IgNS Immunoglobulin National Society

CLINICAL UPDATE

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Beyond Infection: The Realities of Primary Immunodeficiency

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Secondary Immune Deficiencies From Biological Agents
Mark Ballow, MD

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Autoinflammatory Disorders
Lori Broderick, MD, PhD

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The Complex PI Patient: The Tangled Web of Immunodeficiency and Its Complications
Richard Wasserman, MD, PhD

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- **Mark Ballow, MD:** Nothing to disclose
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The Complex PI Patient: The Tangled Web of Immunodeficiency and Its Complications

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OBJECTIVES

1. **Review the range of disorders of host defense**
2. **Understand the non-infectious co-morbidities associated with PI**
3. **Appreciate that pediatric and adult PI patients are subject to distinct but overlapping clinical problems**
4. **Understanding that complexity in a PI patient derives from multiple, interacting problems**

Introduction

Primary immunodeficiency (PI) is, for most patients, a life-long condition that has an ongoing impact on their health, sense of well-being, and quality of life. Although some PI patients are more complex than others, because the immunologist is the captain of the ship, an appreciation of the sources of complexity in the management of PI patients is important. Making a correct diagnosis requires that clinicians be aware of the range of host defense defects. The treatment team must recognize that, in addition to unusual and unusually frequent infections, PI patients are subject to a range of co-morbid conditions. Finally, there must be an appreciation that pediatric and adult PI patients are subject to distinct but overlapping clinical problems.

Primary Immunodeficiencies

The more than 450 PI genotypes have been categorized into ten disorder groupings but can generally be thought of as comprising several phenotypes; the predominantly antibody disorders (e.g., Bruton's X-Linked Agammaglobulinemia [XLA], Common Variable Immunodeficiency [CVID], Selective IgA Deficiency, specific antibody deficiency [vaccine non-responder state], and Hyper IgM Syndrome), the cellular and combined immunodeficiencies (e.g., DiGeorge Syndrome, Severe Combined Immunodeficiency [SCID], Wiskott-Aldrich Syndrome, and Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED]), disorders of innate immunity (e.g., Chronic Granulomatous Disease [CGD], Leukocyte Adhesion Defect Types I and II [LADS], and Toll-like receptor defects), and deficiencies of the classical and alternate complement pathways.

The primary non-Infectious co-morbidities of PI are autoimmunity (e.g., inflammatory bowel disease, arthritis, Granulomatous Lymphocytic Interstitial Lung Disease [GLILD], poly-endocrinopathy, thyroiditis, vitiligo, and others), as well as lymphoid and non-lymphoid malignancies. B-cell lineage malignancies are the most common but any lymphoid cell, at any stage of development, may undergo malignant transformation. Gastrointestinal (GI) malignancy is seen more frequently in XLA and CVID. Patients with NK cell deficiency are at increased risk for genital and oral human papillomavirus (HPV)-related cancers and Epstein-Barr Virus (EBV)-associated liver and smooth muscle tumors.

Severity Fosters Complexity

The complete absence of specific immunity in SCID, for example, creates a broad susceptibility to infections including polymicrobial infections involving viral, bacterial, and fungal pathogens. For these patients, an etiologic diagnosis of their infection(s) is crucial but may be difficult or impossible necessitating empiric multi-drug regimens. There is no effective therapy for many viral pathogens and infections may not resolve without a hematopoietic stem cell transplant. Some PIs are inherently complex because the immunodeficiency is just one feature of a multi-system genetic disorder such as DiGeorge Syndrome (cardiac, parathyroid, immunodeficiency), IPEX (X-linked immunodysregulation, polyendocrinopathy, enteropathy), WHIM Syndrome (warts, hypogammaglobulinemia, infections, myelokathexis), or autoimmune polyendocrinopathy candidiasis ecto-dermal dystrophy (APECED).

Chronicity Contributes to Complexity

Repeated infection causes structural tissue damage that increases infection susceptibility as in chronic sinusitis and bronchiectasis. Some infections, such as chronic osteomyelitis in CGD, chronic HPV vaginitis in LADS I, or respiratory syncytial virus [RSV] pneumonia in SCID, for example, may not be resolvable in the absence of normal host defenses.

The co-morbid autoimmune diatheses and PI-associated malignancies inherently increase management complexity but are further complicated by the use of immunosuppressive biologic (e.g., rituximab [Rituxan], infliximab [e.g. Remicade, Inflectra, and others] and chemotherapeutic (e.g., azathioprine, cyclosporine, and others) agents. Often, the goals of therapy may conflict as in a LADS I patient with both inflammatory bowel disease necessitating anti-Th1 treatment and chronic HPV vaginitis requiring Th1 augmentation.

Case I – Pediatric Patient

A 5-month-old presented with tachypnea and poor feeding. He had been well until about 3½ months-of-age when he developed symptoms of a viral respiratory tract infection. Over the next month, as the respiratory symptoms waxed and waned, he was treated twice by his pediatrician with antibiotics for otitis and purulent rhinitis (amoxicillin and azithromycin). He was also treated with short-acting bronchodilator therapy.

He was hospitalized at a community hospital for respiratory symptoms and cough. At that time, a chest X-ray showed interstitial pneumonitis. He was referred to a pulmonologist who admitted him to a tertiary care hospital where he was treated with frequent aerosol bronchodilators and antibiotics with improvement and was discharged. A nasal culture during that admission grew *Streptococcus pneumoniae* and *Hemophilus influenzae*. He was readmitted one week after discharge.

On admission, he was a well-developed, well-nourished male with normal skin and purulent rhinorrhea. He had a respiratory rate of 60, generalized rales, and moderate wheezes and was treated with IV fluids and antibiotics. Bronchoalveolar lavage showed pneumocysts and evidence of respiratory syncytial virus. The immunologist was consulted.

The immunologist's findings:

- Family history revealed that the patient's mother had two maternal uncles who died of pneumonia before six months-of-age in the pre-antibiotic era
- IgA<6.7, IgG 75, IgM 3.
- The patient was not lymphopenic, but all the lymphocytes were CD 20 positive (maternal)
- No response to stimulation with PHA, PWM, and ConA

Outcome

Despite treatment with pentamidine, trimethoprim/sulfamethoxazole, and high dose IVIG, the patient died eight weeks after admission. Twenty-five years later, a nephew was diagnosed during the first week of life and successfully transplanted.

Case II – Pediatric Patient

A 2-year-old female was referred for recurrent oral candidiasis. She had had a candida diaper rash in early infancy but no generalized rash and no other infections. Her physical examination was normal.

Immunologic evaluation:

- Quantitative immunoglobulins, DT titers normal
- Candida skin test non-reactive
- DT skin test reactive
- Lymphocyte phenotyping normal
- PHA, ConA, PWM, and tetanus in vitro stimulations normal
- Candida antigen in vitro stimulation non-reactive

The patient was diagnosed with Chronic Mucocutaneous Candidiasis (CMC). Several months later, she was seen in the Arthritis Clinic for evaluation of intermittent joint problems. Physical examination demonstrated mild tetany and she was diagnosed with hypoparathyroidism. Over the next ten years, hypothyroidism and hypoadrenalism were diagnosed and treated. Her management comprised vitamin D, thyroid, glucocorticoid and mineralocorticoid replacement, calcium supplementation, and careful management of fluids and electrolytes. She had recurrent episodes of candida esophagitis requiring hospitalization because she was unable to swallow fluids or medications. After one hospitalization her mother asked, "What will I do when she gets diabetes?"

There was a single case report in the literature of transplant for CMC. She was transplanted using a sibling donor. The transplant was complicated by RSV pneumonitis that resolved with engraftment. One-year post-transplant, she developed bronchiolitis obliterans that was treated with pulse steroids and high dose IVIG. Over the next ten years, there was a gradual deterioration of B-cell function that led to the need for immunoglobulin supplementation. She was referred to the APECED program at NIH where genetic studies demonstrated an Autoimmune Regulator (AIRE) mutation. She has developed progressive interstitial pneumonitis that was stabilized with azathioprine and rituximab.

Case III – Adult Patient

A 34-year-old male presented with chronic diarrhea and cachexia. He was diagnosed with polio at age three and in 1958 with XLA. He was treated with IMIG until the late 1970s when IgG was replaced using fresh frozen plasma (FFP). While receiving FFP he developed hepatitis C. When IVIG became available in the early 1980s, he was treated with 100 mg/kg/month but frequent respiratory tract infections continued. During the months before the presentation, he developed progressive anorexia, ascites, and pedal edema.

Physical examination on admission showed malnutrition with muscle wasting, scattered rhonchi, marked ascites, and pitting edema to the mid-tibia, the liver and spleen were not palpable. There was a mild right lower leg weakness that had been present since early childhood. The patient, a petroleum engineer, was fully oriented to time, place, and person.

Initial laboratory studies showed mild pancytopenia, ALT 180 IU/L, AST 210 IU/L, bilirubin 8.7 mg/dL, alkaline phosphatase 135 IU/L, BUN 35 mg/dL, creatinine 0.8 mg/dL and IgG 224 mg/dL.

His sputum grew *H. influenzae*. The stool was negative for blood, mucus, pus, and bacterial pathogens. Viral culture grew Echovirus 11. Chest X-ray showed no active infiltrates, no air bronchograms. Liver biopsy showed severe cirrhosis.

He was treated with parenteral alimentation, appropriate antimicrobials, and high dose IVIG to maintain serum IgG concentration >500 mg/dL. Cerebrospinal fluid examination showed no cells and normal glucose and protein but the fluid grew Echovirus 11. Because of a concern for chronic enteroviral meningoencephalitis, an Ommaya reservoir was placed for intraventricular immunoglobulin therapy. An intraventricular hemorrhage occurred following the first dose of gamma globulin. The patient developed altered mental status with a mild organic brain syndrome. Intraventricular immunoglobulin instillation was discontinued and the altered mental status cleared completely in one week with no residual deficits. He was then treated with higher dose IVIG (500 mg/kg every two weeks).

Due to liver failure, the patient received an orthotopic liver transplant. On day +14 there was an increase in transaminases and a liver biopsy was consistent with mild, acute rejection or hepatitis. The patient was treated with IVIG (1 g/kg/week) and did well. The liver biopsy specimen grew Echovirus 11. Echovirus 11 was ultimately cleared from blood and CSF and the IVIG dose was weaned to 500 mg/kg every two weeks.

Three years post-transplant, the patient had self-weaned IVIG to 500 mg/kg/month when he experienced a generalized seizure. CT scan showed diffuse punctate lesions in gray and white matter. CSF grew Echovirus 11. He was re-treated with IVIG 1 g/kg/week and resolved the neurologic abnormalities. He was maintained on IVIG 500 mg/kg every other week and did well until seven years post-transplant when he experienced another generalized seizure.

Contrast CT showed a 7 cm mass that was thought to be a brain abscess or lymphoma. A brain biopsy showed Aspergillus infection and he was treated with liposomal amphotericin plus itraconazole with the resolution of the brain abscess. He was maintained on chronic itraconazole prophylaxis.

Sixteen years post-transplant, he presented with a right-sided bloody pleural effusion, anorexia, and weight loss. The effusion was resistant to diagnosis and treatment. Liver biopsy showed chronic rejection. The patient died.

Case IV – Adult Patient

A 40-year-old male with CVID initially presented with acute ITP at age 10. He was treated by the hematologist and the ITP resolved but he then developed recurrent respiratory tract infections and was referred to Immunology. His evaluation demonstrated severe pan-hypogammaglobulinemia with absent B cells and normal T cell numbers and function. He was treated with IVIG and, although the infection frequency improved, he continued to have recurrent otitis and sinusitis necessitating multiple surgical interventions.

At age 40, he continues to experience recurrent sinusitis and otitis with otorrhea despite myringotomy tubes and multiple sinus surgeries, including a frontal sinus obliteration. He has intermittent asthma that is well controlled as well as intermittently active enterocolitis and diarrhea that is poorly controlled and has resulted in chronic malnutrition. Additionally, he has chronic disseminated cutaneous HSV I that is partially suppressed with valacyclovir. However, when colitis flares, valacyclovir is not absorbed resulting in severe exacerbations of the HSV I dermatitis.

This patient's management challenges include maintaining adequate nutrition in the context of recurrent abdominal pain and diarrhea, adequately suppressing HSV I without intravenous acyclovir, and finding qualified specialists willing to care for a chronically ill, complex patient who is permanently disabled and relies on Medicaid/Medicare for healthcare coverage.

Summary

Many primary immunodeficiency patients require complex management regimens because of the severity of the immunodeficiency, the chronicity of the problems, and associated co-morbid conditions. Although the immunologist should be the captain of the healthcare ship, a coordinated team including nurses, pharmacists, and other medical specialists is need to optimize the care of these complex patients.