



Letter

Properdin deficiency—associated bronchiectasis

The complement system plays a critical role in host innate immunity against microorganisms. Properdin, a basic glycoprotein of 442 amino acids, is a key component of the alternative complement pathway.^{1,2} Properdin binds to C3 convertase, resulting in amplification and stabilization of the C3bBb complex and thus allowing for alternative pathway activation.³

Properdin deficiency is characterized by *Neisseria meningococcal* infections that present in the second decade of life.⁴ A prior report also described a case of recurrent otitis media and pneumonia due to nonmeningococcal disease in children.⁵ Properdin deficiency associated with chronic infections has not been reported in adults. We report a case of a 44-year-old white woman who was evaluated for recurrent sinopulmonary infections and bronchiectasis.

The patient presented with a history significant for recurrent sinopulmonary infections as a child. Four to 5 years before presentation, she was noted to have severe pneumonias associated with sepsis, requiring prolonged and recurrent hospitalizations. She had multiple positive sputum culture results for *Pseudomonas*, *Aspergillus*, *Fusarium* species, and *Stenotrophomonas*. She required recurrent antibiotic and antifungal treatments. Two to 3 years before presentation, she developed bronchiectasis, with significant decreases in pulmonary function, and became oxygen dependent. At the time of presentation, the patient's pulmonary function test revealed the following: forced vital capacity, 2.78 (74%); forced expiratory volume in 1 second, 1.38 (47%); ratio of forced expiratory volume in 1 second to forced vital capacity, 50; forced expiratory flow between 25% and 75%, 0.62 L (19%). She was empirically being treated with long-term posaconazole for *Aspergillus* and aerosolized tobramycin for *Pseudomonas*. Her remaining medical history was significant for gastroesophageal reflux disease and hypothyroidism. There was no known family history of immunodeficiency and recurrent infections. She did not smoke and had no known secondhand smoking exposure. She did not have history of dextrocardia or sinus diseases. Physical examination revealed diffuse wheezing on both expiration and inspiration and crackles at the bilateral lung bases.

At the time of presentation, our patient had already been evaluated at an outside hospital with a normal cystic fibrosis genetic panel, sweat chloride test, complete blood cell count, basic metabolic studies, and α_1 -antitrypsin measurement. Her initial workup included high-resolution computed tomography of the chest, which revealed mild bronchiectasis noted in lingula and bilateral lower lung lobes, ground glass opacities, and tree in bud nodules in the left upper lung lobe and scatter micronodules in the lower lung lobes (Fig 1). Bronchoscopy findings were unremarkable. On the basis of distribution of her bronchiectasis, clinical concern was for either aspiration or possible immunodeficiency. Nuclear medicine aspiration scan result was negative, and bronchoscopy did not

reveal lipid laden alveolar macrophages, making aspiration unlikely. Findings of initial immunologic workups, which include total hemolytic complement assay of 102 mg/dL, C3 of 94 mg/dL, C4 of 22 mg/dL, quantitative immunoglobulin with tetanus and pneumococcal titers, dihydrorhodamine assay, and lymphoproliferative assay, were within normal limits. No lymphopenia and neutropenia were detected. Further investigation for complement deficiency revealed normal mannose binding pathway but significantly lower activity for alternative pathway (10 mg/dL; reference range, >59 mg/dL). Additional laboratory workup revealed a normal C3C level but a decreased level of properdin (18 mg/L; reference range, 23–67 mg/L). Factor D level was not measured because of the patient's steroid-induced obesity. The results of additional properdin testing were identically low. The patient's early infectious history was attributed to the low alternative pathway activity. Her secondary clinical characteristics of bronchiectasis were likely a complication of continued mucoviscidosis and chronic infection due to her primary innate immune system defect. She currently is receiving antibiotic and airway clearance therapy. Supplemental intravenous γ -globulin is being considered. No clear therapeutic intervention is available for properdin deficiency.

Properdin deficiency cases reported to date are associated with *Neisseria* infections, especially fulminant meningococcal disease.⁶ One properdin deficiency case reported that family members of the index patient had susceptibility to *Haemophilus influenzae* and *Moraxella catarrhalis*.⁵ Our case represents the first case of properdin deficiency identified in the absence of meningococcal disease and in the setting of chronic sinopulmonary infections. This finding raises the question of whether properdin deficiency outside classic *Neisseria* infections is underestimated. Properdin deficiency may be more prevalent than previously estimated. One reason in difficulty of diagnosis may be because of the lack of abnormalities in routine complements, such as total hemolytic complement assay, C3, and C4.

Unlike other case reports, our patient did not present in a singular fulminant infectious state. She presented with symptoms consistent with a chronic disease model. Her clinical course suggests a recurrent smoldering level of infection, leading to chronic inflammation and development of pulmonary bronchiectasis. This clinical picture is more often seen in patients with cystic fibrosis, α_1 -antitrypsin deficiency, immobile cilia syndrome, and common variable immunodeficiency disease. To date, there are 3 types of properdin deficiency described. Type 1 is the most common and is characterized by complete absence of properdin protein. Type 2 includes subnormal level, usually 1% to 10%, of the properdin protein level. Type 3, the rarest form, describes normal level but functionally defective properdin. Most reported cases thus far belong to type 1, presenting with fulminate infection. Our patient has subnormal levels of properdin, likely belonging to type 2 deficiency or the carrier state of type 1. This finding may also

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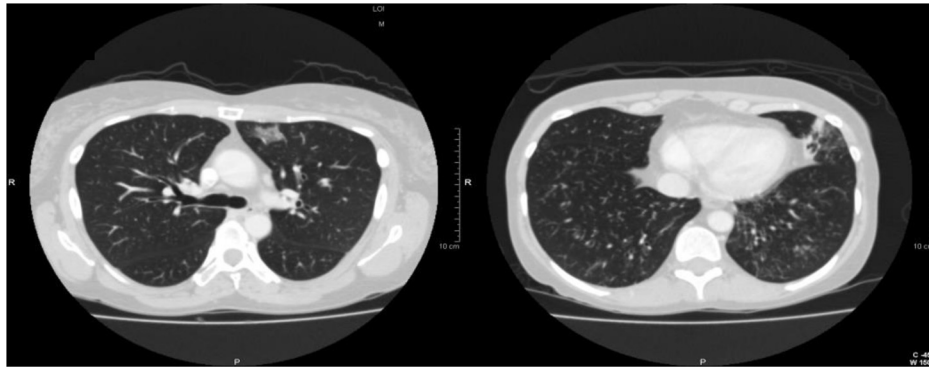


Figure 1. CT chests demonstrating mild and ground glass and scatter micronodules in bilateral lung lobes.

explain why our patient has recurrent chronic infections rather than acute illness. This case illustrates the possibility of properdin playing a role in recurrent chronic infections, which has not been previously appreciated clinically.

Furthermore, the properdin gene localizes to the Xp11.3-Xp11.23 band and is thought to be an X-linked recessive disease.⁷ Our patient is a female patient, and her subnormal level of properdin suggests possible X-inactivation pattern.⁸ Carrier females of properdin type 1 deficiency generally have reduced properdin levels, approximately 50% of the reference range (17–27 mg/L). It was previously proposed that variation in the level of properdin in these female carriers is caused by uneven lyonization of normal and mutated X chromosomes. Interestingly, our patient's daughter was also diagnosed as having properdin deficiency at 11 years of age and had history of recurrent sinopulmonary infection.

In summary, we present a unique case of properdin deficiency that presented as chronic mucosal bronchial infections and bronchiectasis. This case suggests the underuse of alternative complement pathway evaluation in susceptibility to chronic infections. Properdin deficiency and complement alternate pathway evaluation should be considered in chronic infection cases to avoid irreversible anatomical disease.

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