Case Report
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Sicca symptoms and sialoadenitis as immune-related adverse events of nivolumab treatment in renal malignancy

Abstract

Immune checkpoint inhibitors (ICIs) are a promising new type of immunotherapy for solid tumors and various hematologic neoplasms. Nivolumab is one of the ICIs and its target is programmed cell death 1 (PD-1). These therapies may lead to the development of immune-related adverse events (irAEs). We present severe *sicca* symptoms in a 65-year-old patient in association with nivolumab. He was treated with nivolumab (monthly dose 480 mg) after left nephrectomy and secondary radiotherapy. Clinical oral examination revealed an extremely dry, mildly erythematous oral mucosa. The mucosa of the dorsum of the tongue was dry, atrophic, and "wrinkled." Saliva was thick and sticky. The patient was prescribed local therapy: Pilocarpine drops 2%, six drops three times a day for six weeks. An oral antiseptic and an oral antifungal gel were prescribed to treat the oral candidiasis. Salivary gland function was monitored by serum alpha-amylase levels and results of unstimulated (UWS) and stimulated (SWS) whole saliva. The subjective symptom of dry mouth should not go unrecognized in patients treated with nivolumab, as timely therapeutic intervention is critical to preserve salivary function.

Keywords: immune checkpoint inhibitors, nivolumab, sicca syndrome, sialadenitis

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Abbreviations: ICIs, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; CTLA4, cytotoxic T lymphocyte antigen 4; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; irAEs, immune-related adverse events; SD, Sjögren's disease; DM, diabetes mellitus; NF1, neurofibromatosis type 1; PHD, pathohistological diagnosis; CBC, complete blood count; CRP, C-reactive protein; RF, rheumatoid factor; TSH, thyroid-stimulating hormone; T3, triodothyronine; ACTH, adrenocorticotropic hormone; ANA, antinuclear antibodies; ENA, extractable nuclear antigen; UWS, unstimulated whole saliva; SWS, stimulated whole saliva; CTCAE, common terminology criteria for adverse events; MLSGs, minor labial salivary glands; GVHD, graft-versus-host disease; CMV, cytomegalovirus infection; HIV-SGD, HIV salivary gland disease; HCV, hepatitis C virus; TB, tuberculosis

Introduction

Immune checkpoint inhibitors (ICIs) are a promising antitumor therapy and are now used in the treatment of various tumors: metastatic melanoma, metastatic non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC). Their targets include cytotoxic T lymphocyte antigen 4 (CTLA4; target of ipilimumab), programmed cell death 1 (PD-1; target of nivolumab, pembrolizumab, and cemiplimab), and programmed cell death ligand 1 (PD-L1; target of avelumab, atezolizumab, and dervalumab).[1] ICI therapy may be associated with the development of organ-specific autoimmune diseases (up to 60%), whereas systemic and rheumatic diseases are less common.[2-6] Then we talk about the development of immune-related adverse events (irAEs).[7] They can occur *de novo* or by exacerbation of a previously diagnosed autoimmune disease.[1] They include rash, pneumonitis, colitis, autoimmune thyroid disease, hypophysitis, and vitiligo.[8] These irAEs are unique and distinct from those associated with cytotoxic chemotherapy, radiotherapy, or targeted therapies.[6] Side effects associated with immunotherapy tend to occur later and last longer than side effects associated with chemotherapy.[9] *Sicca* symptoms are common in the general population, with a prevalence of up to 30% in people older than 65 years.[10] *Sicca* symptoms, sialoadenitis, and Sjögren's disease (SD) are also side effects of ICIs. Here we present severe *sicca* symptoms in a patient associated with immunotherapy.

Case report

A 65-year-old patient came because of "extreme dryness in the oral cavity" that started suddenly a month ago. Due to difficulties with the oral cavity, he came to the Dental Clinic Split (teaching base of the School of Medicine, study of Dental Medicine, University of Split, Split, Croatia) for the first specialist examination in January 2021. He had no subjective dryness of the eyes, other mucous membranes, or skin. He denied problems swallowing hard, dry food. Family history revealed that his father had died of prostate cancer (at age 63 years) and his sister had died of complications of *diabetes mellitus* (DM) (at age 58 years). From his medical history, he overcame Q fever (30 years ago); he has been monitored for neurofibromatosis type 1 (NF1) since childhood; he is regularly monitored for neurina of the lesser sphenoid wing; in 2018, he underwent a left nephrectomy (PHD – chromophobe carcinoma with sarcomatoid differentiation 75%) and in 2019, he underwent surgery for recurrence of malignant disease, which included resection of the colonic flexure (t-t anastomosis). After surgery, radiotherapy was given to the secondary nodes and left hemiabdomen. Since May 2020, he has been treated with nivolumab (monthly dose 480 mg). He was taking carbamazepine (400 mg, 2x1). He denied allergies as well as drug allergies. He was a nonsmoker. Complete blood count (CBC) was unremarkable. Biochemical findings showed elevated serum levels of alpha-amylase (108), C-reactive protein (CRP) (10.1), IgA (4.74), beta- globulin (9.60), rheumatoid factor (RF) (23), thyroid- stimulating hormone (TSH) (4.100), triodothyronine (T3) (4.16), total cortisol (733), adrenocorticotropic hormone (ACTH) (18.2). Antinuclear antibodies (ANA) (<1:160) showed borderline values, whereas extractable nuclear antigen (ENA) results were unremarkable. Schirmer test

I results showed an extremely dry eye (4 mm/5 mm). Clinical oral examination revealed an extremely dry, mildly erythematous oral mucosa. The mucosa of the dorsum of the tongue was dry, atrophic, and „wrinkled“ (fissured). Saliva was thick and sticky (Figure 1). Vitroadhesion test was positive. Unstimulated whole saliva (UWS, Qs=0.0 ml/min) and stimulated whole saliva (SWS, Qss=0.1 ml/min) showed hyposalivation, which met the diagnostic criteria for the diagnosis SD according to the American-European classification criteria.[11] The severity of dry mouth was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5).[12] The results showed grade 1 for dry mouth (symptomatic without significant dietary alteration) and grade 3 for UWS (<0.1 ml/min). An oral mycological swab was obtained and the native findings were positive. The patient was prescribed local therapy: Pilocarpine drops 2% (six drops three times daily for six weeks). For treatment of oral candidiasis, an oral antiseptic (Hexetidine, 3x daily, 2 weeks) and an oral antifungal gel (Miconazole, ½ scoop 4x daily, 2 weeks) were prescribed.

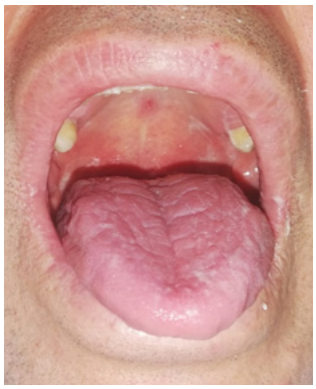

Figure 1 Dry mouth and thick saliva.

Discussion

Nivolumab is one of the ICIs and is used in the treatment of solid tumors and various hematologic neoplasms. The side effects of ICI therapy are numerous, considering the impact on the immune system.[8,13] *Sicca* syndrome associated with ICIs has been reported less frequently, i.e., dry mouth was observed in 6.5% of patients.[14,15] In our patient, dry mouth occurred eight months after the start of treatment with nivolumab, which is consistent with the findings of Capelli et al. (dry mouth occurred after nine months).[14] Our patient suffered from severe subjective dry mouth and hyposalivation. The patient said that “his tongue suddenly became wrinkled and he did not have that before.” Such a clinical sign strongly suggests SD. A biopsy of the minor labial salivary glands (MLSGs) was performed and histological examination revealed salivary gland lobules with regular architecture without inflammatory reaction. Ultrasonography of the major salivary glands was normal, i.e., both parotid and submandibular glands were of adequate morphology and without focal lesions. Immunohistochemistry showed that the infiltrate in the MLSG biopsy of ICI patients’ consisted of an increased number of CD3+ cells, a slight predominance of CD4+ over CD8+ T cells, and a low number of CD20+ B cells, in contrast to the immune cell infiltrates of SD, graft-versus-host disease (GVHD), and IgG4-related sialadenitis.[1,15-18] The incidence of dry mouth and eye varies from 3% to 24% in the general population.[14] It is known that dry mouth can occur as a side effect of more than 400 medications.[19] In the case of our patient, it is important to note that the onset of symptoms was sudden and severe. The results of sialometry could not be associated with the use of medications that affect salivary function. Our patient was taking only carbamazepine, and the decreased SWS findings ruled out the medication as a possible cause. The sialometry findings met the diagnostic criteria of SD according to the American-European classification criteria. Therefore, a biopsy of the MLSG was indicated, which revealed normal histopathologic findings. Because the patient also had negative findings of autoantibodies associated with SD (anti-SSA/Ro and anti-SSB/La), SD was excluded.

A metabolic disorder, i.e., uncontrolled DM, was excluded on the basis of the biochemical findings. In the differential diagnosis, various types of asymptomatic viral sialoadenitis (cytomegalovirus infection (CMV), HIV salivary gland disease (HIV-SGD), hepatitis C virus (HCV), tuberculosis (TB)) were considered. After primary infection, CMV remains latent in the salivary glands. In healthy individuals, reactivation of the virus may occur without clinical signs of the disease.[20,21] HIV-SGD is a disease that may occur with or without xerostomia. The parotid glands are affected in 98% of cases, and bilaterally in 60% of patients.[22-24] The association between HCV and SD is still controversial. In the study by Pawlotsky et al., 14% of HCV patients were found to have SD-like salivary gland disease.[25] TB leads to the formation of granulomas that may also affect the salivary glands, and patients may also suffer from xerostomia.[19] Finally, allergic sialoadenitis has been considered as a diagnosis of exclusion. Allergic sialoadenitis is caused by various medications (phenobarbital, phenothiazine, ethambutol, sulfisoxazole, iodine, isoproterenol, heavy metals) and allergens. Cases without other signs of allergy have been described in the literature. Diagnosis of allergic sialoadenitis is difficult. It is recommended to exclude salivary gland infection and autoimmune disease. It is a self-limiting disease with a favorable outcome.[19]

Our patient had a mild clinical picture of sialoadenitis without damage to the salivary glands, i.e., dry mouth as irAE of nivolumab. Recovery and improvement of salivary gland function was followed by regular monitoring of serum alpha-amylase levels and results of UWS, SWS (Table 1). The therapeutic approach for dry mouth (combination of grade 1 and grade 3) was determined in consultation with a specialist in oncology. It was decided to try to restore salivary function using sialogogue and adequate hydration (artificial saliva) without administering corticosteroids (usually prednisone). For patients with irAEs, we recommend regular follow-up with a dentist or oral medicine specialist every three months, who can maintain the integrity of the oral mucosa by assessing salivary function and prescribing topical fluoridation.[1] He was referred to an internal medicine specialist (clinical immunologist and an endocrinologist) for further diagnosis. The patient was diagnosed with three irAEs: sialoadenitis, autoimmune thyroiditis, and inflammatory arthritis.

Table 1 Values of serum alpha-amylase, UWS, SWS with recovery of salivary gland function

Examination date	Serum alpha-amylase (U/L)	UWS (ml/min)	SWS (ml/min)
5/1/2021	108	0	0.1
2/2/2021	99	0	0.2
27/04/2021	62	0	0.3

*Reference value (23-91 U/L)

Conclusion

Although dry mouth is common, it should not go unrecognized in patients treated with nivolumab because timely therapeutic intervention is critical for preserving salivary function and thus quality of life (QOL).

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None.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Warner BM, Baer AN, Lipson EJ, et al. Sicca Syndrome Associated with Immune Checkpoint Inhibitor Therapy. *Oncologist.* 2019;24(9):1259–1269.
2. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol.* 2016;13(8):473–486.
3. Brahmer JR, Tykodi SS, Chow LQM, et al. Safety and activity of anti–PD-L1 antibody in patients with advanced cancer. *N Engl J Med.* 2012;366(26):2455–2465.
4. Hodi FS. Overcoming immunological tolerance to melanoma: Targeting CTLA-4. *Asia Pac J Clin Oncol.* 2010;6(Suppl 1):S16–S23.
5. Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. *Curr Opin Immunol.* 2012;24(2):207–212.
6. Calabrese LH, Calabrese C, Cappelli LC. Rheumatic immune-related adverse events from cancer immunotherapy. *Nat Rev Rheumatol.* 2018;14(10):569–579.
7. Cappelli LC, Shah AA, Bingham CO. Cancer immunotherapy-induced rheumatic diseases emerge as new clinical entities. *RMD Open.* 2016;2(2):e000321.
8. Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017;28(suppl_4):iv119–iv142.
9. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer.* 2017;5(1):95.
10. Ship JA, Pillemer SR, Baum BJ. Xerostomia and the geriatric patient. *J Am Geriatr Soc.* 2002;50(3):535–543.
11. Shiboski CH, Shiboski SC, Seror, R, et al. International Sjögren's Syndrome Criteria Working Group. 2016 ACR EULAR Classification Criteria for primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involoving Three International Patient Cohorts. *Arthritis Rheumatol.* 2017;69(1):35–45.
12. *Common Terminology Criteria for Adverse Events (CTCAE) v5.0*. National Cancer Institute; 2017. 147 p.
13. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015;26(12):2375–2391.
14. Cappelli LC, Gutierrez AK, Baer AN, et al. Inflammatory arthritis ans sicca syndrome induced by nivolumab and ipilimumab. *Ann Rheum Dis*. 2017;76(1):43–50.
15. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and longterm safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*. 2014;32(10):1020–1030.
16. Christodoulou MI, Kapsogeorgou EK, Moutsopoulos HM. Characteristics of the minor salivary gland infiltrates in Sjögren's syndrome. *J Autoimmun*. 2010;34(4):400–407.
17. Imanguli MM, Atkinson JC, Mitchell SA, et al. Salivary gland involvement in chronic graft- versus- host disease: Prevalence, clinical significance, and recommendations for evaluation. *Biol Blood Marrow Transplant*. 2010;16(10):1362–1369.
18. Baer AN, Gourin CG, Westra WH, et al. Rare diagnosis of IgG4- related systemic disease by lip biopsy in an international Sjögren's syndrome registry. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;115(3):e34–e39.
19. Grisius MM, Fox PC. Salivary gland diseases. In: Greenberg MS, Glick M, editors. *Burket's Oral Medicine Diagnosis & Tretment*. 10th ed. Medicinska naklada: Zagreb; 2006. 249–258 p.
20. Schubert MM, Sullivan KM, Morton TH, et al. Oral manifestations of chronic graft-vs-host disease. *Arch Intern Med*. 1984;144(8):1591–1595.
21. Woo SB, Lee SJ, Schubert MM. Graft versus host disease. *Crit Rev Oral Biol Med*. 1997;8(2):201–216.
22. DiGiuseppe JA, Corio RL, Westra WH. Lymphoid infiltrates of the salivary glands: pathology, biology and clinical significance. *Curr Opin Oncol*. 1996;8(3):232–237.
23. Fox PC. Saliva and salivary gland alterations in HIV infection. *J Am Dent Assoc*. 1991;122(11):46–48.
24. Schiødt M, Greenspan D, Levy JA, et al. Does HIV cause salivary gland disease? *AIDS.* 1989;3(12):819–822.
25. Pawlotsky JM, Roudot-Thoraval F, Simmonds P, et al. Extrahepatic manifestations in chronic hepatitis C and hepatitis C virus serotypes. *Ann Intern Med*. 1995;122(3):169–173.