CASE REPORT

A middle-aged man presenting with unexplained mucosal erosions and progressive dyspnoea

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SUMMARY

Paraneoplastic pemphigus (PNP) is a rare syndrome driven by antibodies (IgG) binding to desmogleins and other epidermal proteins leading to skin erosions. In rare instances, these same IgG proteins may also target the bronchial mucosa leading to an irreversible fibrotic reaction within the epithelium and subsequent obstructive lung disease. A 51-year-old man presented to the emergency department with 2–3-month history of dyspnoea as well as oral and genital ulcerations and inguinal lymphadenopathy. The ulcerations were biopsied and proven to be consistent with pemphigus. Subsequent inguinal lymph node biopsy implicated the hyaline-vascular variant of Castleman's disease (CD), as the primary cause of the patient's pemphigus. The patient underwent pulmonary function testing that demonstrated severe airflow obstruction. The patient was diagnosed with PNP and associated bronchiolitis obliterans syndrome (BOS). He was treated with rituximab for his CD, and oral and inhaled corticosteroids along with azithromycin for his BOS.

BACKGROUND

Paraneoplastic pemphigus (PNP) is a rare syndrome driven by antibodies (IgG) binding to desmogleins and other epidermal proteins, leading to skin erosions.^{1 2} In rare instances, these same IgG proteins may also target the bronchial mucosa, leading to an irreversible fibrotic reaction within the epithelium and subsequent obstructive lung disease. Interestingly, bronchial mucosal oedema has been reported with many cases of bronchiolitis obliterans syndrome (BOS) but was not observed with this patient during bronchoscopy.³ The case also highlights that there will only be one antigen present from the patient's serum in some cases.² Our patient had elevated desmoglein antibodies at 141.3 units (reference range <9 units). This is an important consideration, as patients such as ours often cannot tolerate a surgical lung biopsy.

CASE PRESENTATION

A 51-year-old man presented to the emergency department (ED) with 2–3 months of ulcerative lesions of the conjunctive, mouth and penis, as well as progressive dyspnoea on exertion. He denied cough, chest pain, orthopnoea and lower extremity oedema. Prior to presentation, outpatient therapy with multiple rounds of antibiotics, a brief course of inhaled steroids and bronchodilators had failed. The patient denied having ever smoked and recent travel; and no occupational exposures were discerned. There was no significant respiratory medical

or family history prior to this hospitalisation. On presentation, the patient was afebrile with stable vital signs, and not hypoxic. Physical examination was significant for oral ulcerations and diminished bilateral breath sounds on lung examination. While in the ED, he underwent laryngoscopy for symptoms of dysphonia and odynophagia. Laryngoscopy revealed prominent erythema extending from the oropharynx through the supraglottic region.

INVESTIGATIONS

For evaluation of his dyspnoea, a chest radiograph was performed, which did not show an acute pulmonary process. Multidetector CT pulmonary angiography study did not show evidence of pulmonary embolus but did show lower lobe cylindrical bronchiectasis (figure 1). Transthoracic echocardiography was performed, which showed preserved left and right heart function. Initial laboratory evaluation showed a normal complete blood count and chemistry profile. Serological connective tissue disease evaluation revealed positive antinuclear antibody (ANA) testing with negative anti-Smith, negative ribonucleoprotein, negative Sjögren's syndrome A (SSA) and negative SSB antibodies, and +double stranded-DNA. The ANA was rechecked 1 week later and was negative. Blood and urine cultures were performed and finalised as negative.

Biopsy of the lower lip mucosa was performed. The mucosa exhibited suprabasilar acantholysis and occasional necrotic squamous cells in the squamous epithelium. Serological analysis revealed elevated desmoglein antibodies at 141.3 units (reference range <9 units). When combined with staining consistent with intracellular IgG, C3 and C5-b9 in the squamous mucosa on immunofluorescence microscopy, the diagnosis of PNP was favoured.

Given concerns for PNP based on the presence of suprabasilar acantholysis as well as the desmoglein antibodies, the patient underwent a CT of the abdomen and pelvis, which revealed a 3.5×4 cm lymph node of the right inguinal region that was also avid on positron emission tomography scan (figure 2). Excisional lymph node biopsy of the enlarged right inguinal lymph node demonstrated a regressed germinal center, hyalinised vasculature and prominent stromal changes consistent with the hyaline vascular variant of Castleman's disease (CD; figure 3).

Given his progressive dyspnoea and suspicion for BOS, the patient underwent pulmonary function testing (PFT), which showed a forced expiratory volume in 1 s (FEV₁)/forced vital capacity of 44% with FEV₁ of 0.73 L (18% predicted) without

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Figure 1 Axial chest CT scan showing cylindrical bronchiectasis in the bilateral lower lobes.

significant bronchodilator response. The total lung capacity was 110% with residual volume of 299% predicted consistent with the air trapping of obstructive lung disease. Carbon monoxide diffusing capacity (DLCO) was not measured. Owing to an area of ground glass changes on chest imaging, we performed a bronchoscopy. The bronchoalveolar lavage demonstrated 88% neutrophils, 10% alveolar macrophages and 2% lymphocytes, and grew low levels of β -haemolytic strep, group C. Gross inspection of the airway did not reveal bronchial mucosal oedema as has been reported with some cases of BOS.³ Transbronchial biopsy was deferred based on the limited extent of the infiltrate.

DIFFERENTIAL DIAGNOSIS

The ulcerative lesions could be related to several conditions, including herpes, pyoderma gangrenosum, Behçet's or other

Figure 2 Positron emission tomography CT scan showing focal increased uptake within the right inguinal lymph nodes.

Figure 3 Excisional biopsy revealing atrophic follicles surrounded by small mature lymphocytes with prominent 'onion skin pattern' and expansion of paracortex by numerous blood vessels, fibroblasts and focal hyalinisation.

aetiologies. The respiratory symptoms of progressive dyspnoea could be consistent with chronic obstructive pulmonary disease, asthma, pulmonary vascular disease or parenchymal lung disease. The patient's previous failure to improve with inhaled steroids and bronchodilators would make obstructive lung disease less likely. Pathologically, the suprabasilar acantholysis of the lower lip could represent a number of skin disorders including pemphigus vulgaris and its variants, PNP, Hailey-Hailey disease, Darier's disease and Grover's disease. The clinical presentation and presence of occasional necrotic squamous cells in the squamous mucosa, together with intracellular IgG, C3 and C5-b9 in the squamous mucosa on immunofluorescence microscopy, favoured the diagnosis of PNP. Coupled with obstruction on PFT along with Castleman's syndrome on the excisional lymph node biopsy, it was felt that the patient's disease best fit PNP with BOS.

TREATMENT

The patient was started on budesonide-formoterol 160/4.5 μ g/inhalation as well as azithromycin 250 mg three times weekly along with the previously started oral steroid. These are treatments previously studied in bronchiolitis obliterans (BO) after bone marrow transplantation.⁴ The patient was treated with rituximab for his CD.

OUTCOME AND FOLLOW-UP

The patient experienced improvement in his dyspnoea and was discharged home on 2 L home oxygen. He has required intermittent hospitalisations for exacerbations of his BOS; however, he has continued to reside in his home over 1 year after diagnosis.

DISCUSSION

BOS associated with PNP is a rare cause of obstructive lung disease. It most often occurs in association with non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, CD, thymoma, retroperitoneal sarcomas and Waldenstrom's macroglobulinaemia.⁵ The index case was first described in 1990 in a patient with malignant follicular large cell lymphoma and used five criteria to classify the disease: painful mucosal erosions and a polymorphous skin eruption, cutaneous histological changes, deposition of IgG and complement in the epidermal

intercellular spaces, serum antibodies that bind the cell surface of skin and mucosa, and a complex of four proteins immunoprecipitated from keratinocytes by these antibodies.¹ Our patient met three criteria: painful mucosal erosions, cutaneous histological changes and an antibody against desmosomes.

The mechanism of injury implicated in PNP causing BOS is IgG deposition on the bronchial epithelium with subsequent irreversible fibrotic reaction.^{1–5} Hence, quick suppression of the acute phase of this inflammation is recommended.³ Immunophoresis has been tried with limited success in this setting in BO caused by neoplastic aetiologies.⁶ Our patient was treated with a combination of oral prednisone, budesonide–formoterol and azithromycin 250 mg three times weekly—treatments adopted from the treatment of BO from other aetiologies.²

Approximately 70 cases of PNP had been reported by 2001, of all pathological subtypes. Most of these cases did not have BOS and most were associated with malignancy; only seven cases at that time reported PNP in association with CD.

Learning points

- Castleman's disease (CD) is a rare cause of paraneoplastic pemphigus (PNP) and bronchiolitis obliterans syndrome (BOS).
- When lung biopsy is not feasible, antidesmoglein antibodies may be the only positive findings to make the diagnosis.
- BOS from PNP from CD should be considered in those with new obstructive lung disease complicated by new skin eruptions.

Of those, only two with PNP from CD had BOS. In this patient population, BOS is generally a poor prognostic indicator and these patients generally die within months of diagnosis.² Our patient is significant in that he continues to do well after an advanced age of presentation with infrequent hospitalisations for his BOS.

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