SHORT COMMUNICATION

Azathioprine Hypersensitivity Syndrome Mimicking Herpes Zoster and Linear IgA Dermatosis Presentation: A Case Report

Fatimah M. BUDAIR[1], Maryam M. ALFARAJ[2]*, *Khaled A. ALHARTHI[2], Mohammad W. ALTABASH[2] and Jumana ALRATROOT[2]*
*[1]Department of Dermatology, King Fahad University Hospital, Al Khobar, College of Medicine, Imam Abdulrhman bin Faisal University, Dammam, and [2]College of Medicine, Imam Abdulrhman bin Faisal University, Dammam, Saudi Arabia. *E-mail: info.maryamalfaraj@gmail.com*
Submitted Nov 19, 2024. Accepted after revision Jan 28, 2025
Published Feb 18, 2025. DOI: 10.2340/actadv.v105.42536. Acta Derm Venereol 2025; 105: adv42536.

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an autoimmune disorder characterized by necrotizing inflammation of small vessels (1). Azathioprine, commonly used in the treatment of AAV, is rarely associated with azathioprine hypersensitivity syndrome (AHS), a life-threatening dose-dependent adverse reaction involving multiple organs, including the skin. The cutaneous manifestations of AHS include maculopapular, vesicular, pustular eruptions, purpura, or erythema nodosum-like lesions, and may mimic infections, bullous skin disorders, or disease exacerbations. Due to this wide range of cutaneous presentations, a high index of suspicion is essential for timely diagnosis and discontinuation of the drug, which is generally sufficient to manage this potentially life-threatening adverse reaction (2). Herein, we report a case of AHS in a patient with AAV, presenting with cutaneous features mimicking both herpes zoster and linear IgA dermatosis. Histopathological examination revealed leukocytoclastic vasculitis. This report aims to raise awareness among clinicians regarding the diverse clinical manifestations of AHS to prevent diagnostic delays and late discontinuation of the drug.

CASE PRESENTATION

A 59-year-old Saudi Arabian woman with a 3-year history of AAV affecting the eyes, lungs, and kidneys had progressed to stage 5 chronic kidney disease. The patient was maintained on prednisone and rituximab (20 mg/day). However, rituximab was recently replaced with azathioprine (100 mg/day) due to recurrent severe infections. Two weeks after initiating azathioprine, she presented to the emergency department with a 4-day history of a skin rash. The rash initially appeared as a single red papule on the proximal thigh, accompanied by a burning sensation. It rapidly progressed to painful flaccid bullae and vesicles on an erythematous base, which was warm upon palpation (Fig. 1A). Some lesions subsequently developed a characteristic crown-jewel pattern (Fig. 1B). Additionally, vesicles emerged on an erythematous and oedematous base over the right upper eyelid and postauricular

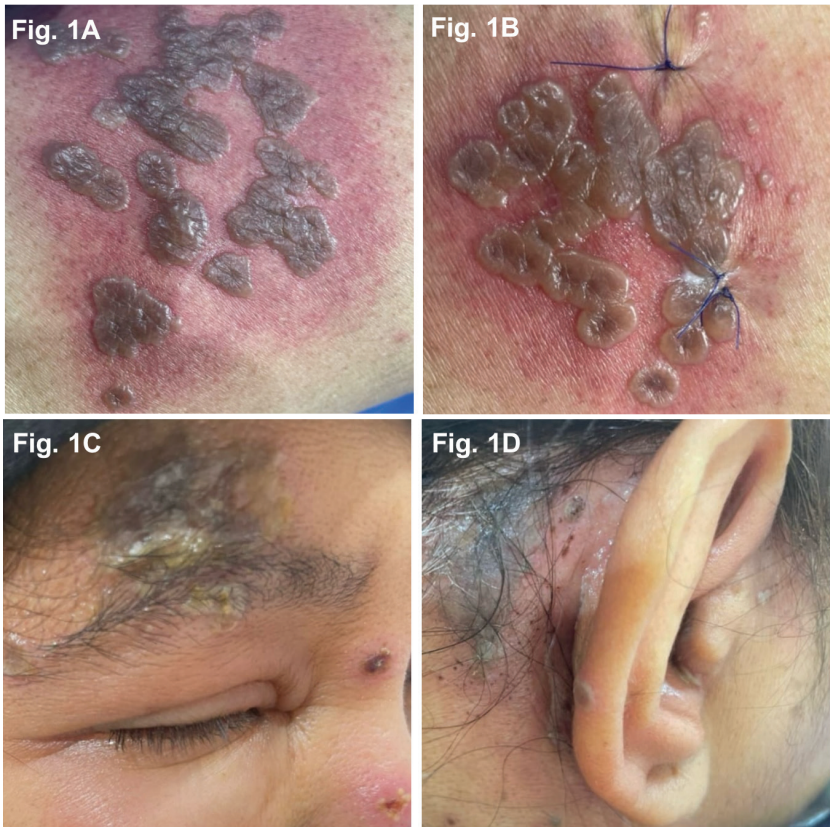

Fig. 1. Clinical presentation during the patient's emergency visit. (A) The patient developed erysipelas under-thigh lesions. (B) Lesions developed the characteristic of crown-jewel pattern. (C) Vesicles distributed along the ophthalmic nerve associated with erythematous and oedematous base. (D) Vesicles located in the postauricular area on an erythematous base.

area, preceded by a tingling sensation (Fig. 1C, D). This was associated with a severe right-sided headache and fever (38°C), unresponsive to paracetamol.

The following day, the vesicles spread to the arms, torso, and mucus membranes. The patient was admitted with a provisional diagnosis of disseminated herpes zoster (DHZ) involving the face, arms, and trunk, as well as bullous erysipelas or linear IgA dermatosis on the thigh. Blood tests revealed elevated C-reactive protein (CRP) at 2.99 mg/dL (reference range: 0.1 to 0.5 mg/dL) and erythrocyte sedimentation rate (ESR) at 72 mm/h (reference range: 0 to 30 mm/h) with normal neutrophils and lymphocyte counts. The renal function test results were consistent with baseline values. The PR3-ANCA, MPO-ANCA, and ANCA assays were negative. The patient had no history of chickenpox or varicella vaccination. Two biopsies were obtained from the annular bullous lesions on the thigh and analysed using haematoxylin and eosin (H&E) staining and immunofluorescence.

Azathioprine was discontinued, and acyclovir (834 mg IV twice per day, adjusted for renal function) and antibiotics were administered. Ophthalmological and ENT evaluations ruled out Ramsay–Hunt syndrome and herpes zoster ophthalmicus. The biopsy results revealed features consistent with small-vessel vasculitis (**Fig. 2**), showing a neutrophil-rich infiltrate within and surrounding the dermal vessels, accompanied by fibrin thrombi in the superficial vessels, with no evidence of granuloma formation in the dermis. Immunofluorescence staining for C3, IgG, IgA, IgM, and fibrinogen was negative, indicating pauci-immune vasculitis.

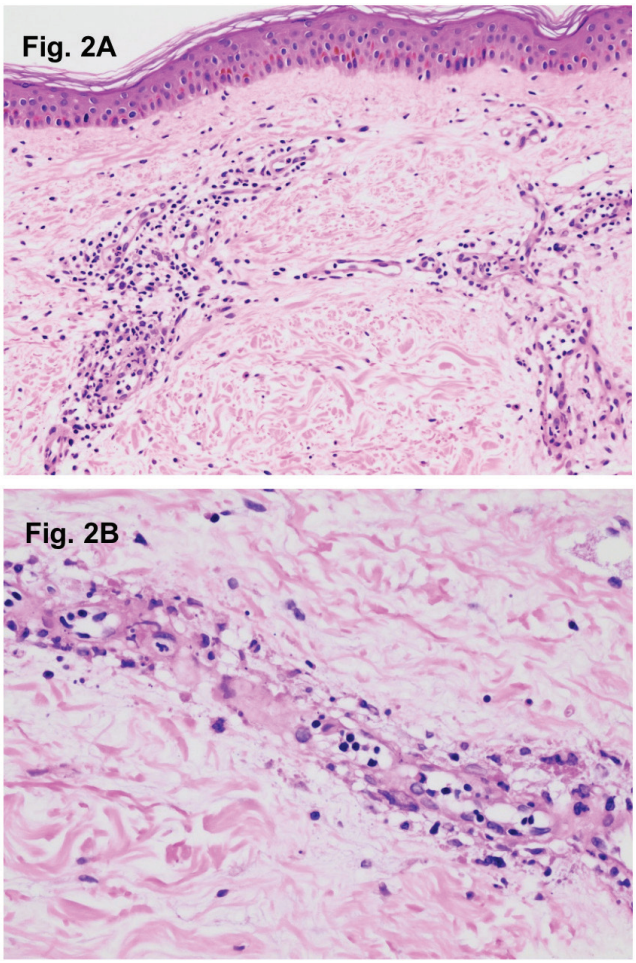

Fig. 2. Histopathology showing features of small vessel vasculitis. (A) Vasculopathic changes in the superficial dermis. (B) Leukocytoclasia.

T-Zanck smears and herpes zoster IgM tests were also negative. The patient completed a 1-week course of intravenous acyclovir. During her hospitalization, she experienced significant clinical improvement and was discharged with a diagnosis of bullous small-vessel vasculitis secondary to AHS. Mycophenolate mofetil (500 mg twice daily) was added to her treatment regimen by the internal medicine team along with prednisone. One month later, the facial lesions showed post-inflammatory hyperpigmentation, while the thigh lesions progressed to atrophic plaques. No new lesions were observed.

DISCUSSION

Immunocompromised patients and those receiving selected immunomodulator therapies, including azathioprine and oral steroids, are at increased risk of developing disseminated herpes zoster (DHZ) and generalized vesicular eruptions beyond the primary dermatome (3). In the present case, several factors initially supported a diagnosis of DHZ, including the use of dual immunosuppressive therapy, the unilateral painful vesicular eruption extending along and beyond the ophthalmic nerve distribution, associated neurological symptoms, and the absence of a history of chickenpox or varicella vaccination. Reactivation of the herpes simplex virus was also considered as a potential differential diagnosis, given its availability to mimic the disseminated vesicular eruptions observed in this patient and its documented occurrence in individuals receiving azathioprine (4, 5). However, due to the dermatomal distribution of the lesions, DHZ remains the leading diagnosis and necessitates antiviral treatment that covers both the varicella zoster virus (VZV) and herpes simplex virus (6). Despite this, the negative varicella IgM and T-Zanck smear results, combined with the histological findings of vasculitis, reduced the likelihood of DHZ or other viral infections, redirecting the diagnosis towards AHS. Nevertheless, intravenous acyclovir was continued for the full 7-day course recommended for DHZ due to the following considerations: reports have documented that immunocompromised patients can develop severe systemic varicella zoster infection, even with negative IgM (7, 8), the limited sensitivity of T-Zanck testing for VZV, and the observed clinical improvement (9). The absence of VZV PCR testing at our hospital, a key diagnostic tool for detecting VZV nucleic acids in clinical specimens, limited the ability to definitively confirm or exclude VZV activation in this case(10). Hence, we strongly recommend ordering VZV PCR testing in similar cases for more accurate diagnosis and management. Regarding the annular thigh lesions, leukocytoclastic vasculitis was found on histology, and the absence of previously reported cases of azathioprine-induced IgA bullous dermatosis helped rule out linear IgA bullous dermatosis (2).

Ultimately, these findings confirm the diagnosis of AHS. The condition presents with rare cutaneous features and histological findings of vasculitis, which are rarely reported in the literature. AHS is generally com-

mon in patients with AAV who receive azathioprine as maintenance therapy. A recent cohort study found that 9% of these patients developed AHS within 14 days despite concomitant oral steroid use associated with CRP elevation (11). Although thiopurine methyltransferase (TPMT) levels were not measured in our patient, studies have shown that TPMT genotype and activity could not predict leukopenia or other azathioprine-related adverse effects (11, 12). Therefore, the key diagnostic indicators include a history of azathioprine use and the onset of skin rash accompanied by fever or systemic symptoms within a short time of starting the drug, in addition to elevated serum CRP and, more importantly, a high sense of suspicion. These clues strongly suggest discontinuing azathioprine while investigating the definitive diagnosis, which is mandatory to avoid fatal complications associated with AHS given its variable clinical presentation.

In conclusion, dermatologists must be aware of the variable cutaneous presentations of AHS to aid prompt recognition and provide appropriate and immediate cessation of azathioprine. AHS should be considered a differential diagnosis in any patient presenting with new cutaneous and systemic symptoms following the commencement of azathioprine.

REFERENCES

1. Yates M, Watts R. Anca-associated vasculitis. Clin Med 2017; 17: 60–64. https://doi.org/10.7861/clinmedicine.17-1-60
2. Bidinger JJ, Sky K, Battafarano DF, Henning JS. The cutaneous and systemic manifestations of azathioprine hypersensitivity syndrome. JAAD 2011; 65: 184–191. https://doi.org/10.1016/j.jaad.2010.04.041
3. Bollea-Garlatti ML, Bollea-Garlatti LA, Vacas AS, Torre AC, Kowalczuk AM, Galimberti RL, et al. Clinical characteristics and outcomes in a population with disseminated herpes zoster: a retrospective cohort study. Actas Dermosifiliogr (English edition) 2017;108:145–152. https://doi.org/10.1016/j.adengl.2016.12.019
4. Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, et al. Recommendations for the management of herpes zoster. Clin Infect Dis 2007; 44.
5. Santos-Antunes J, Abreu C, Magro F, Coelho R, Vilas-Boas F, Andrade P, et al. Disseminated cutaneous herpes simplex infection in a patient with Crohn's disease under azathioprine and steroids: first case report and literature review. J Crohn's Colitis 2014; 8: 326–330. https://doi.org/10.1016/j.crohns.2013.10.011
6. Ahronowitz I, Fox LP. Herpes zoster in hospitalized adults: practice gaps, new evidence, and remaining questions. J Am Acad Dermatol 2018; 78: 223–230.e3. https://doi.org/10.1016/j.jaad.2017.07.054
7. Lin W-C, Chang C, Ko M-C, Lin S-M. A fatal case of severe systemic varicella zoster infection in a patient with chronic use of immunosuppressive agents for cutaneous vasculitis. IDCases 2019;19: e00667. https://doi.org/10.1016/j.idcr.2019.e00667
8. Whitley RJ, Gnann JW, Hinthorn D, Liu C, Pollard RB, Hayden F, et al. Disseminated herpes zoster in the immunocompromised host: a comparative trial of acyclovir and Vidarabine. J Infect Dis 1992; 165: 450–455. https://doi.org/10.1093/infdis/165.3.450
9. Chaiyabutr C, Jantanapornchai N, Apinuntham C, Leeyaphan C, Jiamton S. Comparison of the sensitivity and specificity of Tzanck smear and immunofluorescence assay for the diagnosis of cutaneous herpes simplex virus and varicella zoster virus infections in a real-life clinical setting. Siriraj Med J 2021; 73. https://doi.org/10.33192/Smj.2021.40
10. Stránská R, Schuurman R, de Vos M, van Loon AM. Routine use of a highly automated and internally controlled real-time PCR assay for the diagnosis of herpes simplex and varicella-zoster virus infections. J Clin Virol 2004; 30: 39–44. https://doi.org/10.1016/j.jcv.2003.08.006
11. Hessels AC, Sanders JS, van de Ven AAJM, Kroesen B-J, Lambeck AJA, Rutgers A, et al. Azathioprine hypersensitivity syndrome in a cohort of antineutrophil cytoplasmic antibody-associated vasculitis patients. J Allergy Clin Immunol Pract 2019; 7: 1004–1009. https://doi.org/10.1016/j.jaip.2018.10.018
12. Hessels AC, Rutgers A, Sanders JS, Stegeman CA. Thiopurine methyltransferase genotype and activity cannot predict outcomes of azathioprine maintenance therapy for antineutrophil cytoplasmic antibody associated vasculitis: a retrospective cohort study. PloS One 2018; 13: e0195524. https://doi.org/10.1371/journal.pone.0195524