CASE REPORT

Organising pneumonia in common variable immunodeficiency

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SUMMARY

Common variable immunodeficiency (CVID) is the most common of the primary immunodeficiency disorders. Pulmonary manifestations are characterised by recurrent rhinosinusitis, respiratory tract infections and bronchiectasis. Less commonly the lung may be affected by lymphoid disorders and sarcoid-like granulomas. Organising pneumonia (OP) is a rare pulmonary manifestation. We report the case of a 32-year-old woman with CVID who presented with fever, dyspnoea and persistent lung infiltrates despite antibiotic therapy. CT of the chest showed bilateral patchy alveolar infiltrates. Pulmonary function tests revealed moderate restriction and reduction in diffusion capacity. Initial bronchoscopy with transbronchial biopsies did not yield a diagnosis but surgical lung biopsies identified OP. Significant clinical, radiographic and physiological improvement was achieved after institution of corticosteroid therapy.

BACKGROUND

Common variable immunodeficiency (CVID) is the most common of the primary immunodeficiency disorders. Pulmonary manifestations are characterised by recurrent rhinosinusitis, respiratory tract infections and bronchiectasis. The lung may also be affected by lymphoid disorders and sarcoid-like granulomas.¹ Organising pneumonia (OP) is a rare pulmonary manifestation.^{2–4} We present a case of CVID in which the clinical picture of OP was identified radiographically, physiologically and histologically and was associated with significant improvement following corticosteroid therapy.

CASE PRESENTATION

A 32-year-old woman with CVID treated with monthly intravenous immunoglobulin (Ig) for the past 4 years presented with progressive dyspnoea, non-productive cough, fever and fatigue of 1 month duration. She denied night sweats, weight loss or chills. She had a history of recurrent bronchitis. She had no occupational exposures and has been a lifelong non-smoker. There was no family history of lung disease. Physical examination was normal with the exception of bilateral inspiratory crackles present on lung auscultation.

INVESTIGATIONS

Complete blood cell count was normal; serum Ig levels were as follows: IgG, 279 mg/dL (normal: 800–1800 mg/dL); IgA, <5 (normal: 70–400); IgM, 341 (normal: 40–230); and there were no metabolic abnormalities. Immunological connective tissue

diseases work up was negative. An initial chest roentgenogram (CXR) revealed bilateral patchy opacities. Chest CT revealed bilateral nodular consolidations with bilateral mediastinal and hilar lymphadenopathy (figure 1). Pulmonary function tests (PFTs) showed moderate-to-severe restrictive impairment without airflow obstruction and significantly decreased diffusion capacity: FVC=1.48 L (45% of predicted), FEV₁=1.24 L (69%), TLC=1.66 L (38%), FEV₁/FVC=86 and diffusion capacity of carbon monoxide of the lung (DLCO) was 39% of predicted. An initial course of broad spectrum antibiotics resulted in no improvement of her symptoms and she was referred to pulmonary service for further evaluation. She underwent bronchoscopy with bronchoalveolar lavage (BAL), transbronchial lung biopsies and endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal lymph nodes. Cultures from BAL were negative and differential cell count revealed 73% macrophages, 18% neutrophils, 9% lymphocytes and 0% eosinophils. The lung biopsy showed benign bronchial lymphoid infiltrates that does not extend to adjacent lung parenchyma. Lymph nodes aspiration revealed benign lymphoid tissue. Because of the lack of satisfactory diagnosis, she then underwent video-assisted thoracoscopic surgery (VATS) with surgical lung biopsies which revealed OP and interstitial lymphoplasmacytic infiltrates (figure 2).

TREATMENT

Therapy was instituted with prednisone at 60 mg daily.

Figure 1 Axial CT scan showing bilateral patchy consolidations.

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Figure 2 Plugs of granulation tissue obliterating the alveolar lumen with chronic inflammatory cells in the interstitium (H&E, original magnification $\times 200$).

OUTCOME AND FOLLOW-UP

She experienced significant clinical and radiographic improvement over the next few months. CT scan at 3 months revealed almost complete resolution of infiltrates (figure 3) and repeat pulmonary function tests revealed major improvement in restriction and diffusion capacity: FVC=2.09 L (64%), FEV₁=1.72 (67%), TLC=2.53 L (59%) and DLCO was 49% of predicted.

DISCUSSION

CVID is the most common primary immunodeficiency disorder. It is characterised by impaired B cell differentiation and inadequate Ig production. The common defect in CVID is a block in the normal differentiation of lymphocytes into antigen-producing plasma cells. The exact mechanisms involved in this defect are still unknown and could include intrinsic defects in the ability of B cells to synthesise or secrete Ig, as well as abnormalities in regulatory T cells. Clinical manifestations are heterogeneous and typically involve multiple organ systems.⁵ The lung is commonly affected in this disorder. The majority of the patients tend to have recurrent rhinosinusitis, bronchitis and pneumonia. Chronic lung disease is also a common problem and approximately one-third of the patients will have some type of chronic lung disease by the time the diagnosis is made. These include obstructive lung disease associated with asthma and

Figure 3 Axial CT after therapy showing resolution of infiltrates.

bronchiectasis, restrictive disease associated with granulomatous and lymphocytic infiltrative disease and, less commonly, interstitial lung diseases like lymphoid hyperplasia, follicular bronchiolitis and lymphoid interstitial pneumonia (LIP).¹ OP, formerly known as bronchiolitis obliterans OP or BOOP, is a relatively rare presentation in CVID. OP refers to a non-specific response to an initial injury to bronchial epithelium. These initial insults can be from inhalational injury, infections or drug exposures. OP is called cryptogenic OP when it is idiopathic. Histologically this disorder is characterised by excessive proliferation of granulation tissue consistent of loose collagen-embedded fibroblasts and myofibroblasts. Plugs of granulation tissue are found in alveolar ducts and alveolar spaces with or without bronchiolar intraluminal polyps. Inflammatory cells, mainly lymphocytes and plasma cells, are commonly found in the interstitium. BAL typically reveals an increase in all cell types with lymphocyte prevalence. OP is clinically characterised by a subacute illness with dyspnoea, cough, fever, malaise and weight loss. A typical pattern of bilateral patchy alveolar infiltrates is seen on chest CT scan. PFTs reveal a mild-to-moderate restrictive defect. The histological diagnosis can be made by transbronchial lung biopsy but open lung biopsy might be sometimes required as diagnosis can be missed on small specimens.⁶ Several of these clinical and histopathological features are shared by LIP, which is more commonly seen in association with CVID, and therefore constitute the main differential diagnosis from OP. Like OP, LIP manifest clinically with non-specific symptoms of dyspnoea, cough and fever. Radiographs show typically reticular and reticulonodular infiltrates but alveolar opacities can be seen. PFTs show a similar restrictive pattern with impaired diffusion and BAL reveals increased lymphocytes. Histology reveals similar infiltration of the interstitium and alveolar spaces by lymphocytes and plasma cells; however, granulation plugs and polyps are not present and would be the most helpful element in differentiating between the two entities.⁷

The pathogenetic mechanism of OP in CVID is unknown. The exact pathogenesis of OP itself remains not well-defined. It is thought that OP is a consequence of epithelial injury that leads to leakage of plasma proteins, recruitment of fibroblasts and fibrin formation within the alveolar lumen.⁸ Also dysregulation of vascular endothelial growth factor and matrix metalloproteinase has been associated with OP.⁹ One could speculate on the presence of a pathogenetic relationship between the recurrent infections in CVID and the initial epithelial lung injury that leads to OP. Perhaps we could also speculate on the presence of a relation between the B cell dysregulation and T cell imbalance in CVID and the dysregulation in angiogenesis seen in OP.

The diagnosis of CVID in our case was based on a medical history of recurrent respiratory infections since childhood and low serum IgG and IgA levels. The presence of bilateral lung infiltrates and mediastinal lymphadenopathy raised initially the suspicion for either an infectious process or lymphoproliferative disorder. Also a granulomatous disorder was in the differential. This led to the initial diagnostic procedure that included biopsies from the lymph nodes. BAL cell differential was not typical. Because of the uncertainty of the diagnosis, surgical lung biopsies were performed via VATS and OP was diagnosed. Interestingly the diagnosis of OP required surgical lung biopsy in the all three cases previously reported.²⁻⁴ The clinical picture and pulmonary function tests were compatible with the diagnosis as well. Once the diagnosis was established, corticosteroid therapy was promptly instituted and resulted in dramatic clinical, radiographic and physiological response.

Learning points

- ▶ Organising pneumonia (OP) should be included in the differential diagnosis of non-resolving bilateral infiltrates in patient with common variable immunodeficiency.
- ▶ In the presence of a high clinical suspicion, a surgical lung biopsy is recommended if transbronchial lung biopsies are not diagnostic of OP because it can be missed on small specimens.
- ▶ The response to corticosteroids is usually dramatic and the therapy should be instituted promptly after the diagnosis is made.

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