

Azathioprine-Induced Acute Submandibular Sialadenitis in a Crohn's Disease Patient

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Keywords

Azathioprine · Adverse effect · Sialadenitis · Crohn's disease

Abstract

Introduction: Azathioprine (AZA) is a widely used immunosuppressive drug in inflammatory bowel disease (IBD). The occurrence of adverse effects (AEs) is a major downside in the use of this drug, leading to treatment withdrawal in a variable proportion of patients. **Case Presentation:** We report the case of a Crohn's disease patient who developed sialadenitis as an AE to AZA. **Discussion and Conclusion:** To our knowledge this AE has been reported only once in the literature. Sialadenitis is a common disorder and refers to inflammation of a salivary gland. It has many causes, such as bacterial and viral infections, ductal obstruction, and drugs. There are several AEs related to this drug, categorized as dose-dependent and dose-independent. Their knowledge is essential for therapeutic management in IBD, which is already challenging, requiring an individualized approach.

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Sialadenite secundária a azatioprina em doente com doença de Crohn

Palavras Chave

Azatioprina · Efeitos adversos · Sialadenite · Doença de Crohn

Resumo

Introdução: A azatioprina é um fármaco imunossupressor amplamente utilizado na doença inflamatória intestinal. A ocorrência de efeitos adversos a ele associados é uma desvantagem na sua utilização, levando em muitos casos à necessidade da sua suspensão. **Caso clínico:** Reportamos o caso de um doente com doença de Crohn que desenvolveu quadro clínico de sialadenite secundário à azatioprina, efeito este reportado apenas uma vez na literatura. **Discussão e conclusão:** Sialadenite diz respeito a um processo inflamatório das glândulas salivares que pode ser causado por múltiplos fatores, nomeadamente farmacológicos. Têm sido reportados na literatura vários efeitos adversos relacionados com a azatioprina, sendo categorizados essencialmente em “dose-dependentes” e “dose-independentes”. O seu reconhecimento é essencial na abordagem terapêutica dos doentes com doença inflamatória intestinal, que por si só já representam um desafio de gestão.

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Introduction

Azathioprine (AZA) is an immunosuppressive therapy included in the thiopurines group that is widely used for the management of a range of scenarios in inflammatory bowel disease (IBD), namely in Crohn's disease. It still has a major role despite the new arsenal of available therapies, especially biologic therapies.

The occurrence of adverse effects (AEs) is a major downside in the use of this drug, leading to treatment withdrawal in a variable proportion of patients. The prevalence of AEs reported in the literature ranges between 5 and 30% of patients [1].

The case concerns a patient developing sialadenitis under AZA therapy, an occurrence reported once in literature [2]. Sialadenitis is a common disorder and refers to inflammation of a salivary gland; it is characterized by sudden enlargement and pain of the affected gland, accompanied by foul taste in the mouth and/or xerostomia. The presentation may be acute, chronic, or acute on top of chronic. There are many causes of sialadenitis, such as bacterial and viral infections, ductal obstruction, and drugs. There are some inflammatory disorders associated with sialadenitis, namely Sjögren syndrome, immunoglobulin G4-related, lymphoepithelial, and granulomatous sialadenitis [3]. Management varies with etiology [4, 5].

Case Presentation

We report a 40-year-old male, newly diagnosed with Crohn's disease, A2 L1 B2 according to the Montreal classification, with ileal strictures and perianal fistula. The disease presented with a perianal abscess and intestinal subocclusion. The patient was submitted to surgical drainage and seton placement in the perianal fistula. AZA was the first-line treatment, with a satisfactory clinical response.

Fifteen days after commencing AZA therapy, the patient started complaining of malaise, severe submandibular pain, and xerostomia. Bilateral inflammatory signs in the submandibular glands were noted. Cervical ultrasound showed enlarged and homogeneous bilateral submandibular glands, with no signs of sialolithiasis or abscess. Blood test revealed leukocytosis of $14 \times 10^3/\mu\text{L}$ (for a normal upper value of $11 \times 10^3/\mu\text{L}$) and an increased CRP of 79 mg/L (for a normal upper value of 5 mg/L). Sialadenitis diagnosis was assumed by otorhinolaryngology. Virus serologies were negative (namely negative IgM for mumps, cytomegalovirus, and adenovirus). AZA was discontinued and a complete improvement of the patient's condition occurred.

Given the lack of knowledge of this AZA-related AE, the drug was reintroduced 15 days after the episode. However, the next day after its reintroduction, clinical manifestation of sialadenitis recurred, again with no evidence of an associated infection or other

cause. Given this, AZA was definitely suspended, with complete resolution of the symptoms and with no other interventions required.

We used the Naranjo algorithm [6] for assessing the causality of an adverse drug reaction. It includes data such as existence of a temporal relationship with the administration of the drug, resolution after withdrawal of the drug, recurrence of the AE after re-exposure, absence of another alternative cause, and existence of a previous report on this reaction. The score obtained on this scale was 8, which was compatible with probable cause, so the decision was made to definitively discontinue AZA, with no recurrence of sialadenitis.

After AZA suspension, adalimumab failed to achieve good response and disease control, which was then obtained with infliximab plus methotrexate.

Discussion and Conclusion

AZA has been demonstrated to be an effective therapeutic tool in the treatment of IBD patients over the last 40 years [1]. Its use, however, is limited by the occurrence of AEs, whose incidence is variable in the literature [7]. The variable prevalence reported in the literature may be due to various factors, ranging from the genetic background of the population studied to the nonunivocal definition of the single side effects.

The AEs of thiopurine treatment are classified as "dose-dependent" (myelotoxicity, hepatitis, cancer, opportunistic infections) and "dose-independent." The latter group comprises a range of AEs resulting from allergic (rash, fever, arthralgia) and idiosyncratic reactions (myelotoxicity, pancreatitis, hepatitis) [8–10]. Dose-dependent AEs often respond to dose reduction and rarely require discontinuation of AZA. Idiosyncratic AEs, however, are much more common and regularly demand drug discontinuation [11, 12].

Drug-induced salivary dysfunction manifests in many ways, such as xerostomia, sialorrhoea, saliva discoloration, sialolithiasis, and sialadenitis. There is scarce literature to guide clinicians for the prescription of medications while taking into consideration the relevant AEs on salivary glands. A recent systematic review which identifies and lists medications that could objectively be associated with salivary gland dysfunction did not mention AZA [13].

The mechanism of action for drug-induced salivary swelling is largely unknown, but may include spasm of smooth muscle within the gland, altered autonomic effect with interference in sympathetic vasoconstrictor effect, anticholinergic effect, or hypersensitivity reaction [14]. In this case report, similar to what is believed to occur in

pancreatitis, a hypersensitivity reaction is most likely, since AZA does not seem to have autonomic effects.

Vinayak et al. [14] reported some cases of drug-induced sialadenitis, with the majority manifesting with bilateral swelling and elevation of inflammatory parameters, and 2 cases even presenting with fever. Some of the drugs implicated were oxyphenbutazone, nitrofurantoin, doxycycline, and enalapril. 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.

It is worth mentioning the similarities between this case and the only one described so far in the literature: both presented with bilateral involvement and elevation of analytic inflammatory markers. Furthermore, both events occurred in similarly aged men with Crohn's disease – our case with ileal involvement and the other with ileocolic disease. Although we cannot ignore these similarities, the scarce available data make it difficult to draw any conclusions.

In summary, we report an AE described only once in the literature and consider it an idiosyncratic AE. Given the increasing incidence of IBD, the use of thiopurines is expected to increase in the coming years. Therefore, it is important for physicians to recognize common and uncommon side effects associated with these drugs.

Statement of Ethics

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki), that they followed the protocols of their work center on the publication of patient data, and that no patient data appear in this article.

Disclosure Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

J.I. Alves da Silva: patient assistance during the clinical course and diagnostic investigation; conception, design, and writing of the work; literature review, namely related to the association between AZA and sialadenitis. C. Caetano: patient's assistant physician; conception, design, and writing of the work; checking that accuracy and integrity aspects of the paper were appropriately investigated and resolved; final approval of the version to be published. I. Pedroto: design and writing of the work; final approval of the version to be published.

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