Received: 9 November 2022 | Revised: 25 April 2023 | Accepted: 28 May 2023

DOI: 10.1002/ccr3.7559

CASE REPORT

Clinical Case Reports Open Access WILEY

Azathioprine-induced lymphoma in a patient with Takayasu arteritis: A case report from Iraq

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Key Clinical Message

Azathioprine, used for vasculitis and connective tissue diseases, carries long-term cancer risks. This case report raises awareness among healthcare providers about such risks and emphasizes the need for taking necessary precautions to avoid them while treating such diseases.

Abstract

We present an Azathioprine-induced lymphoma case in a 51-year-old male patient with Takayasu arteritis who presented with painless cervical swelling, itching, weight loss, and decreased appetite. This case report aims to increase awareness of the potential long-term cancer risks associated with azathioprine use in the treatment of chronic diseases.

KEYWORDS

azathioprine, lymphadenopathy, lymphoma, Takayasu arteritis

1 | INTRODUCTION

"Takayasu arteritis is a chronic, granulomatous, large-vessel vasculitis, characterized by stenosis, occlusion, and sometimes aneurysm of the aorta and its main branches, especially of the subclavian, common, and internal carotid arteries".[1] It was first described by Mikita Takayasu".[2] When treating Takayasu, systemic glucocorticoids are typically the first line of treatment.[3,4] However, most patients either do not achieve remission with glucocorticoids or relapse occurs while taking glucocorticoids. In addition, long-term treatment with glucocorticoids is linked to a variety of side effects, some of which can be quite serious. For these reasons, clinicians will often use other non-glucocorticoid drugs for the treatment of Takayasu arteritis.[5,6]

Azathioprine is one of the non-glucocorticoid drugs that has been used for the treatment of Takayasu arteritis.[7] As a result of its ability to suppress the proliferation of B and T cells after administration by inhibiting their synthesis of new purines, azathioprine has found application as an immunomodulator, immunosuppressor, and steroid-sparing agent.[8,9] Azathioprine is associated with a wide range of adverse effects, some of which are common, such as nausea, fatigue, fever, and infections; others, such as pancreatitis, pneumonitis, and tumors, are rare.[10] Using azathioprine for an extended period can compromise immune surveillance and cause DNA alterations, both of

which can lead to cancer. To reduce the drug's potential carcinogenic risk, doctors may prescribe azathioprine with caution or even limit its use in some cases.[11]

There have been several case reports of lymphoma occurrences induced by the long-term use of azathioprine in patients treated for chronic diseases.[12] Two of the most recent cases related to azathioprine-induced lymphoma were reported by Munz et al. and van de Meeberg et al., respectively, in 2018 and 2016.[13,14] To the best of our knowledge, none of these cases has been reported in a patient with Takayasu arteritis. This is the first reported case of azathioprine-induced lymphoma in a patient diagnosed with Takayasu arteritis. The purpose of presenting this case report is to raise awareness regarding the long-term risks of developing cancer while using azathioprine as a part of the treatment of vasculitis and other connective tissue diseases.

2 | CASE PRESENTATION

A 51-year-old self-employed male patient had a medical history of Takayasu arteritis. In June 2021, the patient presented with progressive painless cervical swelling in the right post-auricular region with no overlying skin changes; the condition was associated with generalized itching, decreased appetite, and consequently a weight loss of approximately 9 kg in 3 months. In 1999, the patient presented with sudden, severe pain in the left shoulder and tingling in the hands; further examination and testing revealed a large thrombus in the left axillary artery. The patient underwent bypass surgery, but it was unsuccessful; thus, he had to have his arm amputated above the elbow and was maintained on warfarin without a specific diagnosis. In 2003, the patient experienced a second attack in his right shoulder, and a successful saphenous vein bypass operation was performed. In 2005, the patient presented with right shoulder discomfort, tiredness, and fever, with no history of oral ulcers, genital ulcers, or ophthalmologic complaints; Takayasu arthritis was diagnosed based on the clinical presentation and conventional angiographic evidence of right subclavian artery stenosis with an elevated erythrocyte sedimentation rate of 83 mm/h and a negative work-up for thrombosis or connective tissue disease (protein C, protein S, homocysteine, antithrombin 3, factor V Leiden, anti-phospholipid antibodies, anti-nuclear antibodies, anti-double stranded DNA, and pathergy test). In the same year, oral prednisolone at a dose of 40 mg/day was started and tapered gradually until a regimen of prednisolone 5 mg, azathioprine 150 mg, folic acid 5 mg, vitamin B12 capsules, and calcium supplement 1000 mg/day was maintained. He is a heavy smoker (20 pack-years). He had a family history of cancer, as his first-degree relative had breast cancer. Both parents had coronary artery disease at an early age.

Physical examination revealed vital signs within normal limits and generalized lymphadenopathy affecting the cervical, supraclavicular (as shown in Figure 1A–C), axillary, and inguinal lymph nodes. The largest one is approximately 3×5 cm in diameter, firm, not tender, mobile, with well-defined borders. The overlying skin was intact, with normal color, a smooth surface, and a normal temperature. There was also widespread scratching, particularly on the lower extremities (as shown in Figure 2A,B) and the abdomen (as shown in Figure 2C,D). The femoral artery pulse was weak. The abdominal examination showed multiple ecchymoses. The liver was enlarged with a regular and smooth edge and surface with a span of 15 cm. The spleen was also palpable, 4 cm below the left costal margin. The blood investigation revealed: white blood cells 15.4×10^9/L (showed leukocytosis with absolute eosinophilia and no immature cells were seen), lymphocytes 9.48×10^9/L, monocytes 1.44×10^9/L, basophils 0.233×10^9/L, eosinophils 3.37×10^9/L, hemoglobin 15.0 g/d, platelet 371×10^9/L, C-reactive protein-titer 38.78 mg/dL, lactate dehydrogenase 522 U/L, ESR 93 mm/h, international normalized ratio 2.7, prothrombin time 29.2 s, and serum cholesterol 151 mg/dL. Neck ultrasound showed multiple enlarged cervical lymph nodes, some of which were round. loss of hilum; the largest one on the RT side measures 2.8×2.7 cm. An ultrasound of the abdomen showed that there were many enlarged lymph nodes in the parailiac area on both sides and in the inguinal area. The largest measures 5.4×2 cm and is hypoechoic with a thin hilum.

A venous doppler study of the lower limbs found multiple hypoechoic lymph nodes on both sides that had a different echotexture and had lost helium. In the right and left inguinal regions, the dimensions were 3.6×3.7 cm and 3.8×4.1 cm, respectively.

A bone marrow aspiration revealed a good number of megakaryocytes at different stages of maturation. Granulosis is very well represented with a full spectrum of maturation. Erythropoiesis is represented by normoblastic maturation. Light-chain deposition bone marrow accounts for 9% of the total. Plasma cells constitute about 2% of the cellular composition of bone marrow. The core of the bone marrow biopsy measures about 1 cm and consists of trabecular bone and marrow tissue. The available data do not indicate the presence of a neoplastic process within the bone marrow.

Microscopic examination of sections obtained from the lymph node biopsy (as shown in Figure 3) revealed a complete effacement of lymph node architecture, characterized by a proliferation of atypical lymphoid cells. These cells exhibited enlarged hyperchromatic nuclei, coarse chromatin, and prominent nucleoli, and were accompanied by a high

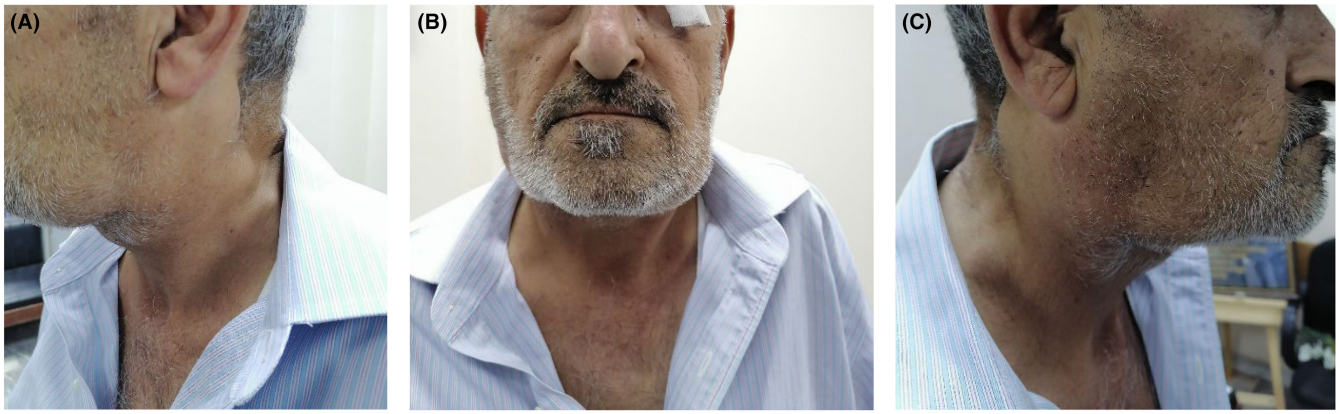

FIGURE 1 (A), (B), and (C) show the lymphadenopathy of the neck.

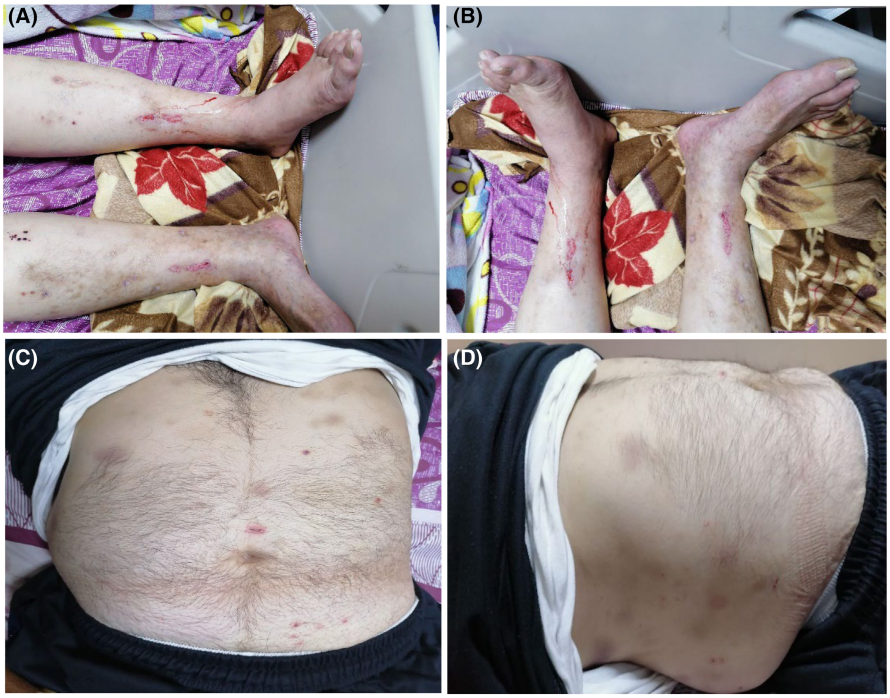

FIGURE 2 (A) and (B) showing widespread scratching marks on the legs, whereas (C) and (D) show scratching marks present on the abdomen.

frequency of mitotic figures, including atypical ones. The morphological assessment indicates a diagnosis of non-Hodgkin's lymphoma B-cell type, specifically the diffuse large B-cell lymphoma subtype with an immunoblastic-non-germinal center morphology subtype as per the Hans algorithm. Immunohistochemical analysis revealed diffuse staining for CD20 (as shown in Figure 3D), while CD3, BCL2, BCL6, CD5, CD23, Cyclin D1, and CD10 were all negative. The Ki67 positivity rate ranged from 85 to 90% (as shown in Figure 3B). Following the diagnosis of diffuse large B-cell lymphoma, the patient's azathioprine treatment was temporarily suspended, and the patient was referred to a hematologist for further management. A therapeutic regimen consisting of Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone was subsequently prescribed for the patient.

3 | DISCUSSION

Takayasu arteritis is a rare, long-lasting autoimmune disease that affects mostly the aorta and its main branches. It is marked by inflammation, thickening, and narrowing of the arteries, which can reduce blood flow to organs and tissues that need it.[15]

Azathioprine, a drug used to treat takayasu arteritis, has been linked to an increased risk of lymphoma, a type of blood cancer that affects lymphocytes. This risk is thought to be related to the drug's immunosuppressive effects on the immune system, which may make patients more vulnerable to infections and cancer. Although the risk of lymphoma is generally regarded as low in patients receiving azathioprine for autoimmune diseases such as Takayasu arteritis, azathioprine patients should be closely monitored

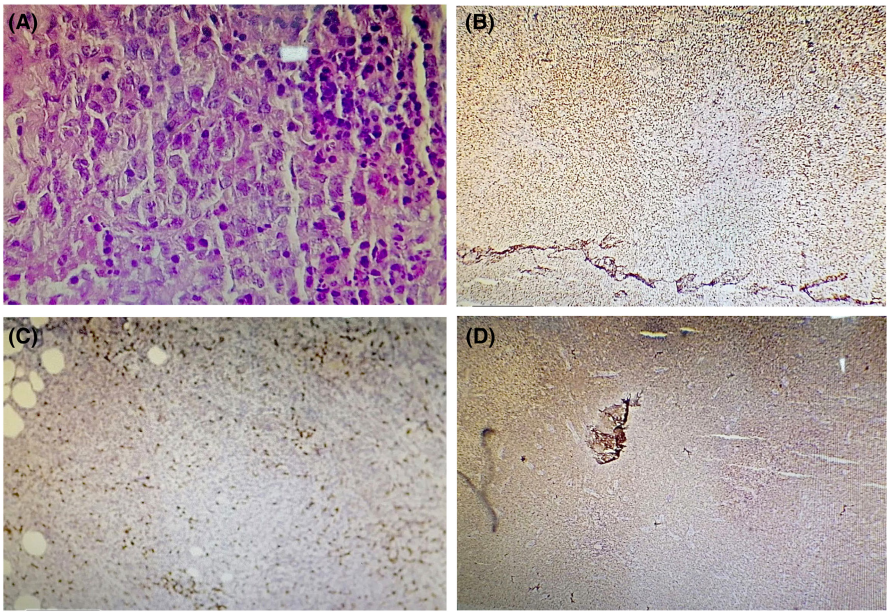

FIGURE 3 Histopathological slides obtained from the lymph node biopsy, including a high-power field view (A), as well as immunohistochemical staining for Ki67 (B), CD5 (C), and CD20 (D).

for any signs of lymphoma or other malignancies, and the benefits and risks of continuing azathioprine therapy should be carefully weighed by the treating physician.[7–9]

The extended use of azathioprine is capable of impeding immune surveillance and inducing DNA alterations, both of which have been linked to an elevated risk of developing cancer.[11] While some reports have highlighted the incidence of Hodgkin lymphoma in several immunological disorders, studies examining the correlation between azathioprine use and Hodgkin lymphoma are scarce. Notwithstanding, despite the observed increased risk of lymphoma in some cases, it is not conclusive evidence to recommend discontinuing azathioprine treatment for patients who require it. This report may be the first to document this rare presentation in Iraq; therefore, it is crucial for clinicians and healthcare providers to consider it during the management and follow-up of patients receiving this medication.

While it is not entirely possible to exclude the possibility that the augmented risk of lymphoma is related to the severity of the underlying disease rather than the medications, the magnitude of the association is unlikely to outweigh the potential benefits of azathioprine treatment for most patients. In fact, if the observed increased risk of lymphoma is partly or entirely due to the severity of the underlying disease, the benefit-to-risk ratio for these medications would be even more substantial.[12]

4 | CONCLUSION

When azathioprine is used in the treatment of vasculitis and other connective tissue diseases, one of the potential side effects of the medication is an increased risk of developing cancer in the long term. The purpose of presenting this case report is to bring awareness to these potential risks and to encourage healthcare professionals to take precautions to avoid them. We encourage healthcare professionals to consider the potential risks and benefits of using azathioprine and, if at all possible, to limit the drug's prescription. We strongly encourage researchers to explore and develop novel medications or therapeutic strategies that could replace azathioprine in the management of chronic illnesses. This could involve investigating new drugs that target specific disease pathways or developing personalized treatment regimens based on individual patient characteristics. Additionally, future studies should prioritize investigating the efficacy and safety of these new treatments through rigorous clinical trials and monitoring long-term outcomes in patients.

AUTHOR CONTRIBUTIONS

Nabaa Ihsan Awadh: Data curation; methodology; resources; writing – original draft; writing – review and editing. **Mohammed Hadi Al-Osami:** Conceptualization; data curation; project administration; supervision; writing – review and editing. **Hashim Talib Hashim:** Conceptualization; data curation; project administration; writing – original draft; writing – review and editing. **Ahmed Dheyaa Al-Obaidi:** Conceptualization; data curation; visualization; writing – original draft. **Mustafa Najah Al-Obaidi:** Formal analysis; resources; software; validation; writing – original draft. **Sumaya Abdulhasan Abdlkarim:** Data curation; project administration; validation; visualization.

FUNDING INFORMATION

No source of funding received.

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data will be available on reasonable request from the authors.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Awadh NI, Al-Osami MH, Hashim HT, Al-Obaidi AD, Al-Obaidi MN, Abdlkarim SA. Azathioprine-induced lymphoma in a patient with Takayasu arteritis: A case report from Iraq. *Clin Case Rep*. 2023;11:e7559. doi:10.1002/ccr3.7559