CASE REPORT

Pemphigus vegetans with coexistent herpes simplex infection and deep venous thrombosis of the lower extremities

Rachel Marchalik,¹ Jeave Reserva,² Malgorzata Anna Plummer,³ Marylee Braniecki⁴

¹Georgetown University School of Medicine, Washington DC, USA

²Division of Dermatology, Loyola University Medical Center, Chicago, Illinois, USA

³Department of Surgery/Division of Vascular Surgery, University of Illinois at Chicago College of Medicine/Advocate Christ Medical Center, Chicago, Illinois, USA

⁴Department of Pathology, University of Illinois at Chicago College of Medicine, Chicago, Illinois, USA

Correspondence to

Rachel Marchalik,
rjb254@georgetown.edu

Accepted 2 July 2015

SUMMARY

An elderly patient presented with a 4-month history of eroded hypertrophic condylomatous plaques with areas of vesiculation on the groin and lower extremities bilaterally, associated with swelling. Biopsy and immunofluorescence studies confirmed the diagnosis of pemphigus vegetans (PVeg). Further clinical evaluation revealed deep venous thrombosis of the lower extremities and septic shock from secondarily infected pemphigus lesions. Fluid obtained from vesicles was positive for herpes simplex virus (HSV) via PCR-based testing. The patient was therapeutically anticoagulated, treated with high-dose corticosteroid therapy, broad-spectrum intravenous antibiotics and acyclovir. This case represents a constellation of diagnoses not previously described. Although pemphigus vulgaris has been linked to thromboembolic events and has been associated with HSV, these associations have not been previously reported in PVeg. The coexistence of these diseases should encourage vigilance in the clinical work up of a patient with PVeg.

BACKGROUND

Pemphigus is an autoimmune disease characterised by lesions on the skin and/or mucosal membranes; two main subtypes of pemphigus exist: pemphigus vulgaris (PV) and pemphigus foliaceus, with PV accounting for approximately 70% of all cases. Pemphigus vegetans (PVeg) is the rarest clinical variant of PV, accounting for 1–2% of all pemphigus. It is characterised by vegetating plaques primarily localised to the flexural areas.¹ Its management is similar to that of PV. However, because of its rarity, data on its prognosis and clinical course are limited. We report a case of PVeg in a patient who presented with septic shock and deep venous thrombosis (DVT) of the lower extremities bilaterally, and discuss its diagnosis and treatment, with special attention to disease associations.

CASE PRESENTATION

An elderly patient with a medical history of traumatic brain injury and dementia presented with a 4-month history of eroded hypertrophic condylomatous plaques with areas of vesiculation on the lower extremities bilaterally, associated with some swelling. The patient had been mostly immobile at home and had experienced worsening appetite for the last several weeks prior to presentation. He reported diffuse pruritus but denied any lower

Figure 1 Hypertrophic vegetating inguinal plaques.

extremity pain, fever, chills, dyspnoea or chest pain. He had a known 30-pack-year smoking history but denied illicit drug use. Vital signs revealed tachycardia. Physical examination revealed macerated hypertrophic, condylomatous confluent papules and plaques in the inguinal region bilaterally, and intergluteal folds with anal sparing, associated with focal erosions and bleeding (figure 1).

Vesicular and pustular confluent hypertrophic papules and plaques were noted on the thighs, shins and dorsal feet, with bilateral pitting oedema and a negative Nikolsky sign (figures 2 and 3). Oral examination revealed poor dentition with small anterior gingival erosions.

INVESTIGATIONS

Laboratory studies demonstrated anaemia and absolute peripheral eosinophilia (1500 cells/ μ L) without leucocytosis. Bilateral DVTs were noted on ultrasonography.

Multiple punch biopsies revealed intraepidermal acantholysis with surface erosion, eosinophilic spongiosis, marked papillary oedema and superficial perivascular mononuclear cells with abundant eosinophils (figure 4). Direct immunofluorescence (DIF) revealed intercellular deposition of IgG and C3

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To cite: Marchalik R, Reserva J, Plummer MA, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-210143

Figure 2 Vesicular and pustular confluent hypertrophic papules and plaques in the thighs, shins and dorsal feet, with bilateral pitting oedema.

(figure 5). A diagnosis of PVeg was rendered on clinicopathological correlation.

Pseudomonas aeruginosa and a few *Staphylococcus aureus* were isolated on wound cultures. Fluid obtained from vesicles was positive for herpes simplex virus (HSV) via a PCR-based testing.

DIFFERENTIAL DIAGNOSIS

The main entity in the differential diagnosis is pyodermitis-pyostomatitis vegetans (PPV), which clinically is indistinguishable from PVeg but has negative DIF findings and is associated with diffuse T-cell lymphoma, ulcerative colitis and visceral malignancies.¹

TREATMENT

In addition to therapeutic anticoagulation, the patient was treated with aggressive fluid resuscitation and broad-spectrum antibiotics and fungal coverage.

The patient was promptly started on 80 mg of prednisone daily. High dose intravenous acyclovir was started when PCR for HSV was found to be positive. Further workup revealed a negative faecal occult blood test suggesting his anaemia was due to chronic disease.

OUTCOME AND FOLLOW-UP

After 4 weeks of treatment, the patient was seen in follow-up at an outpatient clinic. Complete resolution of the inguinal and

Figure 3 Vesicular and pustular confluent hypertrophic papules and plaques in the thighs, shins and dorsal feet, with bilateral pitting oedema.

lower extremity plaques was noted with some post-inflammatory pigmentary alteration (figure 6). The patient was subsequently lost to follow-up and died of unknown causes several months following discharge. We were unable to obtain additional follow-up information from the patient's family; hence, the cause of his death remains unknown at this time.

DISCUSSION

PVeg is a rare variant of PV, an autoimmune disease characterised by flaccid bullae or pustules that erode to form hypertrophic papillated plaques primarily localised to the flexural areas. It is the rarest clinical variant of PV accounting for 1–2% of all pemphigus.²

PVeg is caused by the formation of antidesmosome antibodies, primarily against desmogleins 1 and 3, which are the calcium-binding transmembrane glycoprotein component of desmosomes of keratinocytes. The disease can therefore be diagnosed by noting the presence of these antibodies.³

As an autoimmune disease, PVeg has historically been treated with immunosuppressants (mainly corticosteroids).² Although the mortality associated with pemphigus has declined, long-term systemic corticosteroid use is associated with major side effects such as hypertension, diabetes mellitus and osteoporosis.

Figure 4 H&E sections showing areas of epidermal hyperplasia with intraepidermal acantholysis (A) and surface erosion, eosinophilic spongiosis and abscess formation (B), marked papillary oedema and superficial perivascular mononuclear cells with eosinophils.

Figure 5 Intercellular staining pattern ('chicken-wire') of IgG (A) and C3 (B) on direct immunofluorescence.

Figure 6 Complete resolution of the inguinal and lower extremity plaques with some post-inflammatory pigmentary alteration.

However, isolated steroid treatment is often insufficient in achieving disease remission.⁴ In addition, patients on chronic immunosuppressive therapy are often susceptible to opportunistic infections, which may lead to sepsis. Ruocco *et al*⁵ demonstrated an association between HSV infections and the onset and/or exacerbations of PV. Although it has not been reported in other cases of PV, our patient tested positive for HSV.

Thus, the use of steroid-sparing agents on a long-term basis may be a preferred management option for these patients. Research has shown that agents such as azathioprine, mycophenolate mofetil and dapsone may improve the rate of remission in these patients.^{1–4} Recently, rituximab therapy was shown to be useful in treating recalcitrant PVeg. In a recent meta-analysis by Ahmed and Shetty, 500 patients with recalcitrant PV were treated with rituximab while simultaneously receiving corticosteroid treatment. Remission was noted in 90–95% of patients within 2 months, with complete resolution of symptoms occurring within 3–4 months. Although the incidence of relapse was significant, a small percentage of patients remained in remission without further treatment,³ suggesting that future research

should be directed toward exploring the efficacy of rituximab in the treatment of PVeg.

Aforementioned, the clinical course of PVeg is often complicated by secondary infections due to immunosuppression from therapy. However, septic shock at presentation is not uncommon, as demonstrated by our case. Although it has not been reported in PVeg, onset and/or exacerbations of PV has been associated with HSV.⁵ In addition, there is evidence suggesting that pemphigus increases the risk for venous thrombosis.⁶ However, at this point, the relationship is still an association, and the true aetiology of the thrombi, whether it was PVeg, sepsis or an underlying malignancy, remains unclear. Of note, however, PVeg is much less commonly associated with malignancies compared with its main differential diagnosis, PPV.⁴ Although speculative, it is possible that infectious complications due to chronic immunosuppressive therapy with corticosteroids may have played a role in the patient's death.

Acknowledgements The authors would like to thank Dr Rahel John, MD for providing the immunofluorescence pictures for this case. They appreciate the additional clinical information provided by Dr John Keane, MD, Dr Ruchita Patel, DO, and Dr Mitali Roy, MD. They also greatly appreciate Dr Rasheed Hammadeh MD for allowing them to use Advocate Christ Medical Center's Pathology Department's digital photomicrograph camera.

Competing interests None declared.

Patient consent Not obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- ▶ Little is known about the clinical presentation and treatment of pemphigus vegetans, a rare disease entity representing 1–2% of all pemphigus cases.
- ▶ Pemphigus has been associated with increased risk of thromboembolic events and pemphigus vulgaris has been linked to herpes simplex virus.
- ▶ The association of thromboembolic events and herpes simplex virus with pemphigus vegetans represents a unique and clinically significant disease association.
- ▶ The constellation of these diseases should encourage clinicians to remain vigilant in working up potential associated conditions when treating patients with pemphigus vegetans.

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