

Oral ulcerations in a patient with autosomal dominant hyper-IgE syndrome (AD-HIES)

Johanna Borst ¹, Lawrence Ma²

¹School of Medicine, University of California San Diego, La Jolla, California, USA

²Department of Internal Medicine and Pediatrics, University of California San Diego, La Jolla, California, USA

Correspondence to
Dr Lawrence Ma;
lma@health.ucsd.edu

Accepted 13 October 2020

SUMMARY

A 23-year-old woman with autosomal dominant hyper-IgE syndrome complicated by recurrent pneumonia and sinusitis presented with 1 week of multiple painful oral ulcers unresponsive to empiric antiviral and antifungal treatment. Her ulcers progressively worsened and she required hospitalisation for intravenous hydration and pain control. PCR swab of an ulcer was positive for varicella-zoster virus. Her symptoms never fully resolved despite antiviral therapy, and within 2 weeks, she relapsed with new and worsening ulcers. Biopsy revealed chronic active inflammation with no evidence of viral inclusion bodies or fungal hyphae. She was diagnosed with recurrent aphthous stomatitis and referred to a local dentist for CO₂ laser treatments with rapid resolution of her symptoms. This case highlights the broad differential for recurrent oral ulcers in people with a primary immunodeficiency. It also raises awareness of the benefits of laser therapy for aphthous stomatitis treatment and the importance of partnering with our colleagues in dentistry.

BACKGROUND

Hyper-IgE syndrome (HIES), also known as Job's syndrome, is a rare primary immunodeficiency disease that affects males and females equally.¹ It classically presents with eczema, recurrent staphylococcal skin abscesses, pulmonary infections and elevated serum IgE levels.² Multisystem involvement is common with skeletal, vascular and dental malformations. Heterozygous loss-of-function mutations in the STAT3 gene are responsible for the most common autosomal dominant form of HIES (AD-HIES). STAT3 is integral for the production of both proinflammatory and anti-inflammatory cytokines and also promotes CD4 T_H17 cell differentiation.² Deficient STAT3-mediated oral immunity leads to alterations in the oral mucosal biome and predisposes to severe dental caries and recurrent oral candida infections.³ Recurrent aphthous stomatitis (RAS) is also a common oral manifestation in patients with AD-HIES due to increased production of proinflammatory cytokines such as tumour necrosis factor (TNF)-alpha.³

CASE PRESENTATION

A 23-year-old woman with AD-HIES complicated by recurrent pneumonia and sinusitis presented with 1 week of multiple painful oral ulcers (figure 1). Her oral examination was notable for >10 subcentimetre superficial erosions on the tongue, buccal mucosa and hard palate. There

were no other lesions of the mucosa or skin. She had a history of similar ulcers but prior episodes were infrequent, short-lived and never with this many symptomatic lesions at one time. Prior to presentation, she had no new exposures or illnesses. She has no known allergies. There were no changes to her medication regimen of weekly subcutaneous immunoglobulin therapy, daily fluconazole, and montelukast. Her family history was negative for autoimmune disorders. Her immunologist empirically started her on topical and systemic steroids, oral acyclovir and nystatin suspension to treat a possible viral or fungal infection. However, her symptoms did not improve and her pain continued to worsen requiring hospitalisation for intravenous hydration, pain management and further diagnostic evaluation.

The distribution and appearance of her oral lesions were suggestive of gingivostomatitis; PCR swab of an ulcer was negative for herpes simplex virus but was positive for varicella-zoster virus (VZV). She was treated with intravenous acyclovir but did not demonstrate rapid improvement. Infectious disease was consulted and did not think her presentation was consistent with VZV. Rheumatology was consulted and ordered an extensive autoimmune serological workup; she did not have any autoantibodies against: nuclear, double-stranded DNA, ribonucleoprotein, Sjogren syndrome-related antigen A (SSA), or Sjogren syndrome-related antigen B (SSB). Behcet's syndrome was unlikely as there was no history of genital ulcerations. Her pain eventually lessened on acetaminophen and gabapentin. In the absence of another clearly identifiable aetiology of her oral ulcers besides the positive VZV PCR result, she was discharged to continue oral valacyclovir.

Her symptoms never fully resolved, and within 2 weeks, she relapsed with new and worsening oral ulcers. Repeat viral PCR swabs were negative. She was referred to an otolaryngologist; biopsy of a lesion revealed pseudoepitheliomatous hyperplasia with chronic active inflammation. No viral inclusion bodies or fungal hyphae were noted. In the absence of other identifiable systemic illnesses or infectious aetiologies, her presentation was most consistent with the herpetiform subtype of RAS. Frequent occurrences of oral ulcers have been previously reported in cohort studies of patients with AD-HIES.

OUTCOME AND FOLLOW-UP

She had limited response to topical triamcinolone ointment and chlorhexidine mouthwash, which



© BMJ Publishing Group Limited 2020. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Borst J, Ma L. *BMJ Case Rep* 2020;**13**:e236705. doi:10.1136/bcr-2020-236705



Figure 1 Ulcerations of the hard palate, buccal mucosa and tongue.

are first-line treatments for RAS. She was referred to a dentist who has successfully treated oral ulcers in patients with Behçet's syndrome using topical laser therapy. A CO₂ laser with a wavelength of 9.3 micrometres operating at 10% power was applied to the larger ulcerations in her mouth. No local anaesthesia was necessary and the patient reported significant pain reduction by the end of the first session. She returned for three additional sessions at 2-week intervals before finally becoming ulcer-free. Since her initial presentation, she has had three recurrences of her aphthous stomatitis on her palate and tongue. These episodes were less severe and were treated successfully each time by the same dentist with a different low-level laser that uses photobiomodulation to manage inflammation.

DISCUSSION

AD-HIES is characterised by a number of non-immunological and immunological features. Oral manifestations include delayed dental eruption, abnormal development of permanent teeth and high-arched palates.^{4 5} Characteristic asymptomatic lesions of the palate, tongue and buccal mucosa also occur.⁶ Oral-specific infectious manifestations include mucocutaneous candidiasis, periodontitis and increased susceptibility to multiple viral infections.

The diagnostic dilemma encountered in this case stemmed from the positive VZV PCR swab from one of her oral ulcers. Patients with AD-HIES have a predisposition to VZV reactivation beginning at a young age.⁷ However, VZV is not commonly associated with solely intraoral manifestations. Even more unusual was her persistent development of new lesions despite treatment with appropriate doses of antiviral therapy. The possibility of a false-positive result was considered, but seemed unlikely given the reported high sensitivity, specificity and positive predictive values of commercially available PCR-based tests.⁸ An alternative explanation for her positive PCR is a transient stress-induced subclinical reactivation of VZV. This phenomenon has been

previously described in asymptomatic astronauts during and following space travel, in immunocompetent children hospitalised in an intensive care unit and in fatigued medical residents.⁹ VZV reactivation has been considered as a potential cause for recurrent oral aphthous stomatitis; however, various techniques including viral cultures, smears and in-situ hybridisation have not identified active replication.⁹

In the absence of an identifiable cause, the most likely aetiology for the patient's ulcers was RAS. More than 30% of patients with AD-HIES experience RAS,³ but a review of the literature reveals little discussion of the unique diagnostic and management challenges in this population. RAS has been divided into minor, major and herpetiform variants based on the number, size and healing tendencies of the lesions.¹⁰ RAS is a diagnosis of exclusion; proposed aetiologies include genetic predisposition, stress, local trauma and environmental factors, including the microbiome.¹¹ Prior studies have documented elevated levels of inflammatory cytokines including TNF-alpha in the serum, saliva and biopsied tissues of patients with RAS.¹² In vitro studies of leucocytes from patients with AD-HIES show significantly increased production of TNF-alpha following stimulation by lipopolysaccharide and other bacterial antigens.¹³ This increased inflammatory response may explain why patients with AD-HIES are particularly susceptible to developing RAS.

Treatments for RAS are primarily supportive with the goal of reducing pain and allowing patients to maintain adequate oral intake. Common first-line topical treatments are local anaesthetics, antiseptic rinses and topical corticosteroids. Systemic treatments including oral steroids, colchicine and thalidomide are used in severe cases. Monoclonal TNF-alpha inhibitors have also demonstrated efficacy in recalcitrant cases.¹⁴ Newer therapeutic options include non-ablative low-level laser therapies, which have consistently demonstrated benefits in terms of reduced pain and healing time with excellent safety profiles. The exact mechanism is unknown but proposed theories include increased ATP synthesis, changes in conduction of nociceptors and stimulation of local growth factors with resultant increased granulation tissue formation.¹⁵

Learning points

- ▶ Autosomal dominant hyper-IgE syndrome is a rare primary immunodeficiency disorder affecting multiple organ systems.
- ▶ Recurrent aphthous stomatitis is a common cause of oral mucosal ulcerations. Current pharmacological treatments focus primarily on pain relief but efficacy is limited and recurrence is common.
- ▶ Low-level laser therapy is a safe and effective therapeutic option for recurrent aphthous stomatitis that is under-recognised and underutilised by physicians.

Twitter Johanna Borst @BorstJohanna

Acknowledgements We are grateful for Dr Katya Archambault who was the dentist that provided the topical laser treatments.

Contributors LM managed the case. JB and LM conceived the idea for the article. JB performed the literature search. JB and LM wrote the article. LM is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Johanna Borst <http://orcid.org/0000-0002-1838-0852>

REFERENCES

- Bergerson JRE, Freeman AF. An update on syndromes with a hyper-IgE phenotype. *Immunol Allergy Clin North Am* 2019;39:49–61.
- Yong PFK, Freeman AF, Engelhardt KR, et al. An update on the hyper-IgE syndromes. *Arthritis Res Ther* 2012;14:228–28.
- Abusleme L, Diaz PI, Freeman AF, et al. Human defects in STAT3 promote oral mucosal fungal and bacterial dysbiosis. *JCI Insight* 2018;3. doi:10.1172/jci.insight.122061. [Epub ahead of print: 06 Sep 2018].
- Mogensen TH. Primary immunodeficiencies with elevated IgE. *Int Rev Immunol* 2016;35:39–56.
- Domingo DL, Freeman AF, Davis J, et al. Novel intraoral phenotypes in hyperimmunoglobulin-E syndrome. *Oral Dis* 2008;14:73–81.
- Freeman AF, Domingo DL, Holland SM. Hyper IgE (job's) syndrome: a primary immune deficiency with oral manifestations. *Oral Dis* 2009;15:2–7.
- Siegel AM, Heiwall J, Freeman AF, et al. A critical role for STAT3 transcription factor signaling in the development and maintenance of human T cell memory. *Immunity* 2011;35:806–18.
- Leung J, Harpaz R, Baughman AL, et al. Evaluation of laboratory methods for diagnosis of varicella. *Clin Infect Dis* 2010;51:23–32.
- Pedersen A, Madsen HO, Vestergaard BF, et al. Varicella-Zoster virus DNA in recurrent aphthous ulcers. *Scand J Dent Res* 1993;101:311–3.
- Edgar NR, Saleh D, Miller RA. Recurrent aphthous stomatitis: a review. *J Clin Aesthet Dermatol* 2017;10:26–36.
- Slebioda Z, Szponar E, Kowalska A. Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: literature review. *Arch Immunol Ther Exp* 2014;62:205–15.
- Hegde S, Ajila V, Babu S, et al. Evaluation of salivary tumour necrosis factor-alpha in patients with recurrent aphthous stomatitis. *Eur Oral Res* 2018;52:157–61.
- Holland SM, DeLeo FR, Elloumi HZ, et al. Stat3 mutations in the hyper-IgE syndrome. *N Engl J Med* 2007;357:1608–19.
- de Perosanz-Lobo D, Latour I, Ortega-Quijano D, et al. Severe recurrent aphthous stomatitis treated with adalimumab: a case report in a teenage patient. *Pediatr Dermatol* 2019;36:986–7.
- Suter VGA, Sjölund S, Bornstein MM. Effect of laser on pain relief and wound healing of recurrent aphthous stomatitis: a systematic review. *Lasers Med Sci* 2017;32:953–63.

Copyright 2020 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <https://www.bmj.com/company/products-services/rights-and-licensing/permissions/>
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

Customer Service

If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.

Visit casereports.bmj.com for more articles like this and to become a Fellow