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ORIGINAL ARTICLE

Ofatumumab-associated acute pneumonitis: Not new but still the first case

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Abstract

Ofatumumab is an anti-CD20 humanized monoclonal antibody utilized in the treatment of several clinical conditions resistant to other treatments. In spite there was a general expectation that ofatumumab was less toxic compared to rituximab, side effects have been reported that resemble those of its anti-CD20 chimeric precursor. Here, we describe the first case of Ofatumumab associate lung injury occurring in a 14-year-old boy affected by nephrotic syndrome dependent to prednisone plus cyclosporine A who had been treated with the dose of drug utilized in nephrotic syndrome (1500 mg/173 m^2). The patient developed the full blown picture of rituximab associated lung injury (RALI) after 45 days from ofatumumab infusion at the end of the steroid tapering: severe exertional dyspnea, mild fever and cyanosis, with CT scan showing diffuse ground glass areas in both lungs and D_{LCO} (diffusing capacity of transfer factor of the lung for carbon monoxide) test suggestive for reduction of CO diffusion. Clinical outcome was good with rapid improvement and normalization of all parameters without any specific therapy. After 60 days, chest CT and CO diffusion tests were normal. In conclusion, we describe here the first case of acute pneumonitis associated with ofatumumab that presents the same clinical, laboratory, and radiology features of the lung injury reported for rituximab. Like RALI occurring in patients treated for nephrotic syndrome, this case had a mild clinical expression and recovered in a few months.

Abbreviations

BAL, bronchoalveolar lavage; OALI, ofatumumab-associated lung injury.

Case Report

A 14-year-old boy affected by steroid-resistant nephrotic syndrome, dependent on prednisone (>1 mg/kg) plus cyclosporine A (4 mg/kg), was previously treated with cyclophosphamide and rituximab, without achieving long-lasting remission. Hence, the patient was enrolled in ClinTrials.Gov NCT02394119 and treated with ofatumumab 1500 mg/1.73 m^2 as stated by the protocol. The drug (final dose 1400 mg) was diluted in 1 L saline and infused at constant rates from 12 to 96 mL/h in 24 h (12 mL/h for the first 60 min followed by 24 mL/h 61–120 min, 48 mL/h 121–180 min, and 96 mL/h up to the end). For premedication, we utilized a modification (Bonanni et al. 2016) of the classical schedule utilized for rituximab consisting i.v. methyl prednisolone (2 mg/kg),

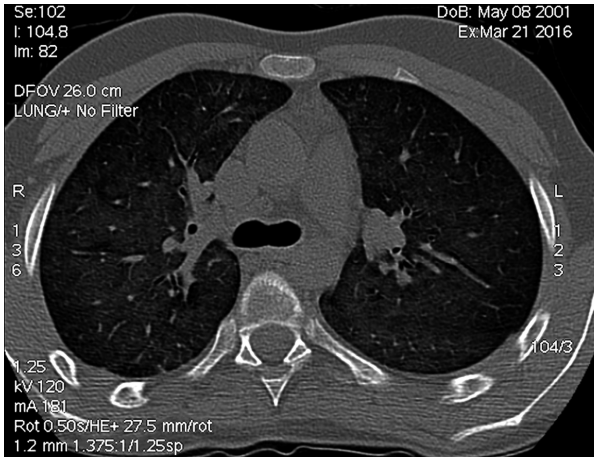

Figure 1. High-resolution chest CT scan performed in the acute phase showing diffuse ground glass areas in both lungs.

oral cetirizine (0.2 mg/kg), paracetamol (15 mg/kg), and salbutamol (0.15 mg/kg). The study was approved by the Ethical Committee Regione Liguria and was published in ClinTrials.Gov NCT02394119. The patient was well-being for 2 months after the infusion, when he finished the steroid tapering; thereafter, he developed severe exertional dyspnea, mild fever, and cyanosis. He was admitted to a local hospital where a high-resolution chest CT scan was performed which showed diffuse ground glass areas in both lungs (Fig. 1). Thus, he was admitted to our institute; the clinical examination as well as the blood pressure, peripheral oxygen saturation, complete blood count, and C-reactive protein were normal. Proteinuria was absent. We performed a CO diffusion study; remarkable interstitial damage and severe carbon monoxide (CO) diffusion reduction were evident. We performed bronchoscopy with bronchoalveolar lavage (BAL) to rule out infectious disease: both culture and polymerase chain reaction analyses were negative for common viral and bacterial causes of pneumonia. Furthermore, we defined the lymphocyte phenotype on BAL and the BAL:blood ratio, highlighting that T-CD8$^+$ lymphocytes were the main subpopulation in BAL, with high relevance of HLA-DR+ phenotype (90%). Low-dose steroid therapy was started with prompt resolution in symptoms. Predominance of T-CD8$^+$ implies activation of an inflammatory process through MHC-I. We hypothesize that apoptotic CD20 may act as trigger the process, a possibility that must clearly be confirmed and better characterized.

Clinical outcome was good with rapid improvement and normalization of all parameters without any specific therapy. After 60 days, chest CT and CO diffusion tests were normal.

In conclusion, we describe here the first case of lung injury associated with ofatumumab that present the same clinical, laboratory, and radiology features of the same lung injury reported for rituximab. Like RALI occurring in patients treated for nephritic syndrome (Wagner et al. 2007, Spatafora et al. 2015), OALI had a mild clinical expression and recovered in a few months. Activation of T8 cells was the main cellular finding.

Disclosures

All the authors declare that they have not received support from any company for the submitted work, have no relationships with any company that might have an interest in the submitted work, and not have financial or non-financial interests that may be relevant to the submitted work. They also declare that their spouses, partners, or children have not had financial relationship that may be relevant to the submitted work.

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