Unusual association of diseases/symptoms

Nasal pemphigoid: a diagnostic dilemma

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Cicatricial pemphigoid is a chronic, systemic, immunobullous disorder affecting mucous membranes. Nasal manifestations of cicatricial pemphigoid are less common than in the rest of the upper aero-digestive tract, and may prove difficult to diagnose and manage effectively. We report one such case presenting with isolated nasal symptoms, in which diagnosis, treatment and ongoing management of the underlying cause was particularly challenging. A literature review was performed to ascertain the incidence of cicatricial pemphigoid and to establish the best evidence-based investigation and treatment.

BACKGROUND

This case report demonstrates how relatively common clinical conditions can sometimes present unusually. The authors have written this case report to remind clinicians to develop a wide-ranging differential diagnosis when investigating such conditions and to adopt a multi-disciplinary approach to treatment if possible.

CASE PRESENTATION

A 35-year-old man referred from rheumatology, presented to the ear, nose and throat (ENT) outpatient clinic with a 4-month history of recurrent bilateral epistaxes but with no history of trauma. They were primarily anterior in origin and had become increasingly frequent. He denied any other nasal symptoms. His medical history included ulcerative colitis for which he was on a maintenance dose of mesalazine, but this was currently quiescent.

Examination revealed large amounts of blood clot and crusting bilaterally within both anterior nares, and scarification of the nasal cavity. (figure 1)¹ Examination of the ears and throat was unremarkable. Biopsies were taken of the nasal mucosa, and the patient was treated conservatively and commenced on 40 mg of prednisolone empirically and a referral to the rheumatology department was made.

At his ENT follow-up appointment, the patient reported a reduction in epistaxes, but complained of ulcers on his palate and an acneiform rash on his head and neck. Clinical examination of the nose and oral cavity demonstrated atrophic nasal mucosa and fluid-filled bullae on the hard palate. The patient was treated with nasal moistening with glycerine as an adjunct to his existing treatment and was consented for further biopsies under general anaesthetic.

The disease further progressed to involve skin flexures despite ongoing treatment; hence, the patient was referred to a dermatology outpatient clinic where skin biopsies were performed.

INVESTIGATIONS

Autoimmune screen revealed a raised perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) titre of 1/20

raising the possibility of an underlying vasculitic process but chest x-ray, urinalysis and renal function were all normal.

Biopsy of lesions within the nasal cavity demonstrated active chronic inflammation and focal necrosis. Further haematological analysis demonstrated detectable levels of immunoglobulin G (IgG) to herpes simplex virus and serum angiotensin-converting enzyme (ACE) levels were elevated at 68 (normal range 8–52).

Mucosal biopsies from the septum and palate showed chronic inflammatory changes with no evidence of malignancy or fungal growth. Additional haematological analysis revealed normal Venereal Disease Research Laboratory serology for syphilis, cytoplasmic-ANCA (c-ANCA) and repeat serum ACE levels were normal.

Figure 1 Endoscopic view of the nasal septum with crusting in Little's area.¹

Figure 2 Direct immunofluorescence microscopy of a skin biopsy in bullous pemphigoid, which was labelled with fluorescein-tagged antibody to immunoglobulin G (IgG). Linear reactivity is seen at the epidermal basement membrane (anti-IgG immunofluorescence, $\times 200$).²

A skin biopsy demonstrated linear IgG and C3 basement membrane deposits consistent with bullous pemphigoid, cicatricial pemphigoid and epidermolysis bullosa acquisita. Other immunofluorescent studies confirmed the diagnosis of cicatricial pemphigoid (figure 2).²

DIFFERENTIAL DIAGNOSIS

- ▶ Wegner's granulomatosis
- ▶ Behçet's disease
- ▶ Herpes zoster
- ▶ Herpes simplex
- ▶ Bullous pemphigoid
- ▶ Toxic epidermal necrolysis
- ▶ Stevens-Johnson syndrome
- ▶ Erythema multiforme

TREATMENT

The patient was treated with Lymecycline, a broad spectrum tetracycline antibiotic. In addition, nicotinamide (vitamin B3) and adcortyl in Orobace were also prescribed with an increased dose of 60 mg prednisolone.

OUTCOME AND FOLLOW-UP

The patient responded well to treatment and is regularly followed up in both ENT and dermatology outpatient clinics.

DISCUSSION

Cicatricial pemphigoid is a chronic, systemic, immunobullous disorder affecting mucous membranes with an incidence of 1 in 12 000–20 000. Typically, fluid-filled bullae gradually manifest on mucous membranes leaving scarring and involution as the disease progresses. Cicatricial pemphigoid is relatively rare with an unknown incidence in the general population. It is twice as common in women and most commonly occurs between the third and seventh decades of life. There is no geographic or ethnic variation. In the head and neck, cicatricial pemphigoid predominantly affects the oral cavity (85–90%) and eyes (66%), but rarely affects the larynx (10–20%) and nose (15–20%).^{3 4}

Oral symptoms include odynophagia and palpable ulcers, which may be noticed by the patient, occurring with or without insult to the oral cavity. Presentation in the larynx comprises dysphonia, cough, laryngeal stenosis, and when severe stridor and airway obstruction. Nasal symptoms include epistaxis (as in this case), rhinorrhoea, crusting, nasal obstruction and perforation of the septum.^{3–6} Nasal obstructive symptoms may arise from a variety of phenomena caused by the underlying disease. Turbulent airflow is commonly known to cause a sensation of obstruction and may occur from scarification, perforation or crusting of the nasal cavity. Stenosis of the nasal valve and choanae through scarification may also contribute to this.

Skin lesions are found in one-third of patients with cicatricial pemphigoid, occurring on the scalp, head and neck, thorax and genitals. While isolated oral cicatricial pemphigoid carries a good prognosis, disease at other sites or in multiple sites carries a worse prognosis and is typically difficult to treat.⁴ Examination reveals vesiculobullous lesions with mucous membrane scarring and involution.

Differential diagnoses should be broad based and encompass a variety of aetiologies including infective and vasculitic. In particular, serious underlying systemic conditions must be excluded such as toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme. Herpes zoster, herpes simplex and varicella should be considered as readily treatable pathogens. Wegener's granulomatosis and Behçet's may also present with chronic granulomatous changes on both mucous membranes and skin and may be difficult to differentiate from cicatricial pemphigoid.⁴ In this case, we note the medical history to include ulcerative colitis. While there is no link with HLA-B27, an association with pemphigoid and HLA-DR4 is known, which is implicated in several other autoimmune conditions.^{4 6}

Investigation of cicatricial pemphigoid, as in this case, may prove problematic, particularly when the biopsy yields non-specific chronic inflammatory change. Culture of fluid released from bullae is unlikely to aid diagnosis without a clear history of preceding viral illness. Ideally, immunofluorescence is necessary and should be obtained from a skin biopsy.⁶ This may be elusive in cases where there are isolated lesions, for instance in the nasal cavity, but would classically demonstrate linear IgG and C3 deposits on the basement membrane in 80–100%.^{3–6}

Treatment of cicatricial pemphigoid is difficult. There is no agreed regimen that effectively treats cicatricial pemphigoid as the disease is rare and randomised control trials are therefore not feasible. Often, a combination of topical and systemic immunomodulatory agents is utilised under multidisciplinary guidance. Commonly, this takes place in a dermatology-led clinic, with representation from ophthalmology, rheumatology, otolaryngology and immunology. Treatment may include steroids that have a stronger evidence base compared to alternative immunosuppressants such as azathioprine, mitomycin C or tetracyclines. A more expensive therapy of late involves intravenous immunoglobulin infusions but the evidence base for this extends to approximately 40 cases and is yet to be extensively used.⁶

Learning points

- ▶ Cicatricial pemphigoid should be considered as part of a wide-ranging differential diagnosis, particularly when presented with vesiculo-bullous lesions associated with nasal crusting and epistaxis that fail to respond to first-line treatment for common conditions.
- ▶ Immunological and histological investigation should be considered when there is evidence of systemic involvement or multifocal pathology to obtain a diagnosis and prevent morbidity associated with the condition.
- ▶ A multidisciplinary approach is advised in order to ascertain the best treatment for the patient, particularly when there is valuable past individual experience, in order to preserve quality of life and prevent disease-related complications.

Competing interests None.

Patient consent Obtained.

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