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Case Report

Rituximab induced interstitial lung disease diagnosis, treatment outcome, and risk's factor, a place for transbronchial pulmonary cryobiopsy

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Rituximab (RTX) is a mouse/human chimeric anti-CD20 IgG1 monoclonal antibody, approved in late 1998 by the FDA. Effectively used as a single agent or combined with a chemotherapy regimen to treat lymphoma, RTX is a significant step forward in the arsenal treatment of idiopathic thrombocytopenic purpura, systemic lupus erythematous, rheumatoid arthritis, and autoimmune hemolytic anemia.

Side effects of RTX are commonly seen during the first infusion in up to 50% of patients and include fever, chills, and rigors. These side effects are generally transient and related to the tumor burden, probably due to a greater degree of complement activation and proinflammatory cytokine release. Severe lung toxicity like cryptogenic organizing pneumonia, pneumonitis, and interstitial lung diseases are infrequent, with most of the knowledge coming from case reports.

Key words: Drug induced lung disease, histology, cytology, anca related vasculitis, drug reactions, rituximab
Abbreviations: RTX: Rituximab, P-ANCA: Perinuclear anti-neutrophilic cytoplasmic autoantibody, R-ILD: Rituximab interstitial lung disease, NSIP: Nonspecific interstitial pneumonia, GPA: Glomerulonephritis granulomatosis with polyangiitis, FVC: Forced vital capacity, TLC: Total lung capacity, DLCO: Diffusing capacity, HSV: Herpes simplex virus, HZV: Herpes zoster virus, HE: Hematoxylin eosin, Trichrome: Masson's trichrome stain

INTRODUCTION

The objective of this article is to peculiarize the syndrome of Rituximab-Induced Interstitial Lung Disease (R-ILD). We proposed a thorough description of R-ILD, based on information's gathered from reported cases and the medical literature reviews. Our emphasis will be on patients' characteristics, treatment options, clinical presentation, risks factors, imaging studies, and Pulmonary Function Tests (PFTs); Standard and new diagnostic procedure such Transbronchial Pulmonary Cryobiopsy (TPC) will also be discussed. In a practical manner, we propose to do so by presenting two such cases.

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CASE REPORT

Case one

A 67-year-old male Caucasian patient presented at the emergency department with a history of progressive dyspnea, fever, and dry cough. Two weeks before the onset of his symptoms, he received his second dose of rituximab (RTX-based regimen of 1 g followed 14 days later of another 1 g dose) in the setting of a P-ANCA granulomatosis with polyangiitis diagnoses by renal biopsy. At the beginning of his condition, the patient presented with isolated renal involvement such as acute kidney injury, strong sediment hematuria, and nephrotic syndrome, 3.5 g/24 hr. No other systemic presentations or functional and radiological respiratory impairment were highlighted (Arnold et al., 2007, American Thoracic Society et al., 2001, Bienvenu et al., 2001, Biehn et al., 2006). At the

emergency department, his initial vital signs were as follows: temperature 36.9°C, with a heart rate of 90 beats/min, blood pressure 140/80 (mm Hg), tachypnea with a respiratory rate of 20/min and oxygen saturation 86% on room air, 91% with 3 L of O2 within a nasal canula. Physical examination was unremarkable except for bilateral scattered inspiratory crackles. (Cho et al., 2019).

Laboratory examination revealed normocytic anemia, a mild inflammatory syndrome, stable CKD (Chronic Kidney Disease) function. A whole review is then launched; because of the current context, during a viral pandemic at SARS-Co-V2, a nasopharyngeal smear is performed to search for SARS-Co-V2 by Polymerase Chain Reaction (PCR) method, which returns negative twice. The extent of other laboratory tests searching for an infectious etiology was negative (Table 1). Computer Tomography (CT-Scan) of the chest revealed diffuse bilateral ground-glass opacities, poorly defined centrilobular nodules, and mosaic attenuation (Figure 1). Cardiac origin was excluded by a 2D echocardiogram that demonstrated an ejection fraction of 55% with no valvular abnormalities (Dhooria et al., 2016, Heresi et al., 2008, Hadjinicolaou et al., 2012, Hiraga et al., 2005, Krishnaswamy et al., 2014).

Differential diagnosis: CT scan images finding, with a diffuse interstitial pathology aspect can be found on Nonspecific Interstitial Pneumonia (NSIP) and can either reflect extrinsic allergic alveolitis, interstitial hypersensitivity pneumonitis, toxic pneumonia, or diffuse infectious lung disease. Compared to the same review conducted for the GNSA's assessment, these lesions are new. Bronchoscopy with Bronchoalveolar lavage (BBL) with transbronchial biopsy is mandatory to rule out an infection etiology, autoimmune features, or presences of malignancy cells. BBL was performed, with a negative result for the presence of SARS- Co-V2 or other infectious (Table 2), as such of atypic cells. A thorough review of the patient's environmental and occupational exposure showed no apparent external cause for hypersensitivity pneumonia.

The favorable evolution of the GPA with the disappearance of Anti-MPO antibodies, besides the absence of alveolar hemorrhage, does not sustain a vasculitis involving lung damage. Spirometry objectified a restrictive syndrome with a decrease of the FVC, TLC, and DLCO. Following this broad assessment, the diagnosis of interstitial lung disease remains the clearest etiology. Nevertheless, the exclusion of pulmonary involvement in the setting of GNSA is challenging in this context. Therefore, in the absence of any counterindications, a TPC is performed. The histologic report revealed strongly suggestive images of nonspecific interstitial pneumonia with enlarging septa, discrete fibrosis, and inflammatory infiltrates (Figure 2). All these findings support the diagnosis of Interstitial Lung Disease (ILD).

Initially, pulse therapy, 250 mg/day of methylprednisolone for three to five days. The patient presented immediate signs of clinical improvements, followed by oral prednisone at a dose of 1 mg/kg per day (using ideal body weight). Subsequent tapering down over six months was conducted with an excellent clinical and functional response.

Table 1. Laboratory results.

Test	Patient value	Normal range
CPR	16,8 mg/dL	<5 mg/dl
BUN	186 mg/dL	17-43 mg/dL
Créatinin	1,97 mg/dL	0,6-1,3 mg/dL
Na	137 mmol/L	136-145 mmol/L
K	4,8 mmol/L	3,5-5,1 mmol/L
Cl^-	99 mmol/L	98-107 mmol/L
Ca^{2+}	2,3 mmol/L	2,2-2,6 mmol/L
GOT-ASAR	46 U/L	<37,0 U/L
GPT-ALT	48 U/L	<45,0 U/L
Gamma-GT	43 U/L	<60,0 U/L
Hb	11,7 g/dL	14,0-18,00 g/dL
WBCs	8,02 × 1000/mm^3	4,0 - 10,0 × 1000/mm^3
Total Proteins	60 g/L	60- 80 g/L
Albumine	33,0 g/L	32-46 g/L
Protein electrophoresis	Normale	Normale
ANCA	Positif	négative
Anti-MPO	0,3 UI/mL	<3,5 UI/mL
Anti-PR3	0,3 UI/mL	<2,0 UI/mL

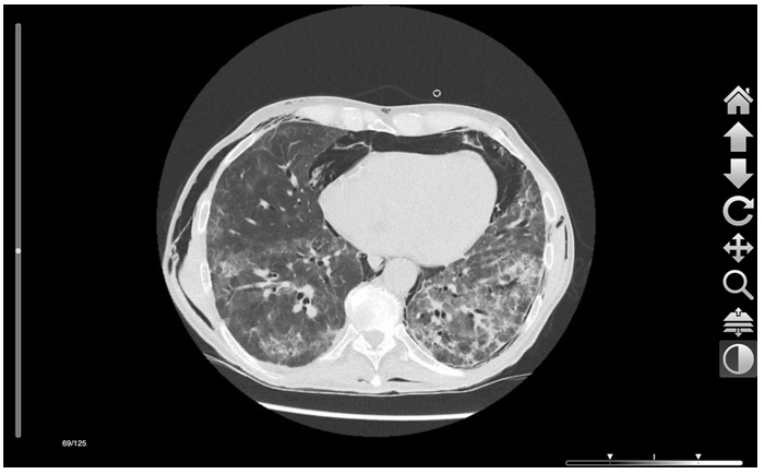

Figure 1. Computer tomography (CT-Scan) of the chest revealed diffuse bilateral ground-glass opacities, poorly defined centrilobular nodules, and mosaic attenuation.

Table 2. Bronchoalveolar lavage, cellular components.

Cells types	Valeur du patient	Norme
Macrophages	17%	85%
Lymphocytes	66%	10%-15%
Neutrophils	17%	<3%
Eosinophils	0%	<1%
Atypical cells	0	0
Culture	Negative	
PCR - SARS CoV2 Méthode CMIA - Abbott	negative	

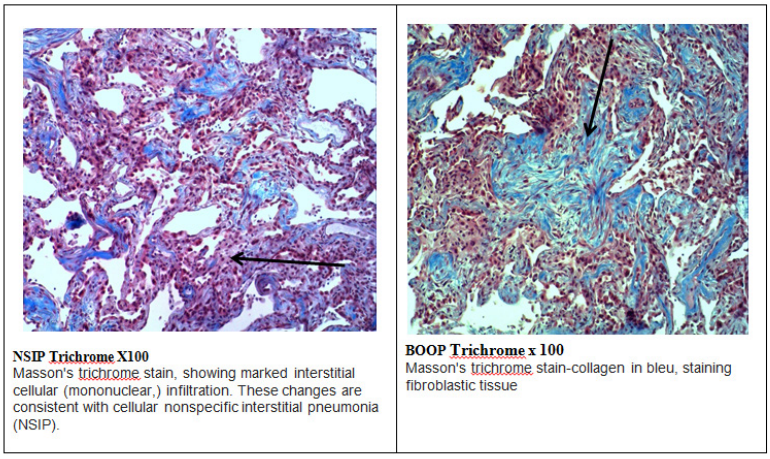

Figure 2. Histologic Result: NSIP: Nonspecific interstitial pneumonia. BOOP: an Organizing pneumonia (previously called bronchiolitis obliterans organizing pneumonia.

Case two

A 65-year-old man diagnosed with stage IV follicular lymphoma received two cycles of RTX and bendamustin with an interval of 2-week. Prior to initiation therapy lung examination was normal and a CT of the chest showed no lung abnormalities (Figure 3). He attended to our emergency department, with dry cough, fever, dyspnea, within 4 weeks after the completion of the second treatment cycle. Lung examination revealed diffuse bilateral scattered inspiratory crackles, tachycardia, tachypnea, and hypoxemia requiring 3 L of oxygen. Laboratory test showed a white blood cell count of 5,900/mm3 (65.9% neutrophils, 24.3% lymphocytes and 1.4% eosinophils), hemoglobin 11.2 g/dl, platelet count 243,000/mm3, blood urea nitrogen 40 mg/dl, creatinine 1.2 mg/dl, calcium 10.4 mg/dl and glucose 92 mg/dl. Chest radiography showed diffuse bilateral lung infiltrates A computed tomography of the chest revealed diffuse bilateral ground-glass opacities, poorly defined centrilobular nodules and mosaic attenuation. Spirometry demonstrated a restrictive pattern with very low diffusion capacity (DLco 26%).

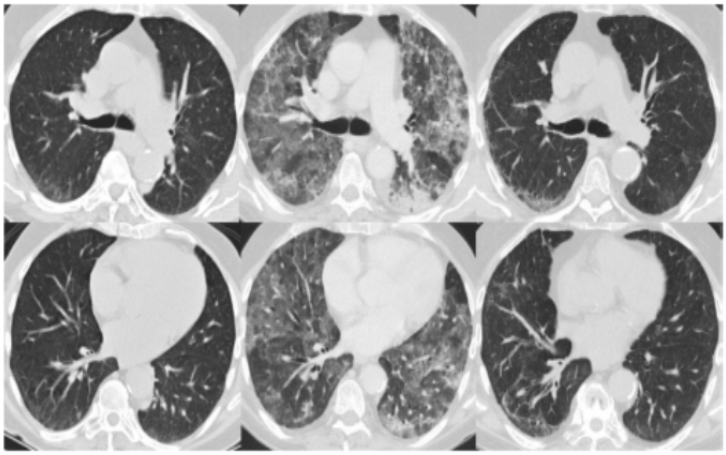

Figure 3. Case two CT scan's evolution .CT of the lungs prior to treatment with rituximab (left panel), during treatment with rituximab (middle panel), and after interruption of rituximab and initiation of corticoids treatment.

A Positron Emission Tomography (PET-SCAN) is requested as part of unexplained hypercalcemia to exclude a malignant tumor and bone metastases and sarcoidosis but did not reveal any malign lesion and ruled out any extra-pulmonary pathological suspicious abnormalities (Figure 4).

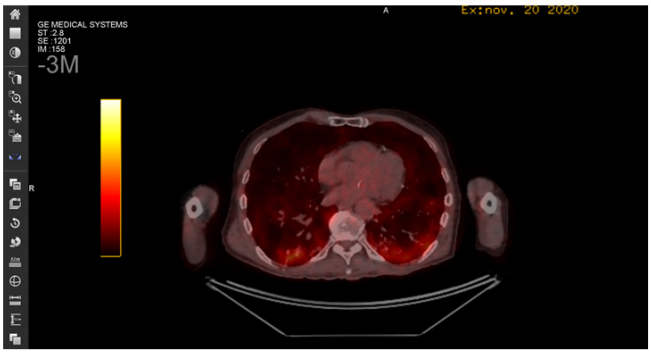

Figure 4. Positron emission tomography (PET-SCAN): Highlighted a consistent fixation of the FDG, at the level of the lower lobes, and the presence of metabolically active pulmonary infiltrates (FDG SUV max: 6.7 g/ml) mainly in the posterior but also at the tops next to lesions in a ground glass as well as of the pleura. No malign lesions identified.

The patient underwent bronchoscopy with bronchoalveolar lavage and transbronchial biopsies bronchoscopy. Bronchoalveolar lavage fluid resumed lymphocytic alveolitis. All bacterial, viral, viral (including SARS-CO-V2) carinii pneumocystis, mycobacteria's and fungous were negative. But no sufficient material was obtained from the transbronchial biopsies to identify a histologic entity (Table 3).

Table 3. Infectious Panel.

Test	Patient results
PCR and Sérologie SARS-CoV-2 :SARS-CoV-2 IgG	Négative
HSV 1 and 2 IgM (CMIA)	Négative
HZV IgM (CMIA)	Négative
Parvovirus B19 : Parvovirus IgM	Négative
Parvovirus B19 : Parvovirus IgG	Positive
Mycoplasma sp: Mycoplasma pneumonia-IgM	Negative
Mycoplasma pneumonia - IgG : <0.100 UA/mL.	Negative
Ag Aspergillus	Negative
Cytomégalovirus : C.M.V. IgM	Négative

Risk Factors and patients' characteristics for rituximab-induced interstitial lung diseases

Epidemiology: The incidence rate of RTX-ILD is unknown but rare early reports indicated meager incidence rates at 0.010.03% (Kang et al., 2012). Nevertheless, much higher incidence rates were reported in post-marketing case series ranging from 3.7 to 10%. (Liu et al., 2008). Those discrepancies might be attributed to the difference in the target population between clinical trials and daily clinical practice. Besides, some cases of RTX-ILD might be regarded as lower respiratory tract infections because of the overlap between the signs and symptoms of these complications.

In a retrospective study of 264 patients with non-Hodgkin's lymphoma treated with rituximab-containing chemotherapy regimens, 9(3.5%) were diagnosed with rituximab-induced ILD, including clinically suspected cases (n = 5).

Clinical settings, timing and images characteristics: Details of RTX-ILD have been described in a systematic review of Liote et al., 2010 and the most common symptoms are dry cough, exertional dyspnea, and fever. Nonspecific symptoms are less common and included fatigue, rigors, wheeze, hemoptysis, skin rash, and pleuritic chest pain. Hadjinicolaou AV and al; in a case series, found that around 20% of patients were asymptomatic at the time of diagnosis, with the disease being detected either by CT or LFT (Nieuwenhuizen et al., 2008). Three clinical presentations were identified based on symptoms onset: Early onset hyperacute forms (less than 7 days) after infusion. Acute/Subacute (7 to 21 days), Chronic (over 30 days) (Rhee et al., 2010).

In a multivariate analysis, poor Eastern Cooperative Oncology Group (ECOG) performance status (odds ratio 10.8 and 95% confidence interval 1.6–74.8, p = 0.016) and age (odds ratio 1.1 and 95% confidence interval 0.0–1.2, p = 0.048) were significant risk factors for rituximab-induced ILD. The most common form on CT scan is an organizing pneumonia

pattern or/and diffuse interstitial pattern (ground-glass opacities, alveolitis, and diffuse infiltrate) diffuse or patchy bilateral consolidation in some cases had been described, with the addition of centrilobular nodules which can indicate the presence of alveolitis. Pleural effusion is uncommon; its presence a co-existing infection should be excluded. Hypersensitivity pneumonitis, ARDS, interstitial pneumonitis, organizing pneumonia, also had been reported. Our findings are consistent with the reported cases in the literature in which alveolitis, fibrosis (Sibilia et al., 2008, Taylor et al., 2007).

Risks Factors: The majority of patients had a diagnosis of NHL (75%), and suggested that the elderly is at the most significant risk of rituximab-associated IL D were elderly (average age 65) (van der Kolk et al., 2001). In the same multivariate analysis, poor Eastern Cooperative Oncology Group indicates that poor ECOG performance status and age are significant predictors of RX-ILD. The average number of cycles of rituximab before the presentation was four. Low serum albumin level was reported as a risk factor for adverse pulmonary reactions associated with the use of monoclonal antibodies in cancer patients (Wagner et al., 2007). A prospective longitudinal study conducted did not find any statistically significant relation in smokers, nether underlying chronic lung disease, or exposure to occupational hazards. Pulmonary function tests have usually shown a reduction in the diffusion capacity (DLCO) in the range of DLCO values 13–33% of predicted and restrictive patterns. Lung biopsy is not usually performed in RTX-ILD, but pulmonary inflammation is a standard feature (Yuchen et al., 2018). The most consistent Lung biopsy in systematic review studies showed histological patterns of organizing pneumonia, interstitial pneumonitis, desquamative interstitial pneumonia, diffuse alveolar damage.

Treatment strategy: Conventionally the treatment of RTX-ILD follows the general principles of drug-induced pulmonary toxicity: 1) discontinuation of the offensive agent, 2) supportive treatment, and 3) corticoster-oid treatment. Steroids can be considered in patients with moderate-to-severe dyspnea, respiratory failure, and severe decline in lung function, particularly the diffusion capacity. No recommendations can be made about the dose, route of administration, or duration of steroid therapy.

RESULTS AND DISCUSSION

Rituximab-induced interstitial lung disease is a rare but known complication. Its low incidence may be attributed to a failure to recognize the complication or due to it spontaneously resolution after discontinuing the medication or after a steroid course.

The definite causal relationship is difficult to prove, but chronological association together with the described clinical and radiological features make a probable diagnosis of RTX-ILD. Another chal-lenge in the diagnosis is the use of concomitant drugs or chemotherapeutic agents particularly in the treatment of lymphoma. For this dilemma some authors used Drug lymphocyte stimulation test, a result strongly positive for rituximab with elevated Levels of TNF-a, interferon g, and interleukin 4 but negative for others immunosuppressive or chemotherapeutic agents (such as cyclophosphamide and vincristine) can be a useful tool to discriminate.

Bronchoalveolar lavage findings may support the likelihood of certain lung diseases; however, the information is not specific, and to obtain a definitive diagnosis, further investigations are required such as Transbronchial biopsy . Other alternative to enhance the diagnostic sensitivity in case of transbronchial biopsy failure could be the realization of a Transbronchial Pulmonary cryobiopsy. This relatively new technic has proved to be reasonably safe and useful as an evaluable tool in the pathological assessment of ILDs.

CONCLUSION

Rituximab-induced interstitial lung disease is a rare pathology and often misdiagnosed. Clinical, laboratory and radiological findings can be inconstant, which can make its diagnosis quite challeng-ing. Strong suspicions, clinic presentation, and well-trained clinicians can help an early diagnostic establish a corticotherapy regimen to prevent life-threatening complications. TPC realization can be considered, this procedure has been proved to be a safe alternative to Surgical lung biopsy in ILD diagnosis. Although this technique may not be applied to all ILD cases, it needs to be included in the armamentarium of techniques available for sampling lung tissue when deemed indicated.

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