

A Case of Interstitial Lung Disease Probably Related to Rituximab Treatment

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Published online: 18 June 2015

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Abstract A 44-year-old male developed interstitial lung disease (ILD) during treatment with rituximab (375 mg/m² weekly intravenous × 4 weeks) for the management of immune thrombocytopenia (ITP). After 1 month of treatment he developed dyspnea, fever (38.9 °C), an increase of C-reactive protein (CRP) and white blood cells with hypoxemia, and decreased platelets. Chest X-ray and high-resolution computed tomography revealed diffuse bilateral lung infiltrates. He was diagnosed with severe ILD; rituximab was discontinued, and treatment with fluticasone combined with salmeterol, methylprednisolone, and omeprazole was started, with an improvement of symptoms over 15 days with normalization in CRP at 30 days. A Naranjo assessment score of 6 was obtained, indicating a probable relationship between the patient's symptoms and the suspect drug. In conclusion, in ITP patients treated with rituximab, we suggest evaluating pulmonary endpoints through pharmaco-epidemiological observational studies.

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by platelet destruction, impaired thrombopoiesis and increased risk of bleeding [1]. The incidence

of ITP is not exactly defined, but is estimated at 3.3 per 100,000 persons annually [2].

Management of ITP involves corticosteroids (i.e., dexamethasone or prednisone) ± intravenous immunoglobulin as initial treatment (recommendation: A). Splenectomy (recommendation: 1B) may be offered to those with chronic and severe (i.e., serious bleeding), or relapsing ITP [3, 4]. In patients failing standard treatments (or with a contra-indication to splenectomy), treatment with off-label rituximab (recommendation: 2C) or thrombopoietin receptor agonists (recommendation: 2C) is available.

Rituximab is a chimeric murine/human immunoglobulin G1 (IgG1) kappa monoclonal anti-CD20 antibody approved for use in lymphoma and rheumatoid arthritis [5, 6]. Considering its mechanism of action [i.e., destruction of CD20(+) B cells and normalization of abnormal auto-reactive T cells responsible for IgG autoantibody], rituximab is also used 'off-label' in other autoimmune diseases [7–9]. Rituximab treatment is frequently efficacious and generally well tolerated. However, some cases of rituximab-associated interstitial lung disease (ILD) have been reported [10–12] and, to date, the incidence of rituximab-induced ILD is estimated at 0.01–0.03 % [13, 14]. We report an additional patient with ITP that developed ILD during treatment with rituximab.

Case Description

A 44-year-old man with an 8-year history of ITP presented with a history of 7 days of diarrhea, fever, vomiting, and asthenia. Initial evaluation revealed the presence of dyspnea, temperature of 38.9 °C, and emesis (six episodes/day), but was normotensive (125/82 mmHg). The patient had been treated for ITP for 5 years with prednisone

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(50 mg/daily, orally). Approximately 1 month before presentation he began treatment with rituximab (375 mg/m² weekly intravenous × 4 weeks). Review of systems revealed no other significant factors. Pulse oximetry and analysis of arterial blood gasses revealed hypoxemia (PO₂ 77 %). The patient had mild elevations of C-reactive protein (CRP; 12 mg/dL; normal range 0.5–10 mg/L), erythrocyte sedimentation rate (ESR) of 7 mm/h (normal range <5 mm/h), white blood cells (14,850 per µL; normal range 4500–11,000 per µL), and markedly decreased platelets (14,000/mL; normal range 150,000–400,000/mL). Chest X-ray and high-resolution computed tomography revealed diffuse bilateral lung infiltrates, while pulmonary-function tests demonstrated a restrictive pattern and a diffusion deficit that was consistent with interstitial disease. Bronchoscopy revealed no endobronchial disease, and a broncho-alveolar lavage fluid analysis excluded the presence of bacterial, viral, and fungal infections. Cyto-immunological analysis revealed increased cellularity (253 × 10⁶/L) with a decreased percentage of macrophages (62 %) and an increased percentage of eosinophils (18 %).

A diagnosis of ILD probably related to rituximab was postulated (Naranjo probability scale [15] score of 6). Rituximab and prednisone were discontinued. Treatment with fluticasone + salmeterol (inhaler), methylprednisolone (1 g/day for 3 days and 500 mg/day for 2 days), and omeprazole (40 mg/day) was started with improvement of symptoms at 15 days and normalization of CRP (6.3 mg/L) and ESR (2.4 mm/h) at 30 days. Chest X-ray at 4 months revealed only minimal peripheral irregularities in apices. At 7 months, the patient had complete remission of both radiologic signs and clinical symptoms. The patient provided written informed consent for the publication of this case report.

Discussion

We report the development of ILD during off-label treatment with rituximab for ITP. Many drugs may induce ILD (i.e., chemotherapy agents like bleomycin, cyclophosphamide, and chlorambucil; cardiovascular drugs such as amiodarone, β-blockers, and statins; anti-inflammatory drugs including sulfasalazine, gold salts, and methotrexate; antimicrobial agents including nitrofurantoin, amphotericin, and minocycline; biological agents such as etanercept, infliximab, and adalimumab; and immunosuppressants including everolimus and sirolimus [16–18]). This patient received none of these agents. Fontana et al. [19] previously identified three ILD patients associated with severe ITP, postulating that platelet destruction may induce the development of pulmonary inflammation. We observed a delayed temporal association

between rituximab treatment and the development of ILD. Respiratory symptoms appeared following rituximab administration (third cycle) and resolved upon its discontinuation.

In agreement with our previous papers [20–23], using the Naranjo probability scale, a Naranjo assessment score of 6 was calculated, indicating a probable relationship between symptom development and use of rituximab. For ethical reasons we did not perform rituximab re-challenge.

Two recent reviews documented the development of ILD during rituximab treatments associated with chemotherapeutic agents [10, 24]; however, the exact role of rituximab in ILD development has not been well defined.

Paradoxically, it has been postulated that rituximab may be used in the treatment of systemic sclerosis and systemic lupus erythematosus-related lung disease [25, 26]. These diseases are B-cell mediated; therefore, rituximab reduction of B-cell activation may reduce cytokine secretion (i.e., IL-1) and resultant tissue damage.

However, in five patients with autoimmune disease, treated with rituximab, Lavie et al. [27] reported a significant increase in serum protein level of cytokine B-cell activating factor [tumor necrosis factor (TNF) family, BAFF] 12 weeks after treatment, probably related to a decrease in BAFF receptors and a resultant release of BAFF, or to a delayed regulation of BAFF mRNA transcription. These effects may induce an activation of B cells with increased production of TNF.

Additionally, Bienvenu et al. [28], in a clinical trial of 400 elderly patients with previously untreated diffuse large B-cell lymphoma randomized to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or to rituximab + CHOP, reported that rituximab increases the therapeutic efficacy of the CHOP regimen without the development of serious adverse drug reactions. However, in the rituximab-treated group, the authors found higher mean plasma levels of TNFα (250 % 1 h after rituximab administration and 180 % 8 h after rituximab administration). We previously reported that cell cultures stimulated by TNFα had activation of p38 MAPK signalling pathway, and this activation may be involved in cytokine release (IL-6, IL-8, and IL-11) with epithelial apoptosis and fibroblast proliferation [29–31] mediating ILD. A similar mechanism has been postulated by other authors who described the development of ILD during treatment with TNFα inhibitors [32–35].

The exact role of TNFα in rituximab induced-ILD is yet to be clarified. An additional possible mechanism of rituximab toxicity may be related to increased activity of immune cells (i.e., lymphocytes) that stimulate the proteolytic activation of IL-1β and IL-18, usually regulated by innate immune receptors which are able to form large

multiprotein signalling platforms, termed inflammasomes [36]. Recently, Kong et al. [12] reported the development of ILD in a 30-year-old man after four cycles of rituximab treatment manifesting an increase in the expression of inflammasome components nod-like receptor pyrin domain-containing protein 3 (NLRP3).

To date, there is a paucity of data associating rituximab with ILD in patients with ITP [11, 12, 37]. Protopapadakis et al. [37] described the development of ILD in a 72-year-old man with ITP receiving four cycles of rituximab in 1 month. This subject was treated with three rounds of 1 g IV methylprednisolone, weaning to 15 mg of oral prednisolone for 3 months, resulting in clinical improvement. Child et al. [11] reported an 88-year-old poly-treated male with ITP that developed ILD during treatment with rituximab. In both reports the authors noted that advanced age may have played a role in treatment with other drugs, and in which corticosteroid treatment induced a clinical improvement.

In agreement with these prior reports, we identified the development of ILD approximately 1 month after initiating rituximab; unlike prior reports, our 44-year-old male subject had no other systemic diseases except ITP, for which he had been treated long term with prednisone (5 years).

To date, this appears to be only the second report, following Kong, associating the development of ILD in a non-elderly adult treated with rituximab for ITP.

Case reports, by definition, have a limited scope of presentation. Pharmaco-epidemiological observational studies of pulmonary endpoints in ITP patients treated with rituximab will be required to validate our observations. We recognize the additional limitation of the lack of an anatomical diagnosis using open-lung biopsy precluded by risk of bleeding in our thrombocytopenic patient. Since ILD was a delayed presentation in our subject, we did not perform therapeutic drug monitoring of rituximab and cannot exclude drug overdose. However, standard rituximab dosing regimens were employed and our patient did not take any other medication known to induce a drug–drug interaction. In conclusion, ILD may present weeks to months after rituximab exposure and can mimic many pulmonary syndromes. We therefore recommend careful respiratory monitoring in patients receiving repeated rituximab administrations.

Acknowledgments Luca Gallelli, Massimo Calderazzo, Pierandrea Rende, Paolo Gambardella, and Giovambattista De Sarro declare that they have no conflict of interest. The authors gratefully acknowledge the technical assistance of Stephen R. Southworth, MD in the preparation of this manuscript.

No financial support was received for the conduct of this study or preparation of this manuscript.

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