Case Reports in Oncology

Case Rep Oncol 2023;16:1095–1099
DOI: 10.1159/000532098
Received: December 20, 2022
Accepted: July 12, 2023
Published online: October 11, 2023

Case Report

Sjögren's Syndrome Caused by PD-1 Inhibition in a Lung Cancer Patient

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Keywords
Sjögren's syndrome · Sicca syndrome · Pembrolizumab · Immune checkpoint inhibition · Non-small cell lung carcinoma · Immune-related adverse event · Case report

Abstract
In this report, we present a patient with metastatic non-small cell lung cancer who developed Sjögren's syndrome secondary to immune checkpoint inhibition. This patient had a typical clinical presentation as well as biochemical signature, developing only 18 months after the start of treatment with PD-1 inhibition (pembrolizumab).

Introduction

Sjögren's syndrome (SS) is a systemic auto-immune disease that mainly affects the exocrine glands which leads to sicca syndrome: dryness of the main mucosal surfaces, such as the mouth, eyes, nose, pharynx, larynx, and genitals [1]. The overall incidence of SS was estimated at approximately 7 per 100,000 person-years [2]. In 5.3% of patients receiving immunotherapy as a cancer treatment, oral/ocular dryness is reported as an immune-related adverse effect (irAE), with a higher frequency for patients who receive chemotherapy (9.4%) and lower for patients treated with CTLA-4 inhibitors (1.4%) [1].

The phenotype of Sicca syndrome induced by immunotherapy; however, is different from the one observed in primary SS: half the cases are men in comparison to only 5% in primary SS, the mean age of diagnosis is 10 years older, and a lower frequency of both oral and ocular

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dryness is reported. Furthermore, the prevalence of SS-associated serum autoantibodies (52% ANA, 20% Ro/SS-A, 9% RF, 8% La/SS-B) is much lower in comparison to idiopathic primary SS. The pathogenesis of immunotherapy-induced sicca/Sjögren's syndrome remains unknown. A genetic predisposition might be a contributing factor [1].

In this case report, we describe a 71-year-old female patient with severe debilitating xerostomia and xerophthalmia who was finally diagnosed with Sjögren's syndrome secondary to PD-1 inhibitory treatment for a non-small cell lung cancer. This case is unique because the patient developed xerostomia and xerophthalmia only 18 months after the start of immune checkpoint inhibition. Furthermore, it encompasses the full clinical and biochemical picture of Sjögren's syndrome.

Case Description

A 71-year-old female former smoker (30 pack-years) with a medical history of mild obstructive pulmonary disease, breast cancer (IDA right breast, treated with broad excision and adjuvant radiotherapy and Tamoxifen until 06-2016), and low-grade non-invasive urothelial carcinoma of the bladder (treated with TURBT) was diagnosed with pulmonary adenocarcinoma of left lower lobe in 09-2020, treated by thoracoscopic lobectomy of the left lower lobe with pathological staging of pT2bN0. Adjuvant chemotherapy was proposed but declined by the patient. Approximately 1.5 years after surgery, regional and distant disease relapse was diagnosed with multiple metastatic para-aortic lymph nodes as well as in the left internal mammary chain on FDG PET-CT. Based on high PD-L1 expression (90% tumor proportion score) in the absence of targetable driver mutations, pembrolizumab monotherapy was started. Partial remission was reached after the initiation of therapy and maintained after 18 months. No severe adverse events were witnessed besides mild myalgias/arthralgias and a possible mild ocular myasthenia (both grade 1) arising after 4 administrations of pembrolizumab. After a treatment with low dose of steroids (methylprednisolone 8 mg) was initiated, these symptoms disappeared rapidly. The steroid dose was slowly tapered and eventually stopped in July 2022. At that moment, the patient first mentioned a dry burning sensation at the level of the throat. The following oropharyngeal symptoms worsened, leading to progressive difficulties swallowing due to the extreme mucosal dryness and self-reported absence of saliva production. In 09-2022, patient had lost 10 kg of body weight because of this severe xerostomia. The patient also experienced crescendo xerophthalmia. Upon examination, she had a dark brown tongue and buccal dryness (shown in Fig. 1). As a first step, pantoprazole, hydroxyzine, and inhalator therapy (beclometasone-formoterol) were stopped as these can contribute to oral dryness. Mouthwash and fluconazole 50 mg once daily were started empirically for a suspected oral fungal infection. These therapy modifications, however, did not affect the symptoms. Odynophagia and xerostomia worsened to the extent that the patient could hardly eat and lost another 5 kg of weight. Subsequently, the patient was admitted. Clinical evaluation at that time showed buccal dryness, oral ulcers, painful erythematous lesions on the lower legs, suggestive for erythema nodosum (shown in Fig. 2), and the known dark brown tongue. Blood analysis showed mild inflammation and a markedly positive antinuclear antibody (ANA) of 1/160 with positive anti-Ro52-SSA differentiation. Ophthalmological investigation confirmed important xerophthalmia with Schirmer test of <1 mm after 3 min, and corneal erosions had been objectified upon examination. Dermatological evaluation confirmed the diagnosis of erythema nodosum on the lower legs.

Based on these findings, the patient was diagnosed with Sjögren's syndrome secondary to pembrolizumab. After rheumatology consultation, a corticosteroid treatment (methylprednisolone

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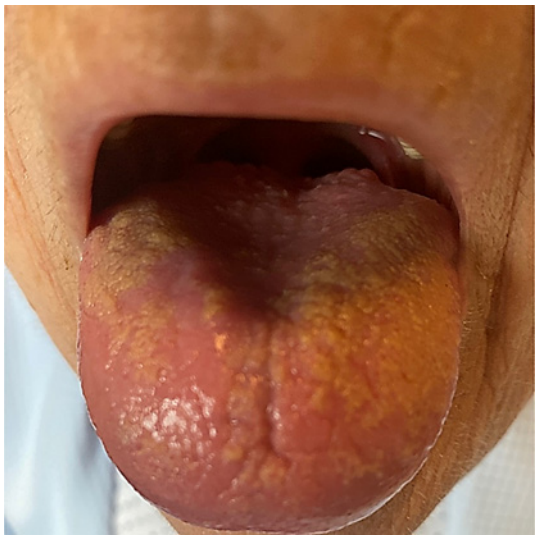

Fig. 1. Dark brown tongue.

16 mg once daily) was initiated. Symptomatic treatment of the xerophthalmia was started with ocular lubricant and cyclosporine 5% as well as oral hydrant with glycerin, xylitol, and hydroxyethylcellulose. Erythema nodosum was treated with local application of betamethasone 0.5 mg/g. Symptoms improved under this therapy, and the patient gained body weight. Methylprednisolone could be tapered until 2 mg/day in January 2023. Until this day, pembrolizumab was not restarted, nor any other cancer treatment. Non-treatment follow-up showed persistent partial remission in 05-2023. A timeline of events can be found in Figure 3.

Discussion and Conclusion

Lung cancer has the second highest incidence of all cancers worldwide (11.4% of all new cancer cases in 2020) and is the main cause of cancer-related deaths (18% of all cancer deaths in 2020) [3]. In patients with non-small cell lung carcinoma (NSCLC) and high PD-L1 expression (tumor proportion sore of at least 50% of tumor cells), both overall and progression free survival have significantly improved since the introduction of immune checkpoint inhibitors targeting the PD-1/PD-L1 axis (such as pembrolizumab). Fewer treatment-related adverse events are seen in pembrolizumab-treated patients in comparison to the former standard of care platinum-based combination chemotherapy [4]. Typical immune-related adverse events (such as thyroiditis, colitis, pneumonitis. . .) secondary to the use checkpoint inhibitors as pembrolizumab are well known and the detection and management of these irAE's are embedded in routine clinical practice. However, some irAE's are extremely rare and present with unclear and difficult to interpret symptoms and clinical signs, often leading to belated diagnosis.

In this case report, we present Sjögren's syndrome, emerging only after 18 months of treatment with pembrolizumab, with the full clinical and biochemical image. As we can see in this case, sicca syndrome with xerostomia and xerophthalmia can be insidious and difficult to recognize. After dermatological and rheumatological evaluation, the correct diagnosis was established, and treatment with corticosteroids (methylprednisolone 16 mg/day) was started. Patient experienced rapid improvement in symptoms after with methylprednisolone could be tapered to 2 mg/day. Because of the severity of the initial symptoms and persistent oncological remission, we decided not to restart pembrolizumab and to continue no-treatment follow-up for undetermined time.

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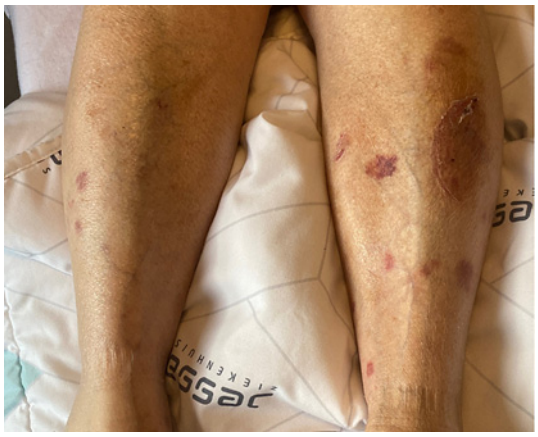

Fig. 2. Erythema nodosum.

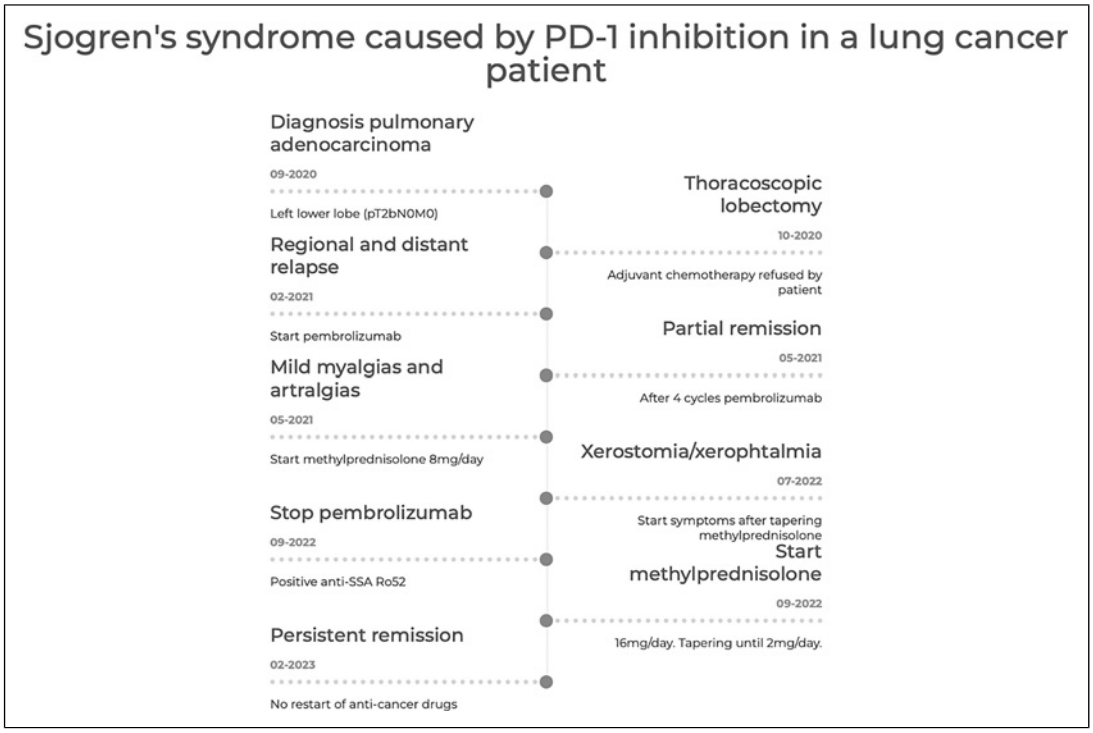

Fig. 3. Timeline of events.

This case report shows the vital importance of a multidisciplinary evaluation of patients treated with immune checkpoint inhibition and difficult-to-interpret symptoms. A multidisciplinary evaluation allows for a more comprehensive and expedited diagnosis, so that an optimal causal and symptomatic treatment can be started, in order to preserve and improve quality of life in these patients. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000532098).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding Sources

No funding was received.

Author Contributions

Aaron Caeyman, Olivia Vandekerckhove, and Kristof Cuppens: drafting the article, revising it critically for important intellectual content and final approval of the version published as well as involvement in clinical assessment and treatment. Karin Pat, Jokke Wynants, Karolien Weytjens, and Isabelle de Wergifosse : reading the manuscript critically and involvement in clinical assessment and treatment.

Data Availability Statement

All data generated or analyzed during this study are included in this article and the supporting files. Further inquiries can be directed to the corresponding author.

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