Clinical Oncology: Case Reports

Case Report

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Successful Treatment with Rituximab of Sjögren's Syndrome-Associated Organizing Pneumonia in a Patient Treated with PD-L1 Blockade for Ovarian Cancer

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Abstract

As the use of immune checkpoint inhibitors in cancer therapy increases across a wide range of tumor types, rarer toxicities including rheumatologic immune adverse events are reported with increasing frequency. We describe the case of an ovarian cancer patient treated with durvalumab, who developed an organizing pneumonia, proved to be related to a preexisting but previously unknown asymptomatic Sjögren's syndrome, confirmed by a positive antibody (anti-SSA and anti-SSB) panel. While resistant to corticosteroids, was ultimately successfully treated with the B-cell depleting antibody rituximab with no impact on the anticancer therapy efficacy. This case shows that patients with preexisting autoimmune diseases should not be systematically excluded from potentially life-saving anti-tumor therapies without a thorough assessment of the potential benefit in terms of efficacy and safety of the therapy.

Keywords

Immune checkpoint inhibitors; Durvalumab; Ovarian cancer; Sjögren's syndrome; Organizing pneumonia; Rituximab

Abbreviations: ICIs: Immune Checkpoint Inhibitors; PD-1: Programmed-Death 1; FDA: Food and Drug Administration; irAES: Immune-Related Adverse Events; SS: Sjogren's Syndrome; OP: Organizing Pneumonia; DMARDs: Disease-Modifying Anti-Rheumatic Drugs; PLD: Pegylated Liposomal Doxorubicin; BAL: Bronchoalveolar Lavage; ILD: Interstitial Lung Disease; EULAR: European League Against Rheumatism; CTLA-4: Cytotoxic T-Lymphocyte-Associated Antigen-4

Introduction

Immune Checkpoint Inhibitors (ICIs) targeting Programmed-Death 1 (PD-1) or its ligand PD-L1 are currently approved by the Food and Drug Administration (FDA) for the treatment of 15 tumor types [1], and are being studied in other malignancies as part of their clinical development program. Their most significant side effects are referred to as Immune-Related Adverse Events (irAEs) and are caused by an off-target tissue injury due to nonspecific T cell activation [2]. The clinical manifestations of irAEs are diverse and depend on the organ system involved. The skin and the gastrointestinal tract are most frequently affected [3].

Due to the increasing use of ICIs, rarer toxicities, such as rheumatic immune side effects, have been more frequently reported in case reports or prospective postmarketing studies. Sjögren Syndrome (SS) is the second most common systemic autoimmune disease characterized by a lymphocytic infiltration of the salivary glands, with resultant dryness of the eyes and mouth [4]. Extraglandular systemic manifestations are frequent and can be divided into non-visceral (skin, joints) and visceral (lung, kidney, endocrine, among others) manifestations [4]. Pulmonary involvement can be present in up to 20% of patients with SS and is mainly characterized by interstitial pneumonitis, bronchiolitis obliterans and/or Organizing Pneumonia (OP) [5]. Standard therapy for SS with pulmonary involvement is not fully established, with a wide range of therapeutic options that include glucocorticoids, conventional non-biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs), and cyclophosphamide. Recently, B-cell depletion with the use of rituximab, a chimeric murine/human anti-CD20 monoclonal antibody, has become an interesting therapeutic option in patients with severe manifestations of SS [6].

We describe the case of a metastatic ovarian carcinoma patient who was treated with anti-PD-L1 immunotherapy and subsequently developed SS associated OP. The disease proved corticosteroid-resistant but demonstrated an excellent response to rituximab. Moreover, the patient is in radiological complete response, witnessing of an optimal ICIs activity under the effect of a selective immunosuppressant therapy.

Clinical Investigation

A 73-year-old female patient diagnosed with a high-grade serous ovarian carcinoma cT3 cN0 cM0, stage FIGO IIIC, underwent neoadjuvant chemotherapy, interval debulking surgery, and adjuvant platinum-based chemotherapy, followed by bevacizumab maintenance. After 9 cycles, newly enlarged lymph nodes were observed in the peri-hepatic region, and the patient was included in a non-randomized, multicenter phase 1/2 study (LUD2014-001 study; NCT02431559) of motolimod (Toll-like receptor 8 agonist, TLR8) and durvalumab (anti PD-L1) in subjects with recurrent, platinum-resistant ovarian cancer, scheduled to receive Pegylated Liposomal Doxorubicin (PLD). As a previous trial had showed that addition of motolimod to PLD did not improve clinical outcomes in that population [7], the phase II was modified to administer durvalumab and PLD without motolimod. Of note, the patient had no significant medical history, and had no known prior autoimmune disorder at time of enrollment.

She received 6 monthly-cycles of PLD in combination with durvalumab. Due to grade 3 mucositis and recurrent grade 3 skin toxicity, PLD was halted and the patient proceeded on durvalumab monotherapy for 2 years, amounting to 25 cycles in total. After

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cycle 25 of durvalumab and 18 months after last dose of PLD, the patient developed moderate dyspnea, dry cough and fever. Figure 1 summarizes the timeline of events.

Clinical examination showed oxygen saturation level of 94% and crackles in both lung bases. C-reactive protein was elevated at 131 mg/l (normal <10 mg/l), and total leucocytes were 10.9 G/L (normal 4-10 G/L). Chest computed tomography scan showed zones of alveolar condensation with ground glass opacities in the left upper lobe and both lung bases (Figure 2A). A 7-day course antibiotic treatment with amoxicillin/clavulanic acid was started and a bronchoscopy was done while under antibiotic therapy. Bronchoalveolar Lavage (BAL) showed no malignant cells and moderately elevated lymphocytes (14.5%, normal below 12%); influenza swabs and bacteriological analyses (including *mycoplasma pneumoniae*, *chlamydia pneumoniae, legionella pneumophila, pneumocystis jirovecii, mycobacterium tuberculosis*) were negative. High-dose corticosteroid therapy (1 mg/kg oral prednisone) was initiated for durvalumab-induced immune-related OP.

While on 10 mg/day of prednisone after a seven-week taper, the patient presented with fever and fatigue and a significant elevation of serum lipase reaching 579 U/l (normal 13-60 U/l) without radiological signs or symptoms of pancreatitis. Both conditions resolved after a transient increase of prednisone. The autoimmune work-up showed positive anti-nuclear factor and anti-SSA/SSB antibodies (anti-SSA at 1013 CU and anti-SSB at 922,6 CU), consistent with SS. The antibody testing was repeated on serum samples obtained before the start of durvalumab therapy, showing an auto-immune profile consistent with pre-existing asymptomatic SS (anti-SSA at 749 CU and anti-SSB at 495,4 CU). We hence concluded that the OP developed in the context of SS.

During the subsequent steroid taper, the patient presented a first clinical relapse with dyspnea, fatigue and fever. Chest CT showed the improvement and resolution of previously observed lung abnormalities and the emergence of new pulmonary opacities localized in different lung segments. The migratory nature of lung lesions strengthened the hypothesis of OP. The BAL analysis, similarly

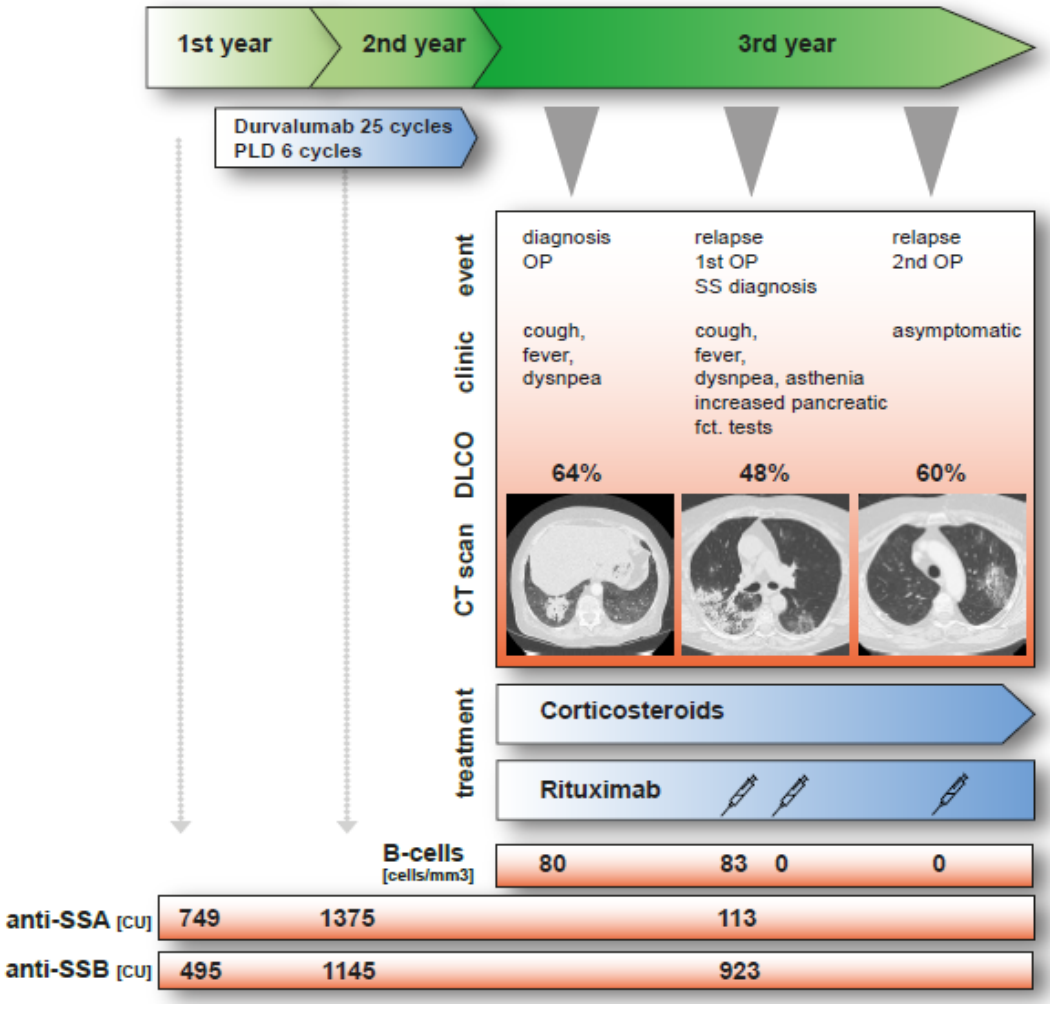

Figure 1: Timeline of events and therapy administered; Abreviations: PLD: Pegylated Liposomal Doxorubicin; OP: Organizing Pneumonia; SS: Sjögren Syndrome; DLCO: Diffusing Capacity for Carbon Monoxide.

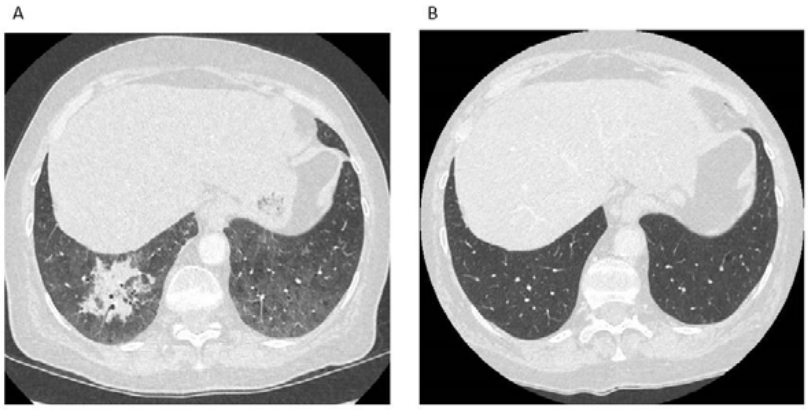

Figure 2: A: Left, alveolar condensation with ground glass opacities in the right lower lobe, baseline; B: Right, disappearance of both the alveolar condensation and ground glass opacities at 4 months from second rituximab dose.

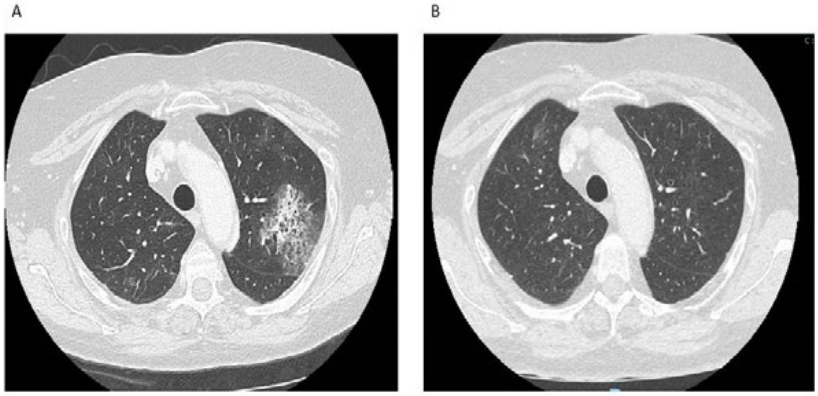

Figure 3: A: Left, appearance of new ground glass opacities in the left upper lobe at 6 months from second rituximab dose; B: Right, disappearance of the new ground glass opacities in the upper left lobe at 3 months from third rituximab dose.

to the first one, was negative for infectious agents. As the patient could not be successfully tapered off steroids, two infusions of rituximab at 1000 mg were administered at a two-week interval, with clinical improvement to resolution of symptoms and radiologic abnormalities (Figure 2B) and no recurrence during the following 6 months.

Six months after the second rituximab infusion, the patient presented with a second asymptomatic OP relapse, with new pulmonary infiltrates observed on her scheduled CT scan (Figure 3A). A third dose of rituximab 500 mg was administered, with subsequent improvement of pulmonary infiltrates at 6 weeks, and resolution at 3 months (Figure 3B), which allowed a progressive complete steroid taper (after 18 months of therapy). Importantly, the patient has been in radiological complete response, and immunosuppressive therapy did not affect this outcome as of 18 months from the first dose of rituximab and 21 months after the cessation of durvalumab.

Discussion

SS is a multisystem autoimmune disease characterized by the infiltration of the exocrine glands by autoreactive lymphocytes, with resultant destruction and development of dry eyes and mouth. In addition to glandular manifestations, SS can present other manifestations such as polyarthritis, pancreatitis, vasculitis, lymphoma, renal, neurological and pulmonary involvement [4]. The most common pulmonary manifestations of SS are airway abnormalities and Interstitial Lung Disease (ILD). Overall, lung manifestations occur in 9% to 20% of SS patients. This prevalence is probably underestimated due to frequent subclinical involvement and to a wide variability in reports [5]. Pulmonary involvement as the first manifestation of SS is present in around 16.8% of cases [8]. Clinically, patients may present with dyspnea, cough, sputum production and/or fever [5]. This constellation, in addition to a decline in pulmonary lung function tests parameters and abnormalities on chest-computed tomography, define lung involvement in SS according to the European League Against Rheumatism (EULAR)-SS Task Force. Anti-Ro/SSA antibodies are positive in nearly 3/4 of SS patients, whereas anti-La/SSB antibodies are positive in only 1/3 of patients [5]. Systemic therapy is indicated in case of organ involvement, and includes

initially glucocorticoids, antimalarial (hydroxychloroquine) and/or DMARDs [9]. Therapy-resistant SS with proven organ involvement is an indication to escalate to biological agents.

The pathogenesis of SS remains unclear and appears to be multifactorial. Environmental factors such as viral infections in genetically predisposed subjects trigger the activation of the innate and adaptive immune system, ultimately leading to the proliferation, maturation and differentiation of self-reactive B cells. These self-reactive B cells are a key contributor to organ damage in SS, because they produce autoantibodies and immune-complexes and form extranodal lymphoproliferation, which is a characteristic feature of SS tissues alteration [10]. As a result, rituximab, a B-cell depleting biological agent targeting the protein CD20 leading to a decrease in antibody production [11], has become an interesting option in the therapy of SS.

Our patient presented with interstitial pneumonitis, characterized by alveolar condensations with ground-glass opacities consistent with OP, which developed during ICIs therapy in the context of an unknown but pre-existing asymptomatic SS, as shown by a positive serology prior to the initiation of immunotherapy. Rituximab was added due to cortico-resistant OP, allowing successful withdrawal of glucocorticoids after several months. Randomized placebo-controlled studies of rituximab in patients with primary SS have generated conflicting results due to design limitations [12]; consequently, rituximab remains an option while further trials with adequate statistical power and appropriate dosing schedules are required in order to draw clear conclusions. In patients with lung involvement, several small reports [13-15] describe a marked improvement after rituximab in symptoms as well as lung functions and radiological infiltrates. Although there is no standard therapeutic regimen for rituximab in this setting, most of these publications report two intravenous infusions of 1000 mg separated by a minimum of 2 weeks.

Data on the prevalence and outcome of SS in patients receiving therapy with ICIs is scarce, as most clinical trials have excluded patients with significant autoimmune disorders. In a series of 81'132 lung and kidney cancer patients in an administrative health care claims database, 0.9% reportedly had concurrent SS [16]. Although exacerbation of pre-existing autoimmune disease on ICIs occur in up to 50% of cases, there is little specific information regarding SS flares. In a retrospective observational study, Menzies et al. analyzed 119 melanoma patients receiving anti-PD-1 therapy with preexisting autoimmune condition, and showed that anti-PD-1 antibodies often exacerbate rheumatologic conditions [17]. Of these 119 melanoma patients, 52 had pre-existing autoimmune disease and 27 (52%) patients had rheumatologic disorders, of which 2 were SS. Of these 27 patients, 14 (52%) had flares of their underlying rheumatologic disorder, including the two SS patients. Another systematic review of 49 publications analyzing 123 solid tumor patients with pre-existing autoimmune diseases reported an exacerbation rate of the disease of approximatively 50% on ICIs. This study included 1 patient (i.e. 0.8%) with preexisting SS that did not presented a flare under ICIs and 1 patient experiencing SS as a *de novo* irAEs [18]. Many other studies [19,20] have shown that ICIs have an impact on the evolution of preexisting autoimmune diseases causing flares in 38% to 47% of patients. Moreover, most flares were mild, occurred more often in patients with active symptoms prior to ICIs treatment and in most cases the underlying disease flare did not warrant discontinuing ICIs therapy [21].

The onset of the SS-related OP in our patient 2 years after the initiation of the ICIs therapy is late compared to the time course of rheumatological exacerbations described in the literature, and we do not have a clear explanation for this. According to Menziers et al. [17], flare of an underlying autoimmune disease occurred between 8 and 161 days, with a median of 38 days, after the first dose of anti-PD-1 therapy.

PLD, a liposome-encapsulated form of doxorubicin, used at the beginning of the clinical trial, could be considered as a potential causal agent for the OP. However, OP developed 18 months after the last dose of PLD. Few case reports of chemotherapy-induced interstitial pneumonitis, but not OP, due to PLD either alone or in combination with other antineoplastic agents, have been published to date [22,23]. Most of them describe the appearance of lung toxicity within the first weeks or months following the initiation of the therapy, and none after chemotherapy was discontinued. Thus, we do not support the hypothesis of PLD being a causative factor for OP development.

Regarding the oncological outcome, despite a prolonged administration of glucocorticosteroids (>14 months) to manage lung involvement, and the use of rituximab, our patient remains in complete tumor response still 21 months after the cessation of durvalumab. The impact between the occurrence of an irAEs, the need for immunosuppressive therapy to mitigate AEs and the potential effect on anti-cancer immune response, has been analyzed in different retrospective studies. Two pooled analysis in melanoma patients receiving anti-CTLA-4 (Cytotoxic T-Lymphocyte-Associated Antigen-4) [24] or anti-PD-1 therapy [25] who developed irAEs requiring immunosuppressive therapy, mainly glucocorticosteroids, showed that the use of these therapies did not seem to have a negative impact on antitumor benefit. Another pooled analysis of 1747 patients with metastatic urothelial cancer treated with anti-PD-1 or anti-PD-L1 showed similar results [26]; patients who responded to treatment were more likely to develop irAEs than non-responders and the use of immunosuppressive therapy did not appear to negatively affect the duration or the overall response. Although there seems to exist more solid evidence that oncological outcome of patients under ICIs may not negatively be influenced by the use of immunosuppressive therapies when needed to manage irAEs, further prospective validation of these findings is required.

Conclusion

In this clinical case, we have demonstrated that managing corticotherapy-resistant OP in the context of SS, as a complication of ICIs treatment, can be a challenge. Adding rituximab to glucocorticoids has improved clinical outcome, and this therapeutic option should be considered in the event of SS-associated organ damage. Moreover, long-term immunosuppressive therapy had no detrimental effect on oncologic outcome. Hence, clinicians should not systematically preclude patients with preexisting autoimmune diseases from potentially life-saving anti-tumor therapies. The underlying autoimmune disease and the severity of organ involvement should be taken into account before initiating ICIs treatment, and patients

should be informed of the potential AEs that could be encountered while receiving this therapy. Management of challenging cases should involve multidisciplinary discussions with specialists in oncology, immunology, pneumonology and/or other field-experts depending on the diseases feature. The patient provided written informed consent for her case to be presented.

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Author Contribution

AO: Main treating physician, analyzed and interpreted the patient's case, wrote and edited the manuscript. KA: Treated the patient and helped writing the manuscript. CP: Treated the patient and reviewed the manuscript. BW: Treated and reviewed the manuscript. CD: Treated the patient and reviewed the manuscript. VCS: Trial coordinator and reviewed the manuscript. SZ: Treated the patient, interpreted the case and reviewed the manuscript. GC: Interpreted the case and reviewed the manuscript. DC: Treated the patient, interpreted the case and reviewed the manuscript .

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

Available upon request.

Competing Interests

G.C. has received grants or research support from or is coinvestigator in clinical trials by BMS, Celgene, Boehringer Ingelheim, Roche, Iovance and Kite, and has received honoraria for consultations or presentations by Roche, Genentech, BMS, AstraZeneca, Sanofi-Aventis, Nextcure and GeneosTx.

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