Respiratory Medicine Case Reports 51 (2024) 102085

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case Report

Paraneoplastic pemphigus with airway involvement

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ARTICLE INFO

Handling Editor: DR AC Amit Chopra

ABSTRACT

We report a case of paraneoplastic pemphigus presenting with acute hypoxemic respiratory failure due to bronchiolitis obliterans which improved with high dose systemic corticosteroids, rituximab, niacinamide and doxycycline. This is the first report, to our knowledge, of paraneoplastic pemphigus with airway involvement which included niacinamide and doxycycline as therapy and demonstrated treatment response.

1. Introduction

Paraneoplastic pemphigus (PNP) is a rare autoimmune disorder most commonly associated with lymphoproliferative disease including non-Hodgkin lymphoma. Clinical symptoms are characterized by painful oral mucosal lesions with involvement of the nasopharynx, conjunctiva and gastrointestinal tract also reported [1]. Pulmonary involvement manifesting as dyspnea and hypoxia due to bronchiolitis obliterans (BO) signals a worse prognosis with progressive respiratory failure or pneumonia typically resulting in death [1,2]. Treatment of PNP associated BO is largely supportive with use of systemic and inhaled steroids and bronchodilators in addition to cancer-directed therapy. However, BO often progresses despite response to therapy of the underlying malignancy [1–3]. Additional studies on potential therapeutics in PNP associated BO is needed. Here we report a case of a patient found to have PNP associated BO presenting with severe hypoxemia with treatment response to high dose systemic steroids, rituximab, niacinamide and doxycycline.

2. Clinical presentation

A 55-year-old female with recent diagnosis of follicular lymphoma is admitted to the hospital after presenting for subacute worsening dyspnea, scant hemoptysis and hypoxemia. Treatment of the lymphoma consisted of rituximab, cyclophosphamide, doxorubicin and vincristine (R–CHOP) with the course complicated by neutropenic stomatitis requiring total parenteral nutrition (TPN). The chemotherapy regimen had been completed three months prior to presentation. The patient described new onset exertional dyspnea and cough with scant bloody sputum over the past month prompting her to seek additional care. She also endorsed ongoing mouth pain with oral ulcers on hard and soft palate, odynophagia, ulceration of the left lower lip and scalloping of the tongue (Fig. 1). She was noted to be hypoxic in the Emergency Department with oxygen saturation of 80 % on room air. She was placed on nasal cannula but subsequently transitioned to high flow nasal cannula (HFNC) requiring 80 % FiO2. Labs were notable for normal white blood cell count, BNP, troponin and procalcitonin. Nasopharyngeal swab for COVID-19, influenza A/B, RSV PCR were negative. HSV PCR swab of her oral lesions was negative. Portable chest x-ray was negative for acute cardiopulmonary disease. CT angiogram of the chest demonstrated a small right lower segmental branch filling defect suspicious for embolus and bilateral lower lobe bronchial wall thickening.

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https://doi.org/10.1016/j.rmcr.2024.102085
Received 11 September 2023; Received in revised form 11 June 2024; Accepted 3 July 2024
Available online 5 July 2024

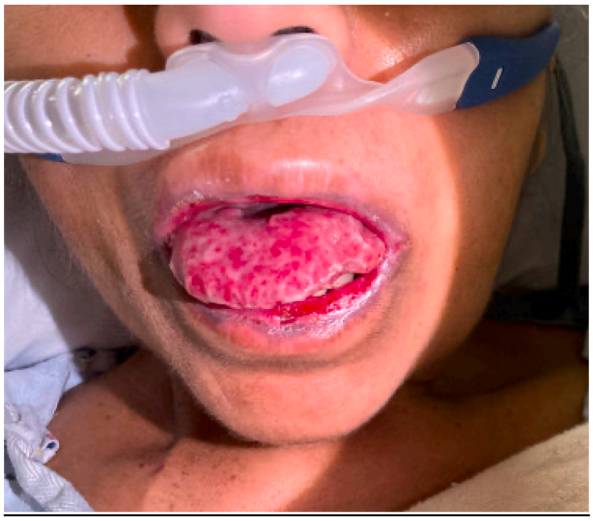

Fig. 1. Severe mucositis with scalloping of tongue.

Therapeutic enoxaparin was initiated for the pulmonary embolus, and she was started on a fluticasone-salmeterol inhaler for airway reactivity symptoms. Dermatology was consulted and given high suspicion for paraneoplastic pemphigus (PNP), prednisone, niacinamide, and doxycycline were initiated. Punch biopsy of her buccal mucosa was performed by Otorhinolaryngology with pathology demonstrating suprabasilar acantholysis with mucosal epithelial detachment, subepithelial chronic inflammation and reactive changes. Immunofluorescence exam noted "lace-like" staining of the lower-third keratinocytes with antibodies to IgG and C3 compatible with a diagnosis of paraneoplastic pemphigus. Serum pemphigus antibody panel and paraneoplastic pemphigus antibody screening panel were negative. Additional therapy was initiated with rituximab. A high-resolution CT Chest (HRCT) was obtained to assess the discordance between the severity of her hypoxemia and the presence of only a small subsegmental PE on initial imaging. HRCT demonstrated lower lung predominant bronchial wall thickening with marked mosaic attenuation consistent with bronchiolitis obliterans (BO) (Fig. 2). Findings on the HRCT were suspected to be a result of airway involvement from paraneoplastic pemphigus given absence of atopy or prior respiratory symptoms. The patient's hypoxemia and respiratory symptoms improved with treatment of systemic and inhaled steroids. She was eventually weaned off supplemental oxygen at rest prior to discharge but required 1 L/min via nasal cannula on exertion. Oral ulcers and odynophagia improved prior to discharge.

Patient was seen in clinic for follow-up one month after discharge and pulmonary function tests were attempted but unable to be completed due to severe anxiety. She continued to require supplemental oxygen on exertion but otherwise had stable symptoms.

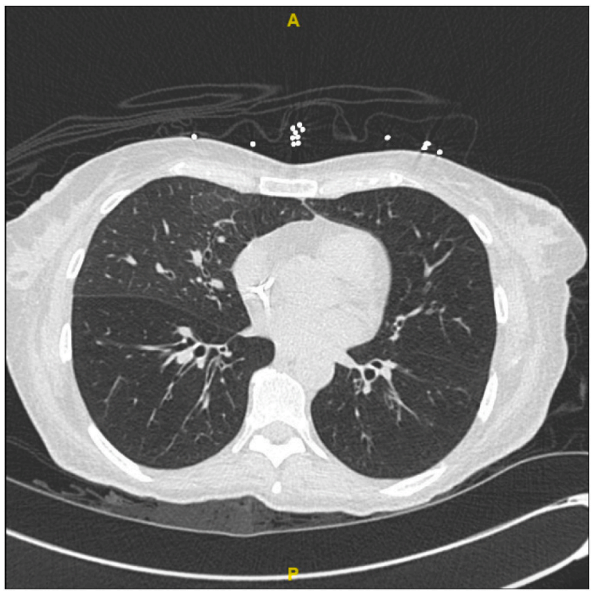

Fig. 2. Axial slice from Computed Tomography of Chest demonstrating mosaicism and bronchial wall thickening.

3. Discussion

PNP is a rare autoimmune disorder that is usually associated with an underlying malignancy. It has a poor prognosis with mortality rates reported as high as 90 % with most patients dying within a year after diagnosis [1]. It is most commonly associated with hematologic disorders including non-Hodgkin's lymphoma, chronic lymphocyte leukemia, Castleman's disease, carcinoma, thymoma, and sarcoma [2]. Manifestations of paraneoplastic pemphigus include painful mucocutaneous lesions, gastrointestinal damage, and bronchiolitis obliterans. Patients can have autoantibodies that target at desmosome-related cadherin-like molecules and plakin proteins that connect the cadherin-like molecules and cytokeratin filaments [2].

Paraneoplastic pemphigus typically presents with painful mucosal erosions and dusky patches on the skin that later desquamate. Most patients also develop widespread, and often severe, mucosal lesions that can be the earliest presenting symptom of the disease [3]. Due to extensive epidermal loss patients can develop extreme dehydration, protein depletion, and have increased risk of infection. These patients should receive care in an intensive care unit and treated similarly to burn patients. Extracutaneous involvement by paraneoplastic pemphigus can occur in the eyes, lungs, gastrointestinal tract, thyroid and kidney [4]. Pulmonary manifestations include shortness of breath, obstructive lung disease, hypoxemia and/or pneumonia that can quickly progress to bronchiolitis obliterans. Association with bronchiolitis obliterans (BO) portends a high mortality rate due to an unknown mechanism but presumably autoantibodies play a role [4].

Diagnosis is based on clinical and histopathological findings, the presence of anti-plankin autoantibodies, and underlying neoplasms [5]. Evaluation of an underlying malignancy is mandatory if paraneoplastic pemphigus is the leading consideration.

Below is listed proposed diagnostic criteria by Anhalt et al. termed “paraneoplastic autoimmune multiorgan syndrome” (PAMS) [6].

- Clinical: painful mucosal erosions with or without accompanying polymorphous cutaneous lesions in the setting of an underlying malignancy
- Histopathology: suprabasal (intraepidermal) acantholysis, interface dermatitis, and keratinocyte necrosis
- Direct Immunofluorescence: IgG and complement (C3) deposition within the intercellular spaces of the epidermis, often with linear, granular basement membrane zone deposition
- Indirect Immunofluorescence: detection of autoantibodies targeting intercellular proteins found in transitional or stratified squamous epithelia
- Immunoprecipitation: precipitation of characteristic proteins – desmoplakin-1, bullous pemphigoid antigen, desmoplakin-2, periplakin, alpha-2-macroglobulin-like-1 antigen

While serum paraneoplastic pemphigus antibodies by indirect immunofluorescence were negative in our patient, her clinical presentation of respiratory failure with bronchiolitis obliterans, history of lymphoma and histopathology with direct immunofluorescence were consistent with a diagnosis of PAMS. Although presence of paraneoplastic pemphigus antibodies has high specificity (up to 98.9 %) [7], sensitivity of these studies varies and when negative, do not exclude the diagnosis of PAMS [8].

No randomized therapeutic trials exist due to the rarity of paraneoplastic pemphigus. Treatment options include systemic glucocorticoids, rituximab, plasmapheresis, intravenous immunoglobulin, topical tacrolimus, and myeloablation with cyclophosphamide. Initiation of high dose corticosteroids is first line therapy along with diagnosis and treatment of the underlying malignancy. Additional systemic immunosuppressants (such as azathioprine or mycophenolate mofetil) may be required if the disease continues to progress or is refractory to treatment with steroids alone [4,9]. While cancer directed therapies and immunosuppression have demonstrated some efficacy in cutaneous and mucosal manifestations of PNP, BO is irreversible and often is the cause of death in PNP patients [10]. Treatment of BO is often supportive with bronchodilators, inhaled and systemic corticosteroids and directed treatments of malignancy. A recent case report offers hope for improved outcomes with specific cancer directed therapies in a patient with BO due to PNP secondary to follicular lymphoma [11]. In select patients, lung transplant may be required. Our patient was also treated with nicotinamide and doxycycline which have been shown to have potential benefit as adjunctive therapy for treatment of pemphigus vulgaris [12]. Her improvement in respiratory status with lymphoma treatment, high dose steroids, nicotinamide and doxycycline demonstrates potential for reversibility of PNP associated airways disease with early aggressive treatment and raises the possible therapeutic role of nicotinamide and doxycycline in BO associated with PNP. Further study is needed to identify treatment options for PNP associated BO.

CRediT authorship contribution statement

Oscar A. Estrada Paz: Writing – original draft. **Timothy J. Young:** Writing – original draft, Writing – review & editing.

Declaration of competing interest

No conflict of interest.

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