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Infantile Systemic Hyalinosis: A Case Report of Compromised Cellular and Humoral Branches of the Immune System Leading to Infections

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Abstract

Infantile systemic hyalinosis (ISH) is a rare disorder characterized by hyaline deposition in the skin as well as visceral organs. Though commonly associated with a protein losing enteropathy (PLE) and loss of immunoglobulins the profile of cellular and humoral branches of the immune system has not previously been described. We describe the immune system deficits in a case of ISH associated with PLE and infections. A history of multiple infections prompted an immunocompetency evaluation in a patient with ISH and PLE. Low immunoglobulin G (IgG), poorly protective pneumococcal titers, and nonresponse to *Candida* on lymphocyte transformation in the face of increasing infections lead to the diagnosis of a combined immunodeficiency. This is the first case report detailing quantitative and qualitative deficits of the humoral and cellular branches of the immune system in a patient with ISH. The understanding of the different aspects of this disease including the immune deficits impacts not only prognosis but also end-of-life decisions as well.

Introduction

Infantile systemic hyalinosis (ISH) is a rare autosomal recessive disease characterized by diffuse hyaline deposits in the skin, muscle, and visceral organs^{1,2} and distinguished by painful arthrogryposis, stiff skin, and facial dysmorphism.³ This syndrome was first described by Nezelof in 1978, and numerous cases have subsequently been documented in the literature. ISH presents with increasing contractures, joint pain, thickened skin, and perianal papules typically within the first 6 months of life.^{1,4-5} A protein losing enteropathy (PLE) with resultant diarrhea and failure to thrive has been associated with ISH.^{1,2,4-6} Infections, including pneumonia, sepsis, and infectious diarrhea have previously been reported in patients with ISH.^{1,2,5-7} The details of immune impairment in ISH have not been previously described.

Case Report

Our patient was the second child of a healthy, nonconsanguineous couple. She had one healthy sibling. She was born full term without complications. However, the mother reported decreased movement during the pregnancy. At 1 week of age, she developed an erythematous rash on her cheeks, which spread to her head, arms, and trunk. At 2 weeks, she developed progressive contractures of her fingers. At 7 weeks, she was hospitalized with a worsening rash, a secondary skin infection, and MRSA bacteremia. At that time, serum electrolytes, immunoglobulin levels, isohemagglutinins, and lymphocyte subsets were normal. A radioallergosorbant (CAP RAST) panel for foods and environmental allergens was negative. She received intravenous antibiotics

and her rash resolved. She was discharged home with instructions to follow-up with Cardiology for a small PDA and ASD identified by echocardiogram.

At 3.5 months of age, the patient was evaluated by Genetics for dysmorphic features, developmental delay, and short limbs. Her karyotype and x-rays of the chest and long bones were normal.

At 7 months, she was hospitalized with increasing abdominal distension and difficulty breathing. Her weight was 5.6 kg (<3rd percentile) and height was 59 cm (<3rd percentile). She had coarse facial features and a large anterior fontanelle. She did not have any gingival hypertrophy. Her abdomen was distended but soft with a small reducible umbilical hernia. There was no hepatosplenomegaly. Her hips were held in a “frog leg” position and she had bilateral upper and lower extremity contractures. She had an erythematous macular rash under her neck that extended to the ears as well as a fleshy nodule in the perianal region. There was a 1/6 systolic ejection murmur but otherwise her cardiac and respiratory examinations were benign.

Repeat x-rays demonstrated wormian bones within the cranium as well as tubularization and decreased mineralization of the long bones. During her hospitalization, she developed persistent diarrhea, hypoproteinemia, and hypoalbuminemia. An abdominal ultrasound and CT scan showed prominent ascites and bowel wall thickening. A fecal alpha 1 antitrypsin level was elevated at 258. Biopsies of her colon and duodenum revealed chronic inflammation but were not pathognomonic for a particular cause of PLE. Initially she was started on a diet of pureed foods and Pregestimil. She was later switched to Neocate in an attempt to eliminate any allergic triggers as a cause of her rash. During her hospitalization, her weight did not improve despite adequate oral nutrition and she continued to remain below the 3rd percentile. This was likely due to her persistent diarrhea, hypoproteinemia, and hypoalbuminemia. In an attempt to improve her nutritional status, she was started on supplemental total parenteral nutrition (TPN). In order to facilitate TPN administration, she required the placement of a femoral central line.

She was evaluated by the Immunology service, after she was noted to have decreased immunoglobulin levels in the face of infections involving multiple organ systems. These included an infected line thrombus, coagulase negative staphylococcal bacteremia, and RSV pneumonia with an oxygen requirement. An immunocompetency evaluation performed initially identified a low IgG level (85 mg/dL)⁸ with normal IgA and IgM. She had protective titers to diphtheria, *Haemophilus influenza* type B, and tetanus. However, despite receiving all vaccinations within the Prevnar series, she only responded to 1/14 pneumococcal serotypes. A lymphocyte proliferation study demonstrated normal responses to tetanus and mitogens, but without response to *Candida*. Peripheral blood lymphocyte subsets demonstrated a high T-cell number with normal percentages and a normal CD4/CD8 ratio. She had normal CD18 and CD11a counts. Her IgG levels decreased to a nadir of 66 mg/dL and, as her clinical status was deteriorating with worsening pneumonia and persistent coagulase negative staphylococcal bacteremia, she was started on intravenous immunoglobulin (IVIG), despite certain loss due to her PLE. Her infections resolved and her IgG levels improved to 420 mg/dL; however, as expected, IgG levels immediately began to decrease due to her PLE. She received 2 subsequent IVIG infusions 2 weeks apart to keep levels above 72 mg/dL until underlying infections were clearly resolved.

Her final diagnosis was established after a skin biopsy demonstrated hyaline collagen deposition in the dermis. After extensive family meetings, IVIG infusions were discontinued and the patient was discharged home with hospice care. She died several months later.

Discussion

To our knowledge, this is the first case report profiling quantitative and qualitative deficits of the humoral and cellular branches of the immune system in a patient with ISH and PLE. Our patient presented with characteristic clinical features of ISH with progressive joint contractures, thickened skin, and a perianal nodule. During the course of our patient's illness, she developed PLE with diarrhea, failure to thrive, and infections (skin, infected line thrombus, bacteremia, and pneumonia with compromised respiratory status). Her immunocompetency evaluation demonstrated IgG hypogammaglobulinemia, lymphocyte proliferation non-responsive to *Candida*, and poorly protective pneumococcal titer levels. It is possible that she would have responded favorably to a pneumococcal booster with a subsequent improvement in her pneumococcal titer levels, which is typically the next step in treatment. However, since she was acutely ill we were unable to administer the booster within the time period prior to her death. Our patient had multiple invasive procedures performed during her hospitalization including multiple endoscopies, colonoscopies with biopsies, and a placement of a femoral central line. It is very unlikely that the endoscopies or colonoscopies were a source of her persistent coagulase negative staphylococcal bacteremia. However, the presence of a central line was likely the source of the infected thrombus and the bacteremia.

In general, the classic immune profile of a patient with PLE includes IgG hypogammaglobulinemia and lymphopenia.⁹ IgA may also be low with a normal IgM. T cells (CD3, CD4, and CD8) are the predominant lymphocytes in circulation and in PLE are found to be significantly lower, with preferential loss of CD4 to a degree that the CD4/CD8 ratio reverses.⁹ Absolute numbers of B and NK cells are typically normal, but with relatively higher percentages of NK cells. There is no significant correlation between duration of disease and the IgG and IgA levels or T-cell numbers.

PLE, due to ISH, is thought to be due to deposition of hyaline material in the intestines.¹ There have been previous reports describing quantitative immune deficiencies in patients with ISH, including IgG hypogammaglobulinemia and lymphopenia, but without identification of qualitative immunoglobulin or lymphocyte dysfunction.⁵ Our patient had both a quantitative decrease in IgG levels as well as a qualitative dysfunction, as assessed by nonprotective pneumococcal titer levels, and the presence of multiple infections responsive to IVIG. Though our patient did not have lymphopenia, a qualitative dysfunction was identified through a lymphocyte proliferation study with a nonresponse to *Candida*.

The mechanism behind the loss of T cells in PLE is not fully understood. The decrease in CD4 and CD8 counts has been suggested to be due to inflammation in the gut, leading to sequestration of CD4 and CD8 cells. We observed intestinal inflammation in our patient, but without a decrease in T cells (CD3, CD4, or CD8).

The gastrointestinal tract is a port of entry for pathogens and infections are a major cause of morbidity and mortality in immunocompromised patients. Infections associated with PLE include skin, gastrointestinal, and lung infections.¹⁰ Administration of IVIG has been shown to effectively manage PLE due to lymphangiectasia and Crohn's disease¹⁰; however, in PLE immunoglobulin levels fall more quickly than in primary or other secondary IgG immunodeficiencies, limiting IVIG as chronic treatment.

Conclusion

We found an abnormal immunologic profile of both cellular and humoral branches of the immune system in a patient with ISH, PLE, and infections. Our patient's infections resolved with IVIG and her clinical status improved, though IgG levels remained low due to continued gastrointestinal loss. IVIG was used effectively to acutely treat infection in a patient with IgG

hypogammaglobulinemia due to ISH and PLE. However, there is no curative treatment for ISH. Therapy is focused on symptomatic relief of pain and infections. It is yet unclear if IVIG can be used for all patients with ISH who have IgG hypogammaglobulinemia. All patients have a varied clinical course and the decision to use IVIG has to be made based on an individual clinical scenario. Given how rare this disorder is, it will require a great deal of cooperation between multiple centers to characterize the immune profile and to determine a guideline for IVIG use. For now, the prognosis for ISH is poor and, though IVIG can be used to acutely treat infections, end-of-life care decisions should dictate the extent of treatment.

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