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## *Pneumocystis jiroveci* Infection in Patients With Hyper-Immunoglobulin E Syndrome

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### ABSTRACT

The hyper-immunoglobulin E syndrome is a primary immunodeficiency characterized by recurrent pyogenic skin and lung abscesses, dermatitis, and elevated serum immunoglobulin E levels. *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) is not typically associated with hyper-immunoglobulin E syndrome. We identified 7 patients with hyper-immunoglobulin E syndrome with *P jiroveci* detected in respiratory or pulmonary pathology specimens. In 5 patients it was the sole pathogen, and in 2 other patients it contributed to a polymicrobial etiology. No consistent prophylaxis was given, and there have been no recurrences on long-term follow-up. Our experience suggests that *P jiroveci* can cause pneumonia in patients with hyper-immunoglobulin E syndrome both with and without chronic lung disease.

**H**YPER-IMMUNOGLOBULIN E (IGE) syndrome (HIES) is a rare primary immunodeficiency disorder characterized by recurrent skin and lung abscesses, dermatitis, and elevated serum IgE levels.<sup>1-3</sup> Nonimmunologic skeletal and morphologic features are associated with the syndrome and include characteristic facies, osteopenia, scoliosis, and retention of primary teeth. Both the genetic etiology and underlying host immune defect are not known, and diagnosis relies on clinical features and supporting laboratory values and may be more difficult in children in whom various features (such as characteristic facies and retention of primary teeth) may not have appeared. Inheritance is autosomal dominant with variable penetrance resulting in phenotypic heterogeneity.

Affected individuals experience predominantly recurrent bacterial pneumonias and skin abscesses typically from *Staphylococcus aureus*, but also mucocutaneous and nail candidiasis, and develop secondary *Aspergillus* infections of residual pulmonary cavities from previous infections.<sup>3</sup> *Pneumocystis jiroveci* pneumonia (PJP), an opportunistic infection in individuals with T-cell immunodeficiencies, is not considered a characteristic infection in HIES. We have identified 7 patients with HIES, all HIV-negative, who were diagnosed with PJP. Because many of these patients have chronic lung disease, *P jiroveci* may colonize the respiratory tract, but it also

seems that, at least in some patients, *P jiroveci* may be a pathogen.

### CASE HISTORIES

Patient 1 presented at 2 months of age with bilateral otitis media and cough (Table 1). At 4 months of age she presented with worsening cough and tachypnea over 2 months, a *Candida* inguinal rash, a right-groin *S aureus* abscess, and otitis media. A chest radiograph demonstrated bilateral hazy infiltrates. An open lung biopsy identified *P jiroveci* on silver stain. She was treated with intravenous trimethoprim/sulfamethoxazole (TMP/SMX), with clinical response, in addition to drainage and antibiotic therapy for the groin abscess. She had a peripheral eosinophilia of 4000 per mL, her serum IgE level was elevated at 46 IU/mL (reference range: <10–26 IU/mL), and she was diagnosed with HIES. After recov-

**Key Words:** hyper-IgE syndrome, *Pneumocystis jiroveci*, immunodeficiency

**Abbreviations:** IgE, immunoglobulin E; HIES, hyper-immunoglobulin E syndrome; PJP, *Pneumocystis jiroveci* pneumonia; TMP/SMX, trimethoprim/sulfamethoxazole; ABPA, allergic bronchopulmonary aspergillosis; CT, computed tomography; FA, fluorescent antibody; DLCO, diffusion capacity; PCR, polymerase chain reaction

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**TABLE 1 Patient Characteristics**

Patient	Peak HIES Score, Points	Age at Peak Score, y	Age at PJP Diagnosis	Clinical Presentation	Method of Diagnosis
1	78	20	4 mo	Increasing respiratory distress over 2 mo	Silver stain on open biopsy
2	65	15	3 mo	Fussiness, respiratory distress	Histologic stains on open biopsy
3	87	24	18 y	Multiorganism pneumonia	FA stain on bronchoscopy specimen
4	68	32	32 y	Death at home	Histologic stains on autopsy
5	33	10	10 y	Dry cough over several weeks and decreased DLCO on PFTs	FA stain and PCR on induced sputum
6	64	15	16 y	Nasal congestion	PCR on induced sputum
7	73	22	22 y	Mild dry cough and decreased DLCO on PFTs	PCR on induced sputum

PFTs indicates pulmonary function tests.

ering from PJP, she continued to experience recurrent skin abscesses, otitis media and sinusitis, chronic eczema, mucocutaneous candidiasis, and elevated IgE levels (maximum: 69 760 IU/mL). According to a diagnostic scoring system including both immunologic and skeletal and connective tissue features of HIES (>40 points is consistent with HIES),<sup>4</sup> her most recent score at 20 years of age was 78 points. Up to the time of this writing, she has not had any recurrence of PJP despite the lack of continuous PJP antimicrobial prophylaxis. In recent years she has been maintained on continuous levofloxacin and fluconazole.

Patient 2 presented at 3 months of age with fussiness and diminished oral intake. Hypoxemia soon developed, leading to intubation for respiratory failure. PJP was diagnosed on open lung biopsy. Intravenous TMP/SMX led to clinical response. PJP prophylaxis with TMP/SMX and then inhaled pentamidine continued until 2 years of age, followed by erythromycin/sulfisoxazole until 7 years of age. He was subsequently diagnosed with HIES (maximum score: 65 points) with eczema, recurrent pneumonias, hyperextensibility, scoliosis, pathologic fractures, osteopenia, failure of primary teeth deciduation, eosinophilia, characteristic facies, high arched palate, and an increased serum IgE level (maximum: 7190 IU/mL). Up to the time of this writing, he has not had skin abscesses, which is attributed to continuous bacterial prophylaxis since the age of 1 year. At 15 years of age, he had not had recurrence of PJP despite not receiving continuous PJP prophylaxis. He is currently maintained on amoxicillin/clavulanate.

Patient 3 presented at 18 years of age with low-grade fevers, increased sputum production, and wheezing. HIES was diagnosed at 16 months on the basis of eczema, recurrent otitis media, skin abscesses, and elevated IgE levels (maximum: 3500 IU/mL). She subsequently developed recurrent pneumonia with bronchiectasis, osteopenia, multiple fractures, scoliosis, and apparent allergic bronchopulmonary aspergillosis (ABPA). Her HIES score was 87 points. At the time of the relevant admission, she was undergoing therapy for *Pseudomonas aeruginosa* pneumonia and ABPA with ceftazidime, amphotericin B, and prednisone, 10 mg every other day. Chest computed tomography (CT) showed a stable right up-

per-lobe cavity and bronchiectasis with increased bronchial plugging in the right lower lobe. Bronchoscopy of the right lower lobe found purulent secretions; Gram-stain revealed many white blood cells, and culture grew *P aeruginosa*. *P jiroveci* was observed on fluorescent antibody (FA) stain. The following day, she developed worsening shortness of breath and hypoxemia (Pao<sub>2</sub>: 26 mm Hg). Steroids and TMP/SMX led to rapid improvement with resolution of hypoxemia. She died 6 years later of progressive pulmonary disease with pseudomonas infection but never had a second positive identification of *P jiroveci* on multiple bronchoscopies or pathology from lung resections. Autopsy showed no *P jiroveci* despite the lack of continuous PJP prophylaxis.

Patient 4 was found dead at home. She was 32 years old and had HIES characterized by recurrent pneumonias, skin abscesses, and pulmonary aspergillomas with previous resections of the left and right lobes. Her HIES score was 68 points. She was undergoing therapy for pulmonary *Aspergillus* at the time of her death. Autopsy showed focal pneumonia with interstitial fibrosis and an encapsulated fungal mass with adjacent *P jiroveci* by silver stain. Death was attributed to acute pulmonary bacterial and fungal infection with underlying chronic lung disease. Both *P jiroveci* and *Aspergillus* were thought to contribute.

Patient 5 presented at 10 years of age with several weeks of dry cough. Her history included eczema, recurrent sinusitis and otitis media, osteopenia, a right patellar fracture, and an elevated serum IgE level (235 IU/mL). Although her HIES score was only 33 points, a sibling (see patient 6 below) had a score of 62 points as well as a clinical history suggestive of HIES, making her diagnosis of HIES more likely. Physical examination on the relevant admission was normal, and she had normal oxygenation. However, chest CT showed prominent interstitial markings bilaterally (Fig 1), and pulmonary-function tests showed diffusion capacity (DLCO) of 53% of normal. Respiratory viral culture from induced sputum was negative. Polymerase chain reaction (PCR) testing on an induced sputum specimen was positive for *P jiroveci*, but an FA stain was negative. Repeat induced sputum was positive for *P jiroveci* by both FA and PCR. Because of an allergy to TMP/SMX, the patient was

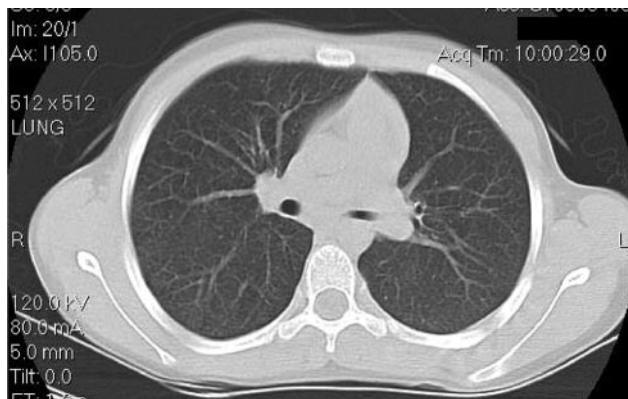


FIGURE 1  
Chest CT of patient 5 showing increased interstitial markings.

treated with oral atovaquone for 3 weeks. For sinusitis diagnosed on CT she received clindamycin. The cough resolved by the 1-month follow-up. The DLCO improved to 78%, and interstitial markings were diminished. She has had no recurrence in 8 months' follow-up despite having had no prophylaxis.

Patient 6, the 16-year-old sibling of patient 5, presented at the same time as her sister with nasal congestion but denied fever and cough. She had an HIES score of 64 points with a history of chronic sinusitis and otitis media, eczema, recurrent skin abscesses, several episodes of varicella-zoster infection, eosinophilic esophagitis, high arched palate, vertebral anomaly, and elevated serum IgE levels (maximum: 7030 IU/mL). Chest CT was largely unchanged from previous examinations, with a small right upper-lobe cavity. Induced sputum, performed because of the sister's diagnosis of PJP, was positive for *P jiroveci* by PCR but negative by FA stain. She was treated with atovaquone (because of a TMP/SMX allergy) for 3 weeks, along with clindamycin for chronic sinus disease. At follow-up, there was little clinical or radiographic change. She has had no recurrence in 8 months' follow-up despite having had no prophylaxis.

Patient 7 presented at 22 years of age for routine HIES evaluation with a slight cough. He had an HIES score of 73 points with recurrent skin abscesses, eczema, pneumonia, failure of primary teeth deciduation, osteopenia, hyperextensibility, scoliosis, characteristic facies, high arched palate, and an elevated IgE level (1870 IU/mL). On the relevant admission, his physical examination was normal, including oxygen saturation, but pulmonary-function tests showed a DLCO of 55% of predicted, reduced from 84% of predicted 1 year earlier. Chest CT was normal. Two induced sputa tests were positive for *P jiroveci* by PCR but negative by FA stain; bacterial cultures grew normal oropharyngeal flora. He was treated with TMP/SMX for 3 weeks, and DLCO improved to 83% of predicted at his 2-month follow-up. He has had no recurrence in 4 months' follow-up despite having had no prophylaxis.

## DISCUSSION

*P jiroveci* is a ubiquitous fungus that causes pneumonia in patients with T-cell immunodeficiency disorders. It is most commonly found in patients with HIV, those receiving long-term corticosteroids, patients with severe malnutrition, and in primary immunodeficiencies involving T lymphocytes such as severe combined immunodeficiency and CD40 ligand deficiency.<sup>5-7</sup> Rarely, PJP has been described in patients without any demonstrable immune defect.<sup>8</sup> PJP typically presents in a subacute manner with progressive dyspnea, nonproductive cough, and low-grade fever.<sup>5,9</sup> Physical examination may be unrevealing, with few symptoms besides tachypnea and tachycardia. Hypoxemia with a normal pH on arterial blood sampling is common. A chest radiograph may be unimpressive; a bilateral interstitial pattern is observed most frequently. Diagnosis requires detection of the organism in a respiratory specimen by conventional stains (such as Grocott's methenamine silver), monoclonal antibody stains, or, increasingly, PCR testing.

*P jiroveci* has not been recognized as a frequent pathogen in patients with HIES. These patients typically develop pneumonias and skin abscesses from an early age with bacterial pathogens such as *S aureus* and *Haemophilus influenzae*.<sup>2,3</sup> Pneumatocoles often result and may become infected with Gram-negative bacteria and *Aspergillus* species. Many patients also suffer from recurrent mucocutaneous candidiasis. Four of the patients we report here (patients 1, 2, 5, and 7) had symptomatic PJP without another pulmonary pathogen identified and experienced clinical improvement with PJP-directed therapy. Although patient 3 had evidence of ABPA and *P aeruginosa* pneumonia, her clinical status improved with specific PJP therapy, suggesting that *P jiroveci* contributed to her respiratory deterioration. Limited history for patient 4 precludes clear causality, but pathologic examination was consistent with PJP contributing to her death.

Patients 6 and 7 were positive for *P jiroveci* solely by PCR testing. Although identification of *P jiroveci* by FA or histology is associated with excellent specificity and positive predictive value for disease,<sup>10,11</sup> the increased sensitivity of PCR has resulted in identification of *P jiroveci* in patients on minimal immunosuppression, in those with chronic lung disease, and in healthy, immunocompetent individuals, with colonization rates of 17% to 20% reported.<sup>10,12-14</sup> However, *P jiroveci* disease did not occur in the majority of reported immunocompetent or minimally immunocompromised patients.<sup>13</sup> It is possible that patient 6 (the sibling of patient 5), who had a paucity of clinical or laboratory abnormalities, was colonized with *P jiroveci* as a result of an exposure similar to her sister's or from exposure to her sister. Geographic clustering has been noted with PJP, and health care workers caring for patients with PJP have had *P jiroveci* detected in nasopharyngeal swabs by PCR.<sup>15-17</sup> Although *P jiroveci* was



only positive by PCR for patient 7, the clinical improvement and return to baseline DLCO suggest a therapeutic response to PJP therapy.

It remains uncertain whether PJP is occurring in HIES secondary to immunologic abnormalities intrinsic to these patients or secondary to abnormalities found in chronic lung disease. In addition to the clear association of CD4<sup>+</sup> T-lymphocyte abnormalities and PJP, other immune mechanisms contribute to the pathogenesis of PJP, including pulmonary macrophages, humoral immunity, and cytokines secreted by inflammatory cells.<sup>18</sup> Three of these patients developed PJP before other lung infections, implying an underlying immunologic defect predisposing them to PJP. Consistent immunologic abnormalities have not been found in HIES, but patients do have other evidence of T lymphocyte abnormalities with mucocutaneous candidal infections and occasional reports of disseminated fungal infections (such as histoplasmosis, *Cryptococcus*, and *Aspergillus*).<sup>3,19,20</sup> In addition, individuals with autosomal recessive HIES suffer from recurrent or chronic herpes, varicella, and *Molluscum contagiosum* infections.<sup>21</sup> One possible etiology of the enhanced susceptibility to PJP would be decreased lymphocyte  $\gamma$ -interferon secretion, which has been reported in individuals with HIES.<sup>22,23</sup> In a CD4<sup>+</sup>-lymphocyte-depleted murine model of PJP, addition of  $\gamma$ -interferon by gene transfer allowed for resolution of infection.<sup>24</sup> However, until the immunologic defect of HIES is elucidated further, the propensity for PJP is likely not to be fully understood.

PJP in HIES may also result from *P jiroveci* exacerbation of chronic lung disease and not immunologic abnormalities. Two of the patients we describe did have chronic lung disease, and otherwise immunocompetent children with chronic lung disease and detection of *P jiroveci* have been reported to improve with *P jiroveci*-directed therapy.<sup>12</sup>

Additional studies are needed to determine the incidence of *P jiroveci* in this population, its association with worsening of lung disease, and the role of *P jiroveci*-directed therapy. Use of PCR to detect *P jiroveci* is likely to identify more cases in patients with HIES; however, pathogenicity may remain difficult to determine for patients with negative histology or antibody staining.

PJP should be included in the differential diagnosis for pneumonia in patients with HIES. The role of prophylactic antimicrobial agents as primary and secondary prophylaxis is unexplored. Although we did not see relapse or reinfection with *P jiroveci* in HIES, the number of patients was small and the overall length of follow-up was limited.

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