Bronchiolitis Obliterans With Organizing Pneumonia and Cold Agglutinin Disease Associated With Phenytoin Hypersensitivity Syndrome*

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Phenytoin hypersensitivity syndrome (PHS) is a rare delayed hypersensitivity reaction which occurs following exposure to phenytoin sodium. Pulmonary involvement is uncommonly described. Herein is reported the first case of histopathologic bronchiolitis obliterans organizing pneumonia (BOOP) found on open-lung biopsy in a patient with severe PHS. New onset, clinically significant, cold agglutinin disease was also documented. Hemodynamic parameters mimicking sepsis were present in the absence of significant clinical infection. Rapid, dramatic improvement followed high-dose steroid therapy.

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Key words: anemia; bronchiolitis obliterans organizing pneumonia; hemolysis; hypersensitivity; phenytoin

Abbreviations: BOOP=bronchiolitis obliterans organizing pneumonia; PHS=phenytoin hypersensitivity syndrome

Provided here is the first description of histopathologic bronchiolitis obliterans with organizing pneumonia (BOOP) in a patient with severe phenytoin hypersensitivity syndrome (PHS). The presence of cold hemagglutinin disease was also documented for the first time. The patient showed dramatic improvement with high-dose steroid therapy.

CASE REPORT

In September 1994, a 40-year-old black man underwent craniotomy and started receiving therapy with phenytoin sodium (Dilantin; Parke-Davis; Morris Plains, NJ), 300 mg daily. A medical history revealed chronic use of tobacco, crack cocaine, and alcohol. Results of a lung examination and a chest x-ray film showed no abnormalities. Four weeks following phenytoin therapy, clear rhinorrhea, myalgia, high fever, diffusely spreading pruritic maculopapular rash, and dry cough developed. The cough became productive and was associated with dyspnea.

Six weeks after phenytoin therapy was initiated, the patient was readmitted to the hospital. Vital signs were as follows: respiratory rate, 24 breaths per minute; heart rate, 112 beats per minute; BP, 100/60 mm Hg; and temperature, 35°C. Examination revealed diffuse skin exfoliation; conjunctivitis; facial edema; tender, enlarged lymph nodes; decreased breath sounds bilaterally with diffuse inspiratory crackles; mild right upper quadrant tenderness; and hepatomegaly.

Laboratory findings included a fall in hemoglobin level from 155 g/L (noted 6 weeks earlier prior to phenytoin treatment) to 133 g/L; WBC count, 29×10^9/L (35% eosinophils); subtherapeutic phenytoin level; mildly elevated liver function tests; while breathing room air, arterial blood gas values showed mild hypoxia; and chest radiograph, diffuse, patchy, asymmetric, reticulonodular infiltrates. Administration of broad-spectrum antibiotics and prednisone, 50 mg daily, was started. Phenytoin treatment was discontinued. Tests for cold agglutinins were positive. The Mantoux test and tests for HIV, heterophile agglutination, antinuclear antibody, rheumatoid factor, Legio¬nella, and sputum cultures for bacteria, fungi, acid-fast bacilli, and Pneumocystis carinii pneumonia were negative. A skin biopsy specimen showed a drug eruption. Serological tests for Mycoplasma, adenovirus, influenza A and B, herpes simplex, cytomegalovirus, and hepatitis A, B, and C were negative. Spiking fevers, marked eosinophilia, and deterioration of liver function tests continued (aspartate aminotransferase, 214 U/L [normal, <40 U/L]; alanine aminotransferase, 247 U/L [normal, <35 U/L]; lactate dehydrogenase, 435 U/L [normal, <260 U/L]; alkaline phosphatase, 237 U/L [normal, <35 to 125 U/L]). The admission hemoglobin level of 133 g/L dropped to 101 g/L within 48 h of hospitalization, and a mild coagulopathy developed. Respiratory insufficiency culminated in ICU admission and intubation. A chest x-ray film revealed asymmetric patchy infiltrates at lung bases (Fig 1). Sepsis-like hemodynamics developed with hypotension; tachycardia (heart rate, 120 to 140 beats per minute); cardiac output, 10 to 17.5 L/min; and systemic vascular resistance, 300 to 500 dynes·cm⁻⁵ (normal, 770 to 1,500 dynes·cm⁻⁵) requiring inotropic and fluid support. Bronchoscopy, BAL, stains, cultures, and cytologic studies were negative for organisms. Urine was treated for a Staphylococcus aureus infection. All other cultures remained negative for organisms.
The anemia continued to worsen with the hemoglobin level dropping to 70 g/L. Direct and indirect antiglobulin tests, negative prior to phenytoin treatment, were positive with anticomplement C3d and negative with anti-IgG. Saline-reactive cold agglutinins with anti-I specificity of low-titer, high thermal amplitude were present, reacting in saline with adult RBCs at a titer of 1:512 at 4°C and 1:4 at 30°C; with albumin, the titer was 1:8 at 30°C. Nucleated RBCs, occasional cell fragments and spherocytes, and 1 to 2% atypical lymphocytes were found on a smear. Transfusion of packed RBCs following crossmatch by prewarm technique failed to show the appropriate rise in hemoglobin and was followed by further transfusion. The coagulopathy worsened (prothrombin time, 20 s; partial thromboplastin time, 35 s; international normalized ratio, 3.0) and was unresponsive to vitamin K, but did improve following administration of fresh-frozen plasma. Factor analysis showed hematocellular injury.

An open-lung biopsy specimen showed myoid organizing granulation tissue present in bronchioles, which was consistent with BOOP (Fig 2, top). A mild increase in eosinophils within a chronic mononuclear inflammatory infiltrate was present in the alveolar exudate (Fig 2, bottom). Lung tissue was negative for acid-fast bacilli, fungi, P carinii pneumonia, vasculitis, or granulomata. Electron microscopy was negative for viral inclusions. BAL culture later grew rhinovirus. Methylprednisolone sodium succinate (Solu-Medrol), 60 mg, was administered intravenously every 6 h for 48 h and then followed by a slow intravenous taper over 1 week. This was followed by high-dose treatment with prednisone (1 mg/kg) for 3 months, followed by a very slow taper for a total steroid course of 1 year. Pulmonary function tests done 10, 21, and 42 days after steroid administration showed a resolving restrictive lung defect and reduced diffusing capacity of carbon monoxide. A chest x-ray film, liver function, and all hematologic abnormalities resolved.

**DISCUSSION**

PHS is rare with few reports describing pulmonary involvement. Fever, cough, dyspnea, hypoxemia, and bilateral infiltrates on a chest x-ray film in the setting of a more generalized hypersensitivity reaction are typical.\(^1\) Herein is the first description of BOOP in PHS. BOOP is characterized by ingrowth of polyloid fibroinflammatory granulation tissue from bronchioles into adjacent alveoli where an organizing pneumonia forms. The infiltrate is predominantly mononuclear, patchy, and thought to be part of the lung’s reparative process after insults, including hypersensitivity reactions. Commonly, BOOP is sensitive to steroid therapy,\(^2\) associated with a restrictive lung defect and decreased carbon monoxide diffusing capacity. X-ray film findings vary and often show multiple, patchy interstitial-alveolar infiltrates like those described here. Use of crack cocaine, implicated in one case of BOOP,\(^3\) was not thought significant here since this patient ceased cocaine use after his first hospital discharge and clearly suffered from a generalized hypersensitivity syndrome, a finding not associated with cocaine.

Rhinovirus found on BAL culture was likely the result of upper airway contamination during bronchoscopy. The clear rhinorrhea at illness onset, multiple other case reports suggesting concomitant respiratory tract infections, and the reported seasonal variation of phenytoin hypersensitivity reactions\(^4\) suggest a role for concurrent infection in triggering or intensifying the syndrome or, conversely, infections may be the result of phenytoin’s effect on immune function. Sepsis-like hemodynamics, responsive to steroids, have been described rarely in PHS.\(^5\)

Coombs’-negative hemolytic anemia has been repeatedly noted in PHS. Coombs’-positive hemolysis, however, was mentioned only once in the present review of the literature.\(^6\) Here is provided the first full description of acute cold hemagglutinin disease in PHS. Clear evidence of new onset cold hemagglutinins with a positive direct
antiglobulin test for complement only and presence of IgM anti-I autoantibodies of high enough thermal amplitude and titer to produce a clinical picture consistent with both intravascular and extravascular hemolysis were found. Such low-titer, high thermal amplitude-type cold agglutinins are responsive to high-dose steroids.7 Currently, no consensus exists regarding the optimal dose or treatment duration of corticosteroids for BOOP, nor are there guidelines for steroid use in PHS. This patient’s response to intravenously administered methylprednisolone, 60 mg every 6 h for 48 h with a slow intravenous taper over a week, was followed by the regimen suggested by Epler and Colby8 for BOOP: prednisone, 1 mg/kg for 3 months with a subsequent slow drug taper so that steroid therapy was used for a total of 12 months. This proved to be satisfactory for the patient reported herein.

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Vasculitis and Bronchiectasis in a Patient With Antibodies to Bactericidal/Permeability-Increasing Protein and \( \alpha_1 \)-Antitrypsin Deficiency*

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A patient with \( \alpha_1 \)-antitrypsin deficiency is reported herein; this subject developed aggressive bronchial disease and recurrent cutaneous vasculitis after pulmonary infection with *Pseudomonas aeruginosa*. Autoantibodies to neutrophil cytoplasmic antibodies were detected, which produced granular cytoplasmic staining by indirect immunofluorescence with specificity for a newly characterized antigen: bactericidal/permeability-increasing protein (BPI). The bronchial disease and vasculitis improved, and the IgA anti-BPI titer fell after antipseudomonal treatment. This raises the possibility that anti-BPI antibodies contributed to both the bronchial disease and vasculitis. (CHEST 1997; 112:1699-1701)

Key words: \( \alpha_1 \)-antitrypsin deficiency; antineutrophil cytoplasmic antibody; bactericidal/permeability-increasing protein; bronchiectasis

Abbreviations: \( \alpha_1 \)-AT=\( \alpha_1 \)-antitrypsin; ANCA=antineutrophil cytoplasmic antibody; BPI=bactericidal/permeability-increasing protein; LPS=lipopolysaccharide; LBP=LPS binding protein

Vasculitis associated with chronic suppurrative lung diseases, such as bronchiectasis and cystic fibrosis, has been reported by researchers.1,3 Antineutrophil cytoplasmic antibody (ANCA), a serologic marker for some small-vessel vasculitides, has been detected in some series1,2 but without a defined antigen specificity or a clear relationship to disease. Bactericidal/permeability-increasing (BPI) protein is an important host defense mechanism against lipopolysaccharide (LPS). Autoantibodies directed against this protein recently have been recognized to be associated with vasculitis, cystic fibrosis, and inflammatory bowel disease.3-5 Herein is the report of a case of bronchiectasis and \( \alpha_1 \)-antitrypsin (\( \alpha_1 \)-AT) deficiency in whom infection with *Pseudomonas aeruginosa* was closely related to the development of recurrent vasculitis, worsening bronchial disease, and raised levels of anti-BPI antibodies. Treatment with antibiotics produced a clinical improvement and was accompanied by a fall in the level of IgA anti-BPI autoantibodies. Findings in this index patient provide further information linking infection, autoimmunity, and vasculitis and suggest an etiologic role of infection in certain vasculitides.

CASE REPORT

A 59-year-old man, a nonsmoker, presented with a 4-month history of daily sputum production, hemoptysis, and a 5-kg weight loss. These symptoms were unresponsive to treatment with clarithromycin and doxycycline (Vibramycin). Examination revealed widespread inspiratory wheezes and coarse crackles at both bases. Spirometry showed an obstructive defect; FEV1 was 1.1 L (predicted, 2.6 L) and FVC was 3.1 L (predicted, 3.3 L). Investigations revealed \( \alpha_1 \)-AT level to be 0.3 g/L (normal range, 0.9 to 1.8 g/L); phenotype Z; cytoplasmic staining of ANCA, *From the Departments of Respiratory Medicine (Drs. Mahadeva and Shneerson), Medicine (Drs. Zhao and Lockwood), and Radiology (Dr. Flower), Addenbrooke’s Hospital, and the Department of Pathology (Dr. Stewart), Papworth Hospital, Cambridge, UK.

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