An Adult with Recurrent Severe Pneumococcal Pneumonia Secondary to Prolidase Deficiency

Ariel Kenig MD, Ofer Perzon MD, Yuval Tal MD PhD, Sigal Svirri MD, Avi Abutbul MD, Marc Romain MD, Efrat Orenbuch-Haroch MD, Naama Elefant MD, and Avi Talmon MD

1Department of Medicine, 2Clinical Immunology and Allergy Unit, 3Medical Intensive Care Unit, and 4Department of Genetics, Hadassah-Hebrew University Medical Center, Ein Kerem Campus, Jerusalem, Israel

KEY WORDS: immunosuppression, pneumonia, prolidase deficiency, Streptococcus pneumoniae, storage disease

IMAJ 2021; 23: 193–195

Immunodeficiencies in the adult possess unique diagnostic challenges and require a high level of suspicion in patients with recurrent or severe infections. We present a case of recurrent severe pneumonia in a 43-year-old male found later to have prolidase deficiency, a rare inherited storage disease, which is usually detected at a younger age.

PATIENT DESCRIPTION

A 43-year-old Jew of Kurdish descent with a past medical history of infertility, lymphedema, and chronic lower limb dermatitis presented initially with 2 days of cough, shortness of breath, and weakness. Later, he developed vomiting, altered mental status, and incontinence and was sent to the emergency department (ED). On arrival he was stupor, dyspneic, hypoxic, and hemodynamically unstable. He was intubated and put on mechanical ventilation. Noradrenaline was initiated. Chest X-ray revealed bilateral diffuse pulmonary infiltrates. Ceftriaxone and hydrocortisone were administered. The patient was transferred to the medical intensive care unit (MICU). Initial laboratory results showed leukopenia with white blood count of 2.6 × 10^9 cell/µl, markedly elevated C-reactive protein at 44.25 mg/dl, elevated creatinine (121 µmol/L), and combined metabolic and respiratory acidosis (pH of 7.25, pCO2 of 53.9 mmHg and HCO3 of 23.2 mg/dl). Echocardiography showed moderately reduced left ventricular systolic function. Microbiological evaluation revealed blood and sputum cultures positive for Streptococcus pneumoniae in addition to positive pneumococcal antigen in the urine.

Despite aggressive therapy and advanced mechanical ventilation requiring high pressures and inspired fraction of O2 and nitric oxide supplementation, the patient remained hypoxic due to...
severe acute respiratory distress syndrome (ARDS). He was connected to venous-venous extracorporeal membrane oxygenation (ECMO) for a period of 7 days. During this time period, ventilation, oxygenation, and hemodynamic parameters improved markedly. During the course of the following weeks of hospitalization and rehabilitation he gradually improved and was weaned from mechanical ventilation. Almost 3 months after presenting to the ED he was discharged home, without disability or need of supplemental oxygen therapy.

During his recovery he was evaluated by the dermatology team. Directed history taking revealed that he presented with recurrent puritic hyperkeratotic rash on his feet and buttocks for at least 20 years. Skin biopsy revealed multiple blood vessels in the papillary dermis with perivascular lymphocytic infiltrates and pigment incontinence in the superficial dermis. The pathologist concluded that the findings are compatible with psoriasiform dermatitis. The severity of the infection in an adult patient without significant medical history raised the suspicion of an immunodeficiency. Therefore, he was evaluated by the genetic and immunological teams. A thorough history taking revealed that the patient was known to have hepatosplenomegaly since childhood and never underwent biopsy or systemic evaluation. He was initially diagnosed with failure to thrive (FTT) but later experienced normal growth and development. He had no prior severe infectious episodes, other than a single episode of a retropharyngeal abscess. Notably, he had chronic thrombocytopenia that was thought to be hypersplenism.

Family medical history was significant for consanguinity as his parents were second degree relatives. In addition, a brother showed similar childhood features including FTT and hepatosplenomegaly in addition to severe pneumonia at the age of 3 month. The brother was evaluated during infancy, including liver biopsy, without revealing a clear diagnosis. On examination, our patient exhibited some dysmorphic features including an elongated face, a beaked nose, protruding eyes, and prominent ears in addition to an enlarged spleen and bilateral lower limb ulcerations. A primary immunodeficiency, possibly secondary to a metabolic storage disease, was suspected. Genetic counseling, an ambulatory post-discharge evaluation in the immunology clinic, and pneumococcal and influenza vaccinations were advised.

Before undergoing ambulatory genetic or immunological evaluation, the patient presented again with severe respiratory distress, almost 3 months after he was discharged. Again, he was intubated. Mechanical ventilation and vasopressors therapy were initiated and he was retransferred to the MICU. Chest X-ray revealed a large consolidation in the right lung compatible with pneumonia. Empirical antibiotic treatment with piperacillin tazobactam, azithromycin, and oseltamivir was initiated. Subsequent microbiological analysis was positive for both H1N1 influenza and Streptococcus pneumoniae infections.

The patient did not receive influenza or pneumococcal vaccinations after he was first discharged. During the second hospitalization he again presented with severe ARDS requiring advanced ventilation and nitric oxide therapy, although this time he was not connected to extracorporeal membrane oxygenation due to rapid initial stabilization. Despite suitable antimicrobial therapy and after a mild initial improvement, the patient deteriorated and passed away after 14 days in the MICU.

During the second hospitalization the patient was re-evaluated by the immunological and genetic teams. Formal thorough immunological screening, including flow cytometry and qualitative immune function tests, were not conducted due to the severe acute infectious process, which would have disrupted the results. Laboratory tests revealed lymphopenia, normal immunoglobulin levels with a slightly decreased IgM levels, normal complement levels, and the presence of specific IgG for cytomegalovirus, Epstein-Barr virus, varicella, and measles. Serology for human immunodeficiency viruses and human T-lymphotropic virus were negative. Due to recurrent severe encapsulated-bacterial infections, in addition to an enlarged spleen, the possibility of functional hyposplenism was addressed.

A blood smear did not reveal Howell-jolly bodies and a planned spleen scintigraphy was postponed due to the patient’s clinical status. Proband-only exome sequencing was performed. The results, arriving unfortunately after the patient passed away, revealed a homozygous 3-base pair deletion in PEPPD. g.ch19:33878370delGGA [hg19]; NM_000285.4:c.1359_1361delGGGA; and p.(Glu453del), a pathogenic variant known to cause prolidase deficiency.

**COMMENT**

The human prolidase is a widely distributed multifunctional metalloenzyme with a unique role in the hydrolysis of dipeptides containing a C-terminal proline or hydroxyproline. Prolidase deficiency is a storage disease caused by autosomal recessive inheritance of mutations in PEPPD gene on chromosome 19, resulting in reduction or loss of prolidase activity [1]. Prolidase deficiency is rare, with approximately 100 cases diagnosed globally as of 2018 [2], but is probably underestimated and under diagnosed due to low disease awareness. Most cases are detected after birth or in early childhood. Rarely, late-onset diagnosis such as in our case has been reported. The main clinical characteristics include skin ulcers (and other dermatologic presentations such as telangiectasias, erythematous popular eruptions, and photosensitivity), respiratory manifestations, splenomegaly, and mental retardation. Dysmorphic features are common and include low hairline, facial hirsutism, saddle nose, hypertelorism, mandibular protrusion, high arched palate, and bird-like facial appearance. Prolidase deficiency can be
suspected on the basis of imidodipeptiduria. Confirmation of the diagnosis can be obtained by either the detection of decreased or absent levels of prolidase activity in erythrocytes, lymphocytes, or fibroblasts, or by mutation analysis of the PEPD gene, which can also assist in prenatal diagnosis. Currently there is no known cure for the condition [3].

Our patient presented with recurrent severe pulmonary infections. Nir et al. [2] collected the pulmonary manifestations of 21 patients with prolidase deficiency. Recurrent respiratory infections were the most common manifestation, affecting 12 of the 21 patients. Ten of the patients presented with chronic lung disease and computed tomography findings included cystic changes, bronchiectasis, and ground glass attenuations. The mechanism of lung involvement is not clear, although abnormal collagen recycling, the promotion of necrosis-like cell death, and increased oxidative stress were suggested. The average age of the patients described was 21 years, much younger than our patient, who first presented at the age of 43 years.

Dermatologic involvement is the most common clinical manifestation of prolidase deficiency, present in up to 85% of patients. Ulceration and scarring are particularly common and approximately half of the patients have lower limb ulcers at the time of diagnosis, similar to our patient. Other dermal manifestations include eczematous lesions, purpura, telangiectasias, and photosensitivity. Biopsy usually reveals inconsistent findings. The ulcers are resistant to treatment and tend to recur [4].

In this case report we presented a patient with the classic characteristics of prolidase deficiency but with atypical age of onset. This case represents the diagnostic difficulty of immunodeficiencies and inborn metabolic disease when first encountered at adult age. Following the results, the patient’s family was invited for further genetic consultation.

CONCLUSIONS
Although there is no cure for prolidase deficiency, an early diagnosis, in addition to information about prognosis and family implications, might emphasize the risk for recurrent respiratory infections and encourage patients and their primary physician to complete influenza and Streptococcus pneumoniae immunization.

Correspondence
Dr. A. Kenig
Dept. of Medicine, Hadassah-Hebrew University Medical Center, Ein Kerem, Jerusalem 9112001, Israel
email: kenig.ariel@gmail.com

References

Immune system dysfunction is paramount in coronavirus disease-2019 (COVID-19) severity and fatality rate. Mucosal-associated invariant T (MAIT) cells are innate-like T cells involved in mucosal immunity and protection against viral infections. Flament and colleagues studied the immune cell landscape, with emphasis on MAIT cells, in cohorts totaling 208 patients with various stages of disease. MAIT cell frequency is strongly reduced in blood. They display a strong activated and cytotoxic phenotype that is more pronounced in lungs. Blood MAIT cell alterations positively correlate with the activation of other innate cells, proinflammatory cytokines, notably interleukin (IL)-18, and with the severity and mortality of severe acute respiratory syndrome coronavirus-2 infection. The authors also identified a monocyte/macrophage interferon (IFN)-α–IL-18 cytokine shift and the ability of infected macrophages to induce the cytotoxicity of MAIT cells in an MR1-dependent manner. Together, these results suggest that altered MAIT cell functions due to IFN-α–IL-18 imbalance contribute to disease severity, and their therapeutic manipulation may prevent deleterious inflammation in COVID-19 aggravation.

Nature Immunol 2021; 22: 322
Eitan Israel