



Case report

Unicentric castleman disease complicated by paraneoplastic bronchiolitis obliterans and pemphigus

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ABSTRACT

Bronchiolitis obliterans (BO) and paraneoplastic pemphigus are rare and ominous complications of Castleman disease. Collectively, these processes have been reported as part of paraneoplastic autoimmune multiorgan syndrome (PAMS), and they can occur in the setting of various hematologic malignant tumors, carcinoid tumors, and melanoma. Irrespective of the underlying malignancy driving PAMS, the clinical outcomes are uniformly poor, and there are no standard treatment regimens, given the clinical rarity of the syndrome. We describe 2 patients with unicentric Castleman disease complicated by paraneoplastic pemphigus and bronchiolitis obliterans. In addition to primary surgical resection for Castleman disease, we also used therapy from a treatment protocol used for bronchiolitis obliterans resulting from hematopoietic stem cell transplant (HSCT). We were able to treat the patients using intravenous immunoglobulin; rituximab; fluticasone, azithromycin, and montelukast (FAM); and rosuvastatin therapy. One patient demonstrated a favorable response, while the other demonstrated minimal response to this therapy.

1. Introduction

Bronchiolitis obliterans and paraneoplastic pemphigus (PNP) are rare, ominous complications of Castleman disease [1], and they have been reported as part of paraneoplastic autoimmune multiorgan syndrome (PAMS) [2]. Irrespective of the underlying malignancy driving PAMS, the clinical outcomes are uniformly poor because of secondary respiratory failure and no standard treatment regimen, given the clinical rarity of the syndrome. We describe 2 patients with PAMS secondary to Castleman disease. In conjunction with treatment for Castleman disease, the patients also received therapy based on a transplant protocol for bronchiolitis obliterans and standard therapy for pemphigus [3–5] (intravenous immunoglobulin [IVIg], rituximab, and rosuvastatin; and fluticasone, azithromycin, and montelukast [FAM therapy]) [3–5].

1.1. Case reports

A 39-year-old woman without a smoking history was evaluated for dyspnea on exertion. She had a history of recurrent unicentric Castleman disease complicated by PNP (Fig. 1). Her initial pulmonary function tests (PFTs) in August 2017 showed a forced vital capacity (FVC) of 63% and a forced expiratory volume in the first second of expiration (FEV₁) of 37% (FEV₁/FVC ratio, 59%). Computed tomography (CT) showed mild, diffuse bronchial wall thickening and multiple patchy areas of air-trapping consistent with small airway disease (Fig. 2). After initiation of the above treatment regimen, the patient's respiratory symptoms began to improve (Fig. 3). However, shortly thereafter, she discontinued azithromycin and rosuvastatin because of muscle aches, which she said were intolerable. Repeat PFTs in December 2017 showed progressive respiratory failure (FVC, 55%; FEV₁, 23%; FEV₁/FVC ratio, 43%). Currently, she is undergoing extracorporeal photopheresis, which has been used to treat patients with

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Abbreviations

CT	computed tomography
IVIg	intravenous immunoglobulin
FEV ₁	forced expiratory volume in the first second of expiration
FVC	forced vital capacity
HSCT	hematopoietic stem cell transplant
PAMS	paraneoplastic autoimmune multiorgan syndrome
PFT	pulmonary function test
PNP	paraneoplastic pemphigus

2. Discussion

Among patients with Castleman disease who succumb to PAMS, the most common cause of mortality is progressive respiratory failure due to bronchiolitis obliterans, for which there are no agreed upon therapeutic options. The mechanism for this respiratory failure, initially proposed by Nousari et al., [6] is related to the unique autoantibodies in PNP. Unlike pemphigus vulgaris, which has autoantibodies to desmogleins 1 and 3 that do not cross-react with respiratory epithelia, various autoantibodies of PNP do react (desmoplakin I, bullous pemphigoid antigen I, desmoplakin II, envoplakin, periplakin, plectin, a previously unidentified 170 kD protein, and α -2-macroglobulin-like-1) [6–8]. Rat

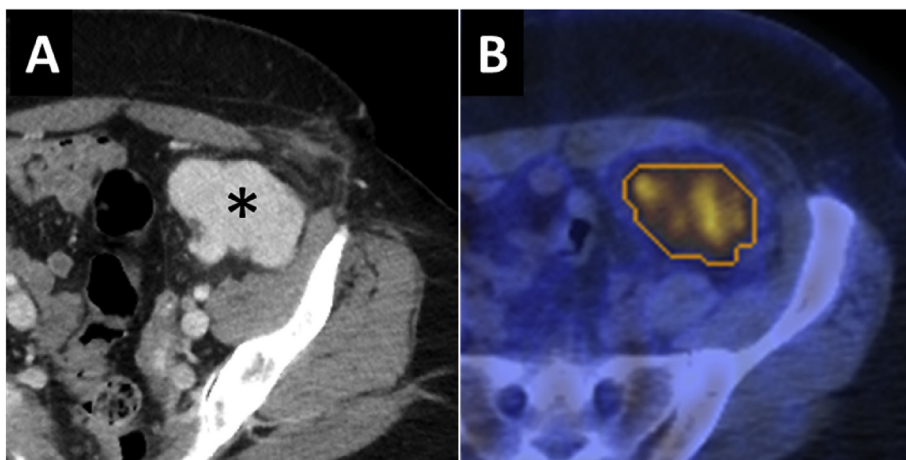


Fig. 1. Axial Image From Contrast-Enhanced Computed Tomography (CT). A, Homogeneously enhancing mass in the left hemipelvis (*) was consistent with an enlarged lymph node. The degree of enhancement suggested hypervascularity, a characteristic finding in Castleman disease. B, The lesion was fluorodeoxyglucose-avid on subsequent positron emission tomography–CT.

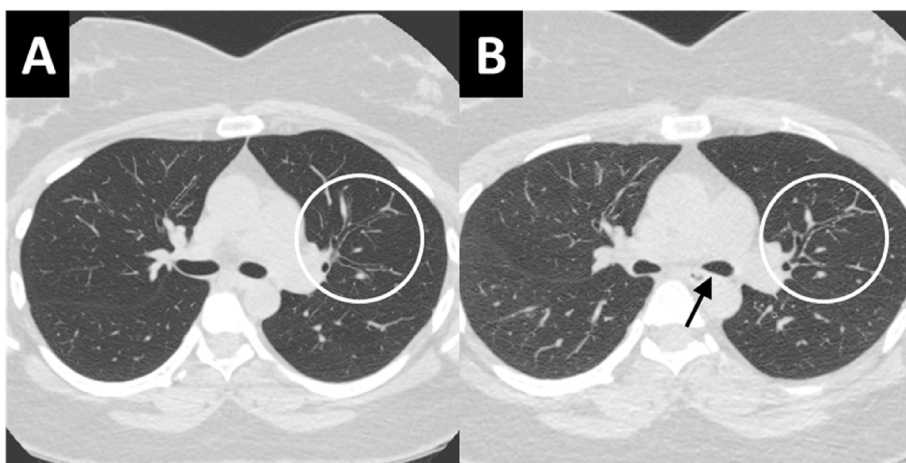


Fig. 2. High Resolution Axial Computed Tomography Scan. A, Inspiratory phase. B, Expiratory phase. There is persistent hypoattenuation of the pulmonary parenchyma in the expiratory phase, consistent with diffuse air-trapping. The posterior membrane of the bronchi has collapsed (arrow), confirming the expiratory technique. There is mild, diffuse bronchial wall thickening (circles). These findings are consistent with bronchiolitis obliterans.

bronchiolitis obliterans after hematopoietic stem cell transplant (HSCT).

A 40-year-old man without a smoking history was evaluated for dyspnea on exertion. He also had a history of unicentric Castleman disease complicated by PNP (Fig. 4). Initial pulmonary function tests (PFTs) in November 2016 showed a forced vital capacity (FVC) of 69% and a forced expiratory volume in the first second of expiration (FEV₁) of 41% (FEV₁/FVC ratio, 58%). Computed tomography (CT) showed mild, diffuse bronchial wall thickening and multiple patchy areas of air-trapping consistent with small airway disease. After initiation of the above treatment regimen, the patient's respiratory symptoms began to improve (Fig. 5). He remained therapy compliant, and repeat PFTs in October 2017 showed a relatively stable condition (FVC, 88%; FEV₁, 60%; FEV₁/FVC ratio, 68%). On most recent follow-up in April 2018, his chest CT showed stability of his respiratory disease (Fig. 6).

bladder antibody testing by immunofluorescence is often used as a surrogate for antibodies to envoplakin, periplakin, and desmoplakins, although desmogleins 1 and 3 (the autoantibody targets in non-PNP) are not present [8].

The mainstay of therapy for paraneoplastic manifestations of Castleman disease is definitive treatment of the neoplasm. However, autoimmune features can persist, especially in recurrent disease [9]. IVIg and rituximab were effective in resolving our patients' mucocutaneous lesions after surgery for Castleman disease recurrences. FAM therapy and rosuvastatin are given to patients for bronchiolitis obliterans after HSCT and for chronic lung rejection because of their anti-inflammatory effects: orally inhaled fluticasone (topical anti-inflammatory effects), azithromycin (impaired interleukin-8 production), and montelukast (blockade of leukotriene production). Our first patient initially improved but then had progressive respiratory decline, which may have resulted from noncompliance to therapy or the natural course

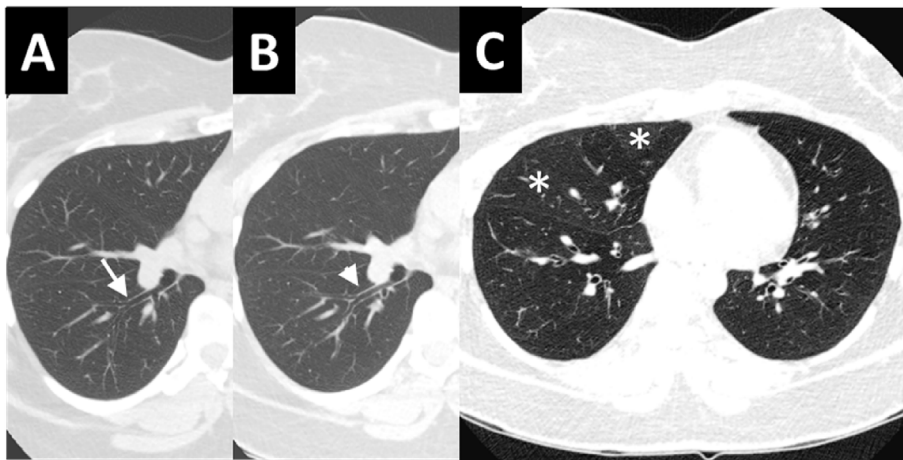


Fig. 3. Axial Computed Tomography 3 Months Before Patient Admission. A, Normal-appearing airways (arrow). B, Airway at the time of diagnosis. Bronchial wall thickening developed in the interval between scans (arrowhead). C, Another axial image at diagnosis with narrow window display settings showing diffuse air-trapping with a few scattered normal areas of lung (*).

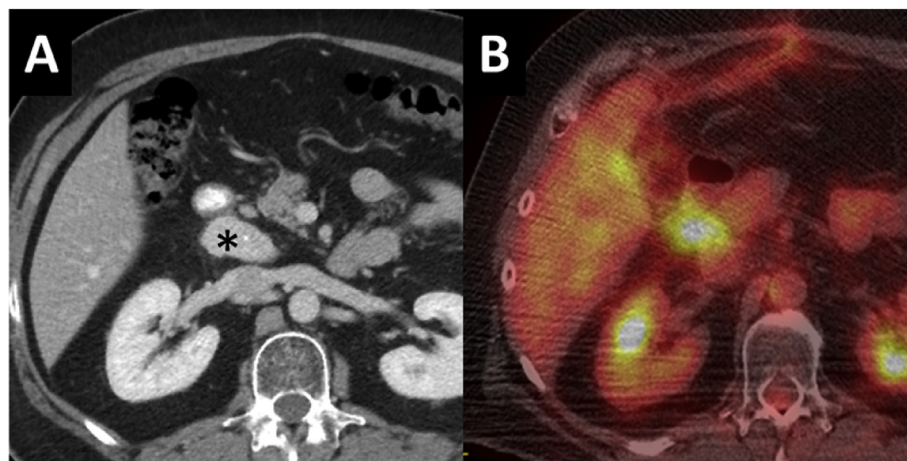


Fig. 4. Axial Image From Contrast-Enhanced Computed Tomography. A, Hypervascular mass in the precaval region (*), consistent with an enlarged lymph node related to Castleman disease. B, This node was fluorodeoxyglucose-avid on subsequent positron emission tomography–computed tomography.

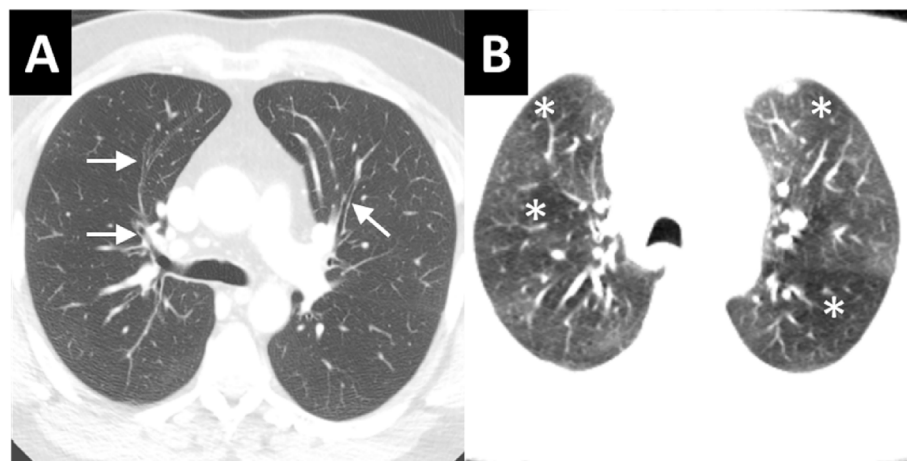


Fig. 5. Axial Images From Computed Tomography. A, Inspiratory phase. B, Expiratory phase. Mild, diffuse bronchial wall thickening (arrows) and patchy areas of air-trapping (*) were consistent with bronchiolitis obliterans.

of her disease. The paraneoplastic respiratory manifestations in our second patient have all but resolved, however, as demonstrated by improvement in symptoms, PFTs, and chest imaging. Further study is needed to further characterize the context in which this treatment regimen may be most beneficial. We believe the therapy regimen we used for our patients may be valuable for treating this rare clinical condition.

Conflicts of interest

Aaron R. Mangold, MD: Scientific advisory board for Genentech, specifically for rituximab.
None of the other authors have any conflicts of interest to disclose.

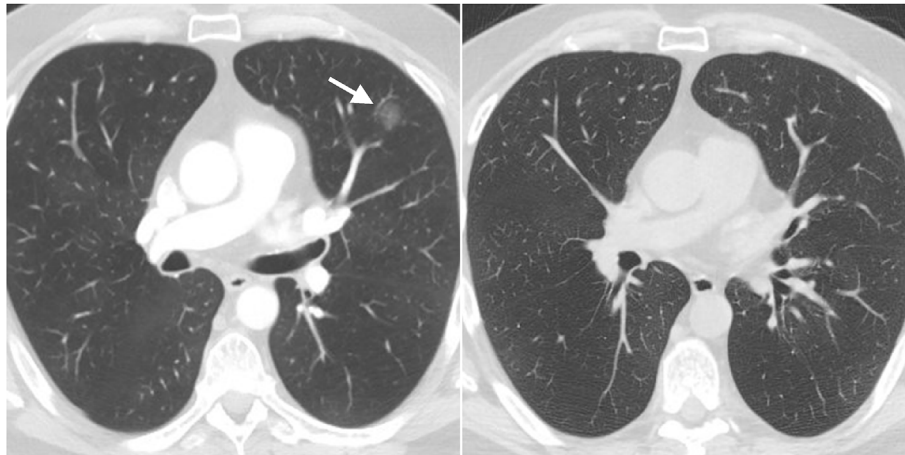


Fig. 6. Axial images from a CT scan performed at time of presentation (A) and several months later (B) demonstrate interval resolution of lingular ground glass opacity (arrow) consistent with improvement.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.rmcr.2018.08.002>.

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