal necrosis and degeneration of the mucosal glands, focal epithelium ulceration extending into the sub-mucosal layer, some aspects of regeneration of the glandular epithelium (figure 2), together with mild and moderate meta-flogistic dysplasia due to the ischemic damage. Patient interrupted pharmacologic therapy with Rituximab and he was treated with physiologic infusion. In few days, pan-colitis clinical symptoms disappeared.



**Figure 1** Hematoxylin and eosin slide of rituximab induced colitis: picture highlights mucosal involution/necrosis and a focus of ulceration. Near the ulceration, at the edge of sub-mucosal layer is detectable some granulation tissue.



**Figure 2** Ki67 IHC slide: regeneration activity of gland crypts as a result of an ischemic damage is highlighted by a relative high index of Ki67 expression

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### 3. Discussion

Since its approval rituximab has shown promising efficacy in the treatment of several hematological malignancies, especially B-cell lymphomas. Although its large success, rituximab therapy has been reported to be associated with a relative high incidence of adverse effects. For example Ahmed MS et al noted that 27% of children treated with rituximab for refractory nephrotic syndrome manifested adverse reactions to this drug. Among these reactions, bowel perforation, ischemic colitis, ulcerative colitis, and ulcerative colitis reacerbation represent a clinical emergency. Several hypothesis have been placed to determine the cause of these reaction. Some case report suggested an association between colitis and a torovirus infection following a rituximab treatment. [17] However rituximab-induced unbalance between pro-inflammatory and anti-inflammatory immune mediators, in the gastro-intestinal district it is a potential cause of colitis. Depletion of B lymphocytes and specifically B regulatory cells localized in Peyer patches or in lymphovascular system could cause the onset of various forms of colitis. A potential explanation to these reaction could be theorized on the clinical observation of auto-antibodies in the serum of patients that develop an ulcerative colitis as a consequence of rituximab therapy. Detection of anti-goblet cells antibodies, perineuclear antineutrophil cytoplasmic antibodies and tropomyosin 5 antibodies in the serum of the treated patients suggest a “rupture” of immune tolerance to self-antigens B lymphocytes of gut lymphoid tissue have shown to mitigate autoimmune responses promoting tolerance to self-antigens by secreting a specific cytokine profile. These cells produce TGF-Beta, IL-4 and IL-10 that negatively modulate the immune response in absence of inflammatory stimuli. B cells also regulate CD4 T lymphocytes antigen-presenting cells and promote clearance of mucosal apoptotic bodies. Depletion of B cells following rituximab account for loss of the previous function and consequent dysfunction of T regulatory cells and auto reactive helper and cytotoxic T cells [18].

CD20 is believed to play a role in Ca<sup>2+</sup> influx across B-cell plasma membrane. CD20 is also involved in the regulation of intracellular Ca<sup>2+</sup> concentration influencing B-cell activation.

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### 4. Conclusion

In the presented case, a rituximab colitis is reported. Through the histological picture, speculation about pathogenesis of this iatrogen colitis has been made.

In this view, molecular interaction between B cell CD20 antigen and rituximab in mucosal associated lymphoid tissue could be responsible of the observed tissue damage for the alteration of intracellular Ca<sup>2+</sup> concentration.

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### Compliance with ethical standards

#### *Disclosure of conflict of interest*

Authors declare that there are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

#### *Statement of informed consent*

Informed consent has been obtained from the subject included in the study.

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