CASE REPORT

Pemphigus vulgaris: a rare cause of dysphagia

Ali Al-Janabi,¹ Simon Greenfield²

¹East and North Hertfordshire
NHS Trust, Stevenage, UK
²Lister Hospital, Stevenage, UK

Correspondence to
Dr Ali Al-Janabi,
ali.al-janabi@nhs.net

Accepted 8 October 2015

SUMMARY

Pemphigus vulgaris is a rare autoimmune blistering disease of the skin and mucous membranes. The case reported presented unusually with dyspepsia that was not responsive to protein pump inhibitor (PPI) therapy. This progressed to severe dysphagia and odynophagia. An esophagogastroduodenoscopy showed extensive ulceration of the esophagus, and direct immunofluorescence of an esophageal biopsy showed bright intercellular staining with C3 and IgG, confirming the diagnosis of pemphigus vulgaris. Immunological remission was achieved after a number of courses of pulsed intravenous methylprednisolone and cyclophosphamide. The patient has remained in remission for 5 years, but has required regular dilation of esophageal strictures for symptom relief. During this period, a chronic lymphocytosis was incidentally noted on routine blood tests, and chronic lymphocytic leukaemia was diagnosed. It is essential to investigate PPI-resistant symptoms, dysphagia and odynophagia, as they may indicate a serious underlying cause.

BACKGROUND

Pemphigus vulgaris is a disease of the skin and mucous membranes, and carries a risk of significant morbidity and mortality. Esophageal disease is rare but usually occurs in the context of previously diagnosed cutaneous pemphigus. This case is unusual in that esophageal disease was the only presenting feature. The patient was initially treated for suspected gastroesophageal reflux disease (GERD), but protein pump inhibitor (PPI)-resistant symptoms and significant ulceration of the esophagus in the presence of normal pH manometry prompted consideration of alternative diagnoses. Once the diagnosis was reached, treatment was successful with high-dose immunosuppression. This demonstrates the importance of considering rare conditions in any differential diagnosis.

CASE PRESENTATION

A 72-year-old man presented to a gastroenterology clinic, with a history of dyspepsia that was not responding to omeprazole. Over the following 2 years, he developed a progressive dysphagia, such that he felt food was becoming stuck in his throat; he often had to regurgitate it. He was eventually unable to swallow solid food, and developed odynophagia. There were no cutaneous or mucosal lesions on clinical examination at initial presentation, though at follow-up appointments, oral erosions were present. The patient's grandfather had died of pharyngeal cancer, though there was no other relevant family history.

INVESTIGATIONS

An initial esophagogastroduodenoscopy (EGD) showed an esophageal web at 22 cm and erosions consistent with grade 3 esophagitis. Twenty-four-hour pH manometry was normal, excluding GERD as a cause of his symptoms. At a subsequent EGD, the left vocal cord was inflamed, and the esophagus was ulcerated, had a friable lining and had a stricture at 22 cm (figure 1). A biopsy sample stained with H&E showed stratified squamous epithelium with acute and chronic inflammatory cell infiltrate. There was no evidence of vasculitis, and immunohistochemistry excluded esophagitis caused by herpes simplex virus or cytomegalovirus. Given the lack of response to high-dose PPI and normal pH manometry, a blistering disease of the esophagus was considered. Direct immunofluorescence showed bright intercellular staining with C3 and IgG, confirming the diagnosis of pemphigus vulgaris (figure 2). Indirect immunofluorescence detected intercellular IgG on monkey esophagus at a titre of 1/10, and desmoglein-3 antibodies were identified on ELISA. Blood tests on initial assessment were normal, but there was a persistent lymphocytosis noted at follow-up, with a white cell count of $24.2 \times 10^9/L$, lymphocyte count of $10.16 \times 10^9/L$, haemoglobin of 12.6 g/dL and platelet count of $232 \times 10^9/L$. The patient was referred to haematology, and was diagnosed with chronic lymphocytic leukaemia following peripheral blood flow cytometry.

TREATMENT

There was an inadequate response to 80 mg of oral prednisolone. Azathioprine was started as an adjunct, but 1 week later the patient developed an acute hypersensitivity reaction characterised by a generalised, target-shaped maculopapular rash affecting the trunk and all four limbs (erythema multiforme). He was then started on pulsed intravenous methylprednisolone and cyclophosphamide. After this, his symptoms improved and he was found to be in immunological remission, confirmed by negative direct immunofluorescence. He was

Figure 1 Inflamed left vocal cord. Area of stenosis and ulceration in the distal esophagus.

CrossMark

To cite: Al-Janabi A, Greenfield S. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-212661

Figure 2 Direct immunofluorescence showing bright intercellular staining with C3 and IgG, diagnostic of pemphigus. Image courtesy of St John's immunofluorescence laboratory.

switched to oral prednisolone, 50 mg oral cyclophosphamide and 1.5 g mycophenolate mofetil daily. After 2 years of weaning down prednisolone, all immunosuppressants were stopped.

OUTCOME AND FOLLOW-UP

The patient has remained in immunological remission for 5 years since stopping all immunosuppressant medications. He still requires regular gastroscopies and dilations due to recurrent esophageal strictures.

DISCUSSION

Blistering in pemphigus vulgaris results from a loss of intercellular adhesion of keratinocytes (acantholysis) caused by IgG autoantibodies against desmoglein. Untreated, pemphigus vulgaris is often fatal. Mortality has been reduced to 5–15% with corticosteroid therapy.¹ Morbidity results from skin failure and steroid side effects. While mucosal involvement is common, esophageal disease is rarely reported and usually occurs in the context of previously diagnosed oral or cutaneous pemphigus vulgaris.² Only three published cases could be found where esophageal involvement was the sole manifestation of the disease.^{2–4} In this case, oral lesions were not present until 2 years after initial presentation. Pemphigus is not known to cause cancer, though the co-occurrence of esophageal pemphigus vulgaris and squamous cell carcinoma has been reported.⁵

Esophageal pemphigus vulgaris most commonly presents with dysphagia and odynophagia.⁶ Haematemesis is rare but has been reported.⁷ It is speculated that the majority of esophageal pemphigus cases are asymptomatic, and that its incidence has been underestimated. One study demonstrated positive direct immunofluorescence of esophageal specimens in patients with pemphigus vulgaris, several of whom had no suggestive clinical, macroscopic or histological features.⁸ Blisters, erosions and an easily detached esophageal lining (Nikolsky sign) are the most common findings on endoscopy.⁹ As with cutaneous pemphigus vulgaris, acantholysis and intraepidermal vesicles are the characteristic histological features,¹⁰ this has been demonstrated in previous cases (figure 3).^{2 7 11} Interestingly, acantholysis was not seen in the samples examined in this case, and only inflammatory infiltrates and reactive epithelial changes were present. The definitive diagnosis of pemphigus vulgaris is made by direct immunofluorescence.

Figure 3 Histology of pemphigus vulgaris, demonstrating suprabasal epidermal acantholysis and an intraepidermal vesicle. Image used with permission from DermNet NZ.

Oral corticosteroids are the primary agents used to treat pemphigus vulgaris. If unsuccessful, adjuvant immunosuppressants such as azathioprine can be used. In particularly severe or steroid-resistant disease, treatment options include pulsed intravenous steroid and cyclophosphamide, mycophenolate mofetil, intravenous immunoglobulin or plasma exchange.¹² Ultimately, the goal is to induce remission and then minimise the steroid dose to avoid treatment complications and side effects. Three relatively recent cases demonstrated success in symptom control with high-dose oral prednisolone, though in two of these, long-term prednisolone was required for symptom control.^{2 4 13} Houghton *et al* used intravenous methylprednisolone first line to induce clinical remission, presumably due to the severity of the clinical presentation and endoscopic findings.

Paraneoplastic pemphigus (PNP) can occur as a consequence of chronic lymphocytic leukaemia as well as from other malignancies. As in pemphigus vulgaris, blistering occurs due to autoantibody-mediated acantholysis. However, it usually

Patient's perspective

- My initial consultation I felt was disappointing. There was no examination, based on the assumption I had a hiatus hernia. Things were getting worse with my mouth and throat getting very sore, and also having several mouth ulcers. I again visited my GP and was referred to the Gastric Clinic. This resulted in having a device inserted down my throat for 24 h. I was told to obtain the results from my GP. I visited my GP, who suggested I get the result from the Consultant. This was totally unacceptable as I was told there was nothing wrong. When I asked what to do, I was told to 'change my lifestyle'. I pointed out that I was a 99% teetotaler and 100% non-smoker. I was very disappointed and returned to my GP for more help at this point. I was referred to the Endoscopy Unit and, for the first time, I felt a doctor was taking an interest, and things started to improve. From then on the care and treatment I received were second to none.
- As an adjunct to this, my grandfather had died of 'throat cancer' (death certificate). My father did not have a problem and died aged 75 years. It may well be a genetic condition.

manifests clinically as a progressive, painful stomatitis, and the diagnosis requires the demonstration of antipapilloma antibodies, acantholysis on histology and the diagnosis of a lymphoproliferative neoplasm.¹⁴ These are the four diagnostic criteria for PNP, proposed by Anhalt in 2004. The absence of progressive stomatitis and acantholysis made a diagnosis of PNP unlikely in this case.

Learning points

- Persistent esophageal ulceration in the context of normal esophageal manometry should raise suspicion of other disease processes.
- Pemphigus is a rare but serious cause of esophageal disease.
- Esophagogastroduodenoscopy and biopsy are the most important investigations if the diagnosis is uncertain.
- Remission in pemphigus vulgaris can be achieved with pulsed intravenous steroids and cyclophosphamide.
- Pemphigus may be a paraneoplastic manifestation, so it is important to investigate for underlying malignancy.

Contributors AA-J conducted the review of the patient's case notes, review of the literature and the writing of the case report. SG was responsible for identifying and managing the case, as well as reading and suggesting improvements to several drafts, and in agreeing on the final report.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Ahmed AR, Moy R. Death in pemphigus. *J Am Acad Dermatol* 1982;7:221–8.
- 2 Faías S, Lage P, Sachse F, *et al.* Pemphigus vulgaris with exclusive involvement of the esophagus: case report and review. *Gastrointest Endosc* 2004;60:312–15.
- 3 Württenberger A, Barnert J, Wienbeck M. [Long-lasting odynophagia and haematemesis—the only clinical signs of a pemphigus vulgaris]. *Z Gastroenterol* 2002;40:419–24.
- 4 Salem Z, Strippoli A, DePasquale JR. Isolated esophageal pemphigus vulgaris. *Am J Gastroenterol* 2003;98:201.
- 5 Takahashi O, Okushiba S, Kondo S, *et al.* Esophageal pemphigus vulgaris with carcinoma: post-operative steroid therapy based on pemphigus-related antibodies. *Dis Esophagus* 2005;18:413–17.
- 6 Khamaysi I, Eliakim R. Esophageal pemphigus vulgaris: a rare manifestation revisited. *Gastroenterol Hepatol* 2008;4:71–2.
- 7 Houghton JP, Iannosi-Irimie M, Trooskin SB, *et al.* An unusual presentation of pemphigus vulgaris. *Gastroenterol Hepatol* 2008;4:68–70.
- 8 Trattner A, Lurie R, Leiser A, *et al.* Esophageal involvement in pemphigus vulgaris: a clinical, histologic and immunopathologic study. *J Am Acad Dermatol* 1991;24:223–6.
- 9 Greenwald DA, Brandt LJ. Esophageal disorders due to systemic disease. In: DiMarino AJ, Benjamin SB, eds. *Gastrointestinal disease: an endoscopic approach*. 2nd edn. Thorofare, NJ: SLACK Incorporated, 2002:231–2.
- 10 Sawant P, Satarkar RP, Chopda N, *et al.* Esophageal involvement in pemphigus vulgaris. *Indian J Gastroenterol* 1994;13:133–4.
- 11 Dermnetnz.org. Image display. DermNet NZ. 2015 (cited 29 Sep 2015). <http://www.dermnetnz.org/common/image.php?path=/pathology/img/e/pv-figure-1.jpg>
- 12 Harman KE, Albert S, Black MM. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003;149:926–37.
- 13 Palleschi GM, Cipollini EM, Lotti T. Development of oesophageal involvement in a subject with pemphigus vulgaris: a case report and review of the literature. *J Eur Acad Dermatol Venerol* 2002;16:405–8.
- 14 Anhalt GJ. Paraneoplastic pemphigus. *J Invest Dermatol Symp Proc* 2004;9:29–33.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-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

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

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