Received: 25 July 2022 | Revised: 15 March 2023 | Accepted: 8 June 2023

DOI: 10.1002/ccr3.7662

CASE REPORT

Clinical Case Reports Open Access WILEY

Azathioprine induced acute sialadenitis: A case report

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Funding information
Qatar National Research Fund

Key clinical message

Patients presenting with acute sialadenitis need careful review of their medications. Azathioprine is one of such drugs, which can rarely induce acute sialadenitis. Prompt discontinuation of the medication leads to reversal of the patient condition.

Abstract

Acute sialadenitis is one of the rare adverse effects of azathioprine. We report a case of acute submandibular sialadenitis following initiation of azathioprine which resolved upon discontinuation of the drug.

KEYWORDS

acute sialadenitis, adverse effect, azathioprine, drug induced

1 | INTRODUCTION

Azathioprine is an immunosuppressive agent used in the treatment of a wide range of medical conditions.[1–4] Many adverse effects have been reported after using this medication.[5,6] However, to the best of our knowledge, azathioprine-induced sialadenitis was only reported once in the literature in a patient diagnosed with Crohn's disease.[7] In our case, we report acute sialadenitis following 1 week of azathioprine therapy in a patient with malignant papillary thyroid carcinoma and Grave's ophthalmopathy.

2 | CASE PRESENTATION

Thirty-nine-year-old Yemeni gentleman diagnosed with toxic multinodular goiter (Graves' disease), malignant papillary thyroid carcinoma, and thyroid orbitopathy. He underwent total thyroidectomy and received steroids along with retrobulbar radiotherapy for his orbitopathy. After failure to respond to initial treatment, patient was referred to rheumatology team, and was started on AZA (100 mg daily) and Rituximab (2 doses of 1 gram iv rituximab, 2 weeks apart).

On his first presentation to emergency department (ED), 1 week after starting the immunosuppressive medications, patient complained of neck pain and swelling associated with fever, pain and difficulty to swallow, and difficulty to breath while lying supine. Patient was conscious, oriented with stable vital signs. The physical examination revealed diffuse submandibular swelling. Trachea was central with normal cardiopulmonary examination. Proper airway assessment was carried out by the ENT team and reported that his airway is patent with normal findings in indirect and fiber-optic laryngoscopy. The laboratory investigations showed leukocytosis and elevated inflammatory markers with normal thyroid function test (TFT). Blood cultures showed no growth. Emergency neck ultrasound was performed, and it ruled out any collection or abscess. Chest and neck soft tissue X-rays were normal.

So patient was discharged on empiric antibiotics (amoxicillin/clavulanic acid) with plan to do neck CT Imaging as outpatient.

However, patient had discontinued his immunosuppressive medication since he developed his symptoms until he was reviewed by the Rheumatology team 2 days later in the clinic. As these medications were not commonly known to cause sialadenitis, plan was made to proceed with dose of second dose of rituximab and continue on daily AZA.

Unfortunately, patient returned to the ED with the same complaints in addition to drooling of saliva, 1 day after restarting AZA therapy. (Figure 1). The clinical examination and airway assessment findings were similar to his first presentation with no significant change in the size of the swelling. The CT imaging of the neck showed bilaterally enlarged submandibular glands with postcontrast heterogenous enhancement. (See Figures 2 and 3). No collection or abscess formation were seen.

Patient was admitted in ED observation unit, and rheumatology team was consulted. Based on the association of the symptoms with restarting medication, diagnosis of azathioprine-induced sialadenitis was made. Thus, AZA was stopped, and his steroid sparing agent was changed to Mycophenolate mofetil (MMF). Two days later, patient condition improved dramatically and was discharged home with plans to continue MMF and rituximab.

3 | DISCUSSION

Azathioprine (AZA) is an immunosuppressant drug that belongs to the thiopurine class. It is widely used in management of various medical disorders including inflammatory bowel diseases, autoimmune diseases, and in preventing organ transplant rejection.[1–4]

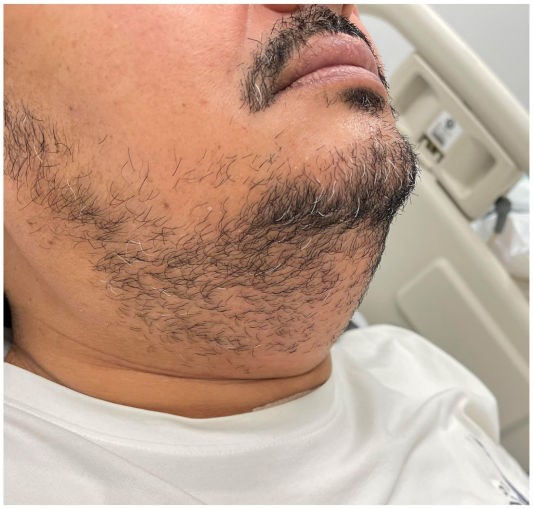

FIGURE 1 Photograph showing diffuse submandibular swelling.

Azathioprine converts to its active metabolites, mercaptopurine (6-MP) and thioguanine (6-TGN), by the action of hypoxanthine-guanine phosphoribosyltransferase (HPRT) and thiopurine methyltransferase (TPMT) enzymes.[8] The mechanism of action of azathioprine involves antagonism of purine metabolism, thus, resulting in the inhibition of DNA, RNA, and protein synthesis.[1,2,8] Its metabolites are incorporated into the replicating DNA and halt division. AZA metabolites also mediate most of its immunosuppressive and toxic effects.[8]

One of the major concerns of azathioprine treatment is the occurrence of adverse effects which consequently mandates the discontinuation of the therapy.[5,6] The reported incidence of the side effects ranges from 5% to 30% and those can be dose related (bone marrow suppression, hepatotoxicity, opportunistic infections, and risk of cancer) or dose independent (idiosyncratic and allergic reactions).[2,5,6,9] Dose-dependent side effects often need decrease of the dose and rarely require discontinuation of AZA. Dose independent reactions, however, are more common and frequently demand drug discontinuation.[9–11]

Sialadenitis is inflammation of the salivary gland. Acute sialadenitis is characterized by sudden pain and enlargement of the affected gland and chronic sialadenitis, in general, is less likely to be painful and often characterized by recurrence and abnormally firm gland. Sialadenitis may be due to obstruction, bacterial/viral infections, inflammation, or drugs.[12]

Drug-induced sialadenitis manifests in several ways, such as xerostomia, sialorrhea, saliva discoloration, sialolithiasis, and sialadenitis. A recent review has identified several drugs that may be linked with salivary gland dysfunction; however, AZA is not included in the list.[13] The etiology of drug-induced salivary dysfunction is not clearly identified, but it may involve spasm of smooth muscle of the gland, altered autonomic function interfering the sympathetic vasoconstrictor effect, anticholinergic effect, or hypersensitivity reaction.[14]

In our case, the patient was started on azathioprine for ophthalmopathy, following failure of the initial therapy, as a steroid sparing agent. 1 week later, patient developed acute sialadenitis involving the submandibular glands, which resolved upon stopping the medication. However, when patient was re-challenged with the same medication, he developed the same symptoms and signs, which supports that his sialadenitis was drug induced. We calculated the score using the Naranjo Algorithm, or Adverse Drug Reaction Probability Scale, to assess whether there is a causal relationship between the event and the drug. We got a total score of 9, suggestive of definitive drug-induced adverse drug reaction.[15]

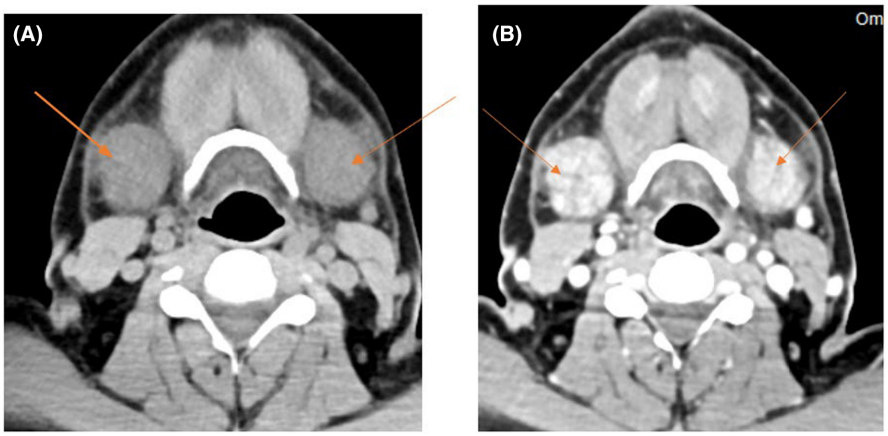

FIGURE 2 (A) Plain CT axial shows mildly enlarged bilateral submandibular salivary glands. (B) Post contract CT axial shows mildly enlarged bilateral submandibular salivary glands with heterogenous enhancement.

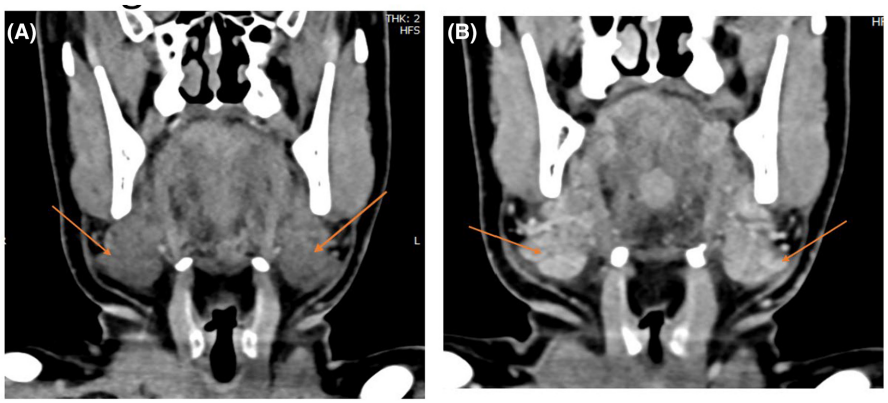

FIGURE 3 (A) Plain CT coronal shows mildly enlarged bilateral submandibular salivary glands. (B) Post contract CT coronal shows mildly enlarged bilateral submandibular salivary glands with heterogenous enhancement.

Joana da Silva reported a case of acute submandibular sialadenitis in a Crohn's disease patient treated with azathioprine.[7] That patient developed symptoms of submandibular sialadenitis 15 days after starting azathioprine, whereas our patient developed in a week time. However, in both cases, patient responded to discontinuation of the medication and had recurrence of sialadenitis on the next day of rechallenge with same drug.

In 2013, Vinayak et al. reported some cases of drug-induced sialadenitis.[14] Majority were presenting with bilateral swelling and elevation of inflammatory parameters, and two cases even presenting with fever; a clinical picture similar to our case. Some of the drugs implicated were oxyphenbutazone, nitrofurantoin, doxycycline, and enalapril, but there were no cases of azathioprine-induced sialadenitis reported in this study. As in our case, in most of the reported cases, the salivary gland swelling subsided after cessation of the offending drugs, with or without corticosteroid therapy.

4 | CONCLUSION

Acute sialadenitis is one of the rare, but reported adverse effect of azathioprine. Physicians need to be aware of it and discontinuation of the drug will lead to resolution of the condition.

AUTHOR CONTRIBUTIONS

Priyanka Moovara Cackamvalli: Conceptualization; data curation; formal analysis; funding acquisition; methodology; project administration; validation; visualization; writing – original draft; writing – review and editing. **Faten Mohammed Abdullah Al Bakri:** Conceptualization; data curation; formal analysis; investigation; writing – original draft. **Izzat Ali M. Khanjar:** Data curation; formal analysis; investigation; supervision; visualization; writing – review and editing.

ACKNOWLEDGMENTS

The authors acknowledge Syed Intekhab Alam, radiologist at Hamad Medical Corporation for reviewing the CT scan and providing images.

FUNDING INFORMATION

The publication of this article was funded by Qatar National Library.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

ETHICS STATEMENT

There is no ethical concerns relating to this case report.

CONSENT

Written informed consent has been taken from the patient to take photograph and publish this case report.

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How to cite this article: Moovara Cackamvalli P, Al Bakri FMA, Khanjar IAM. Azathioprine induced acute sialadenitis: A case report. *Clin Case Rep*. 2023;11:e7662. doi:10.1002/ccr3.7662