IgNS Immunoglobulin National Society

CLINICAL UPDATE

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Beyond Infection: The Realities of Primary Immunodeficiency

Jointly provided by Educational Review Systems and Ig National Society, Inc.

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Target Audience

This activity is intended for physicians, nurses, pharmacists, and other healthcare professionals who care for patients in need of immunoglobulin therapy and specialty biologics.

Educational Objectives

Upon completion of this activity, participants should be able to:

Lesson 1: Secondary Immune Deficiences from Biological Agents

- Review the nomenclature for monoclonal antibodies
- Explain the mechanisms for prolonged hypogammaglobulinemia with Rituximab
- Review the immune and infectious consequences of some of the most frequently used biologics on the immune system
- Review the adverse effects of immune check point inhibitors

Lesson 2: Autoinflammatory Disorders

- Define autoinflammatory disorders
- Discuss the role of phenotyping and family history in the diagnosis of autoinflammatory disease
- Describe the basis of inflammasome-mediated inflammation
- Describe the role of cytokine-targeting biologics as therapy for these disorders

Lesson 3: Immune Dysregulation – A New Facet of Primary Immunodeficiency Disease (PIDD)

- Discuss non-infectious presentations and manifestations of primary immunodeficiency
- Formulate a differential diagnosis for children with suspected immunodeficiency
- Identify new rare defects of the immune system that cause immunodeficiency

Lesson 4: Pulmonary complications of primary immunodeficiency

- Explain key aspects of the pathogenesis and clinical presentation of pulmonary disease in primary immunodeficiency
- Summarize our understanding of asthma and chronic obstructive pulmonary disease in primary immunodeficiency
- Recognize the physiology, clinical presentation, and therapeutic approach to bronchiectasis in primary immunodeficiency
- Identify distinct forms of interstitial lung disease occurring in primary immunodeficiency

Lesson 5: The Complex PI Patient: The Tangled Web of Immunodeficiency and Its Complications

- Learn the range of disorders of host defense.
- Understand the non-infectious co-morbidities associated with PI.
- Discern pediatric and adult PI patient differences pertaining to treatment and clinical outcomes.
- Learn the complexity of PI patients' comorbidities and risk factors.

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Secondary Immune Deficiencies from Biological Agents

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OBJECTIVES

1. Review the nomenclature for monoclonal antibodies
2. Understand the mechanisms for prolonged hypogammaglobulinemia with Rituximab
3. Review the immune and infectious consequences of some of the most frequently used biologics on the immune system
4. Review the adverse effects of immune check point inhibitors

Introduction

There are many risk factors for the adverse effects of drug therapy. These factors include the action of the drug itself, the dose that is used for the drug, and the duration of treatment with the medication. For example, a patient who receives a drug while undergoing stem cell transplant for malignancy may have more immune complications than a patient receiving the drug for chronic stable disease. Hospitalized patients and the elderly are more likely to develop immune complications from medication.

Drugs used for the treatment of rheumatic disease or anti-inflammatory medication can cause decreases in immunoglobulin levels. Anticonvulsants, particularly phenytoin anticonvulsants, may lower serum IgA. The mechanism for this drug-induced hypogammaglobulinemia is not known.

In this presentation, we will discuss the secondary immune deficiencies caused by biologic drugs.[1] A biologic drug is a medicinal product that is produced from living organisms. Biologic products may contain proteins that control the action of other proteins or cellular processes, such as gene transcription, hormone regulation, or regulation of the immune system. Biologic drugs are sometimes referred to as *biologic response modifiers* because they change the manner of operation of natural biologic intracellular and cellular actions.

Biologic response modifiers include substances that are nearly identical to the body's own key signaling proteins. Some are receptor constructs that mimic a receptor on the surface of a cell and are usually linked to the constant region of the immunoglobulin frame. Others are monoclonal antibodies similar to the antibodies of the human immune system used to fight off bacteria and viruses. These monoclonal antibodies are custom designed and may be produced to specifically counteract or block a given substance in the body or to target a specific cell type to achieve a specific therapeutic effect. The nomenclature for monoclonal antibodies is shown in Table 1. In addition to their therapeutic effects, biologics can have unintended effects on the immune system that can compromise host defenses and lead to serious infections.

Monoclonal antibodies to B cells

Rituximab (Rituxan) is a *chimeric* human mouse monoclonal antibody used for the treatment of hematological malignancies and autoimmune diseases. It is directed at the CD20 receptor expressed on B lymphocytes (B cells). Treatment with this monoclonal antibody results in a rapid depletion of B cells. It may take 9 to 12 months for the B cells to return after treatment is completed. However, if therapy is coupled with chemotherapy, B cell recovery may take 18 to 24 months. Typically, when the B cells recover, the majority of patients do not have any residual immune dysfunction that may result in infections. In most patients, rituximab does not significantly reduce the levels of existing antibodies. However, a subset of patients develops hypogammaglobulinemia, which can be persistent and clinically significant, resulting in serious infections and necessitating antibiotic prophylaxis or immune globulin replacement therapy to prevent infections. In a small study by Kaplan et al., patients treated with rituximab who were receiving intravenous immunoglobulin (IVIG) because of infections and hypogammaglobulinemia were analyzed by retrospective chart review.[2] Eleven patients had received rituximab for autoimmune disorders or lymphoma. Nine patients had prolonged hypogammaglobinemia (13 to 54 months) after completion of the rituximab treatment. Five of these patients also had undetectable B cells. The authors hypothesized that patients who develop recurrent infections while on rituximab treatment may have some type of baseline subclinical immune dysfunction that is unmasked and/or augmented by rituximab. Barmettler et al. reported on a large retrospective cohort study of 4479 patients who had received rituximab at a large tertiary referral medical center.[3] Eighty-five percent of the patients did not have their immunoglobulin levels checked before therapy. Of those who had levels measured, 48% had low serum IgG levels before rituximab. Following treatment with rituximab, the serum IgG levels were reduced even lower. Many of these patients had severe infections. Increased mortality was associated with age, male sex, and prior complications of severe infection. A total of 4.5% received immunoglobulin therapy following rituximab therapy to reduce the risk of serious infection. These authors concluded that many patients are not screened for low serum IgG levels prior to or after rituximab therapy. Screening these patients before and after therapy may allow for earlier identification of patients at risk, and help identify patients who may benefit from immunoglobulin replacement therapy. Rituximab therapy may impair vaccine responses, especially to polysaccharide vaccines. Immunization prior to starting rituximab therapy is recommended. A common question is how long to use immunoglobulin replacement therapy for hypogammaglobulinemia after rituximab therapy. Barmettler and Price[4] have suggested that in patients who recover B cells but who have prolonged hypogammaglobulinemia it may be helpful to measure switched ($CD27^+IgD^-IgM^-$) or unswitched ($CD27^+ IgM^+$) memory B cells. In those patients with a decrease in these B-cell subpopulations, health care providers may wish to continue immunoglobulin replacement therapy.

TNF Inhibitors

Blocking tumor necrosis factor (TNF) can markedly disrupt granuloma architecture and, ultimately, enable dissemination of mycobacteria. Patients are also at risk for other intracellular pathogens such as *Aspergillus fumigatus*, *Coccidioides* species (the causative agent of coccidioidomycosis), *Histoplasma capsulatum, Listeria monocytogenes,* and nontuberculous mycobacteria. The most frequent issue with TNF inhibitors is reactivation of latent mycobacteria, usually from the lung. Patients should be skin tested and have a chest X-ray prior to therapy. The risk is higher with infliximab (Remicade, Inflectra, and other brand names) and adalimumab (Humira) than with etanercept (Enbrel). Other biologics may also be associated with reactivation of mycobacteria. Abatacept (Orencia) and tocilizumab (Actemra) have an intermediate risk of causing reactivation, and anakinra (Kineret) and rituximab have a low risk of reactivating tuberculosis (TB). Older age, diabetes, smoking, glucocorticoid dose, and previous infection history are important risk factors for serious infections. The most serious infections occur within the first 1–2 years of exposure to biologics, with the highest risk in the first few months of biologic use. Patients on these biologics should not receive live viral vaccines. Influenza vaccines administered by injection are without risk.

Complement inhibitors

Eculizumab (Soliris) is a humanized monoclonal antibody that blocks the cleavage and activity of complement factor 5 (C5). This monoclonal biologic is approved for paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS)- associated thrombotic microangiopathy. Eculizumab increases the risk of infection by inhibition of complement effector mechanisms (C5–C9). The most common infection associated with Eculizumab is *Neisseria meningitidis.* Other infections include those associated with *Pseudomonas aeruginosa*, *Aspergillus* species, and herpes simplex viruses.

Biologics directed at cytokines

There are many biologic therapies that target cytokines directly. Some of these are shown in Table 2. For the most part, these biologics have few adverse effects and generally do not cause an increase in infectious disease susceptibility. The IL-1 blocking agents (e.g., anakinra, canakinumab [Ilaris], and rilonacept [Arcalyst]) have been an important therapeutic approach in the treatment of several autoimmune and autoinflammatory diseases. Although they have been associated with an increased risk of respiratory infections, they are usually well tolerated. With the IL-5 blocking agents (e.g., mepolizumab [Nucala], reslizumab [Cinqair] and benralizumab [Fasenra]), published studies have not shown any significant increase in infections, although in two studies herpes zoster infections were reported in two patients treated with mepolizumab. The manufacturers suggest vaccination with herpes zoster vaccine and treatment of patients with pre-existing helminth infections. Dupilumab (Dupixent), a fully human monoclonal antibody directed at the alpha subunit of the IL-4 receptor, blocks both IL-4 and IL-13 signaling. It is approved for the treatment of moderate-to-severe atopic dermatitis and as add-on therapy for moderate-to-severe eosinophilic or steroid-dependent asthma. There are also several IL-17A blocking biologics. Secukinumab (Cosentyx) is approved for the treatment of plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis. The major issue with this group of IL-17A inhibiting biologics is mucosal or cutaneous candidiasis.

A more serious infectious process related to JC virus (JCV) is progressive multifocal leukoencephalopathy (PML).[5] PML is caused by reactivation of latent polyoma JC virus. Cognitive impairment and behavioral changes are the earliest clinical manifestations. The diagnosis can be confirmed by quantitative detection of JCV DNA in the cerebrospinal fluid (CSF). Prior chemotherapy or immunosuppressive drug use increases the risk of PML by 2- to 4-fold. PML was first recognized with the use of natalizumab (Tysabri), a humanized monoclonal antibody against the cellular adhesion molecule α4-integrin, for treatment of multiple sclerosis and Crohn's disease. This biologic was removed from the market but subsequently reintroduced for multiple sclerosis. PML can occur with a number of biologics (see Table 2).

In summary, biologic therapies can be associated with a variety of adverse effects due to the fact that they target immune responses and host protection mechanisms that protect against environmental pathogens. The risk of immune complications and the type of infection is dictated by the specific biologic response modifier and its target(s). There are also patient-specific factors that play an important role such as the underlying disease, the patient's immune status and comorbid conditions, and the use of concomitant combinations of other immunosuppressive agents. The use of biologic agents to treat diseases is a rapidly growing field of medicine. Physicians and patients have to be vigilant when new biologic agents are being used due to the fact that phase III clinical trials used by the FDA to approve drugs may not have uncovered all possible adverse consequences in every patient population.

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Table 1 Nomenclature for monoclonal antibodies

- Suffix - *mab* - used for mAb
- Animal source of the mAb
  - Mouse - *omab*
  - Chimera - *ximab*
  - Humanized - *zumab*
  - Human – *umab*
- Disease or target class
  - Immune - lim (dac li(m) zumab)
  - Tumor - tum- (Ri tu(m) xi mab)
- Unique prefix -
  - Nata li(m) zu mab (Tysabri)
  - Mepo li(m) zu mab (Nucala)
  - Oma li(m) zu mab (Xolair)
  - Ada lim umab (Humira)
  - Cana kin umab (Ilaris)

The use of stems in the selection of International Nonproprietary names (INN) for pharmaceutical substances. *World Health Organization, Geneva INN Working Document* 17.406 20/01/2017

Table 2 | Secondary immunodeficiency induced by biologics

Biologic	FDA Approved	Target	Immune Effects	Infections
Abatacept	RA, kidney transplant, PJIA	B7-1/B7-2	Disrupt CD28 co-stimulation	Pneumonia, cellulitis, UTI
Alemtuzumab	Chronic B-cell leukemia, MS	CD52	Profound depletion of T cells (and B cells)	TB reactivation, DNA viruses, opportunistic
Basiliximab	Renal transplantation	CD25(IL-2R-a chain)	Block IL-2 receptor on T cells	CMV reactivation
Belimumab	SLE	BlyS/BAFF	B cells	Influenza, pneumonia, PML
Cetuximab	Metastatic colorectal cancer	Epidermal growth factor	Bind and inhibits Epidermal growth factor receptor	Anaphylactic reactions - IgE Abs to galactose-α-1,3 galactose (sensitization to lone star tick)
Eculizumab	PNH, aHUS	C5	Binds C5/inhibits terminal C activation	Neisseria infections
IL-1 antagonist (anakinra, canakinumab, rilonacept)	RA, Periodic fever syndromes, SJIA	IL-1α and IL-1β	Block IL-1R – anakinra Neutralize IL-1β – canakinumab Neutralizes IL-1β - rilonacept (fusion protein IL-1 R components)	Bacterial and viral infections
Natalizumab	MS, Crohn	α4 integrin antagonist	Block migration of leukocytes into CNS	PML, CNS VZV and HSV
PD-1 antagonist (pembrolizumab, nivolumab)	Melanoma, NSCLC, HNSCC	PD-1	Hypothyroidism, hepatitis, colitis, pneumonitis	85% bacterial infections -pneumonia; other infections herpes viruses
Rituximab	NHL, CLL, GPA, RA	CD20	Profound depletion of B cells	DNA viruses, PML, HBV and HCV, Parvovirus
Secukinumab	Psoriasis, AS	IL-17A	Block the IL-17 pathway	Candidiasis (2%-5%)
TNF inhibitors	RA, UC, Crohn, Psoriasis, AS, PJIA, Uveitis	TNF-α	Innate immune system	Mycobacterial infections (reactivation), fungal infections
Tocilizumab	RA, SJIA, PJIA	IL-6R	B cells, Treg cells	Pneumonia, HZ
Ustekinumab	Psoriasis, Crohn	P40 subunit (IL-12/IL-23)	Blocks IL-12 and IL-23	URI, pneumonia
Vedolizumab	Crohn, UC	α4b7 antagonist	Block migration of gut homing lymphocytes	PML, URI

aHUS – atypical hemolytic uremia syndrome, AS – ankylosing arthritis, AS – ankylosing spondylitis, CLL – chronic lymphocytic leukemia, CMV – cytomegalovirus, GPA – granulomatosis with polyangiitis, HBV – hepatitis B virus, HCV – hepatitis C virus, HNSCC – Head-neck squamous cell carcinoma, HSV-herpes simplex virus, HZ – herpes zoster, MS – multiple sclerosis, NHL–non-Hodgkin lymphoma, NSCLC – non-small cell lung cancer, PJIA – polyarticular juvenile idiopathic arthritis, PML – progressive multifocal leukoencephalitis (infection with JC virus), PNH – paroxysmal nocturnal hemoglobinuria, RA – rheumatoid arthritis, SJIA – systemic juvenile idiopathic arthritis, TB – tuberculosis, TNF– tumor necrosis factor, UC – ulcerative colitis, URI – upper respiratory infection, UTI – urinary tract infection, VZV – varicella zoster virus

Adapted from Davis BP and Ballas ZK [6] and Ballow M and Fleisher T[1]

Autoinflammatory Disorders

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OBJECTIVES

1. **Define autoinflammatory disorders**
2. **Appreciate the role of phenotyping and family history in the diagnosis of autoinflammatory disease**
3. **Describe the basis of inflammasome-mediated inflammation**
4. **Describe the role of cytokine-targeting biologics as therapy for these disorders**

Introduction: Genotype-phenotype correlation and rare diseases

Patients with immunologic diseases have provided clues that have led to a better understanding of immunology, often through the discovery of single gene mutations that have redefined the extremes of immunity.[1] Patients with primary immunodeficiency, for example, have defects in the immune defenses that protect the host. Often presenting in the first few years of life with severe infections, these genetically-defined disorders include severe combined immunodeficiency (SCID), phagocytic disorders such as chronic granulomatous disease and Mendelian susceptibility to mycobacterial disease (MSMD), and humoral defects such as X-linked agammaglobulinemia.[2,3] Other patients with syndromes such as autoimmune lymphoproliferative syndrome and syndrome of autoimmune polyglandular endocrinopathy with candidiasis and ectodermal dysplasia (APECED) have disease that is attributed to mutations in a single gene, yet have laboratory findings consistent with autoimmunity including high-titer autoantibodies, and antigen specific T cells (reviewed in Davidson and Diamond, 2001[4]). However, rare patients with episodic or chronic inflammation, in the absence of autoimmunity, and without evidence of infection, challenge this classic paradigm.[5] With symptoms driven by innate immune dysregulation, these patients have ultimately been labelled as having disorders of autoinflammation.[6]

Innate immunity and dysregulation

Traditionally considered "non-specific," it is now well-accepted that the innate immune system recognizes nearly 1000 conserved protein and nucleic acid patterns, leading to rapid immune responses against pathogens and metabolites. Pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide and peptidoglycan, are biochemically distinct from host proteins, and are identified by germline-encoded pattern recognition receptors, such as the toll-like receptors, RIG-like receptors, NOD-like receptors, and C-type lectin receptors (reviewed in Netea et al., 2011[7]). Similarly, damage-associated molecular patterns (DAMPs), such as ATP and uric acid, are upregulated in response to cell activation and cell death. This immune response is carefully coordinated for a rapid response to PAMP and DAMP danger signals.[7] A failure at any checkpoint in the system may lead to perpetuation of the innate immune response that could be damaging or even lethal to the host.

Three main principles underlie our understanding of immune dysregulation in autoinflammatory disease. First, an inborn error occurs in a component of the immune system. This leads to secretion of a predominant inflammatory mediator, and ultimately to disease presentation.[5,8] A number of different types of these inborn errors have been identified including those in intracellular sensors that lead to increased pattern recognition receptor function, errors in the cellular stress response that increase molecules that mediate intracellular stress, errors in negative regulator proteins that prevent inhibitor circuits, and those that enhance the signaling of innate immune cells.[8] Each of these pathways leads to an enhancement of the innate immune system inflammatory response, the auto-amplification loop known as autoinflammation.[6,8] The cases below serve to emphasize how the presentation of inflammatory symptoms can lead to a suspicion of these rare autoinflammatory disorders.

Case 1. Urticaria in infancy

The patient was a female infant who was the product of a di-zygotic twin pregnancy with no known complications.[9] The perinatal period was uneventful. The baby was in a normal state of health until 3 months of age, when she developed a raised, erythematous rash diagnosed as dermatographism. The rash resolved without medical intervention, but recurred at age 9 months, for which she was treated with antihistamines, as needed, for idiopathic urticaria. There were no known exposures, and intermittent therapy with antihistamines was successful. At 14 months of age, the patient developed an acute episode with prominent urticarial-like rash, 8 days of fever to a maximum temperature of 104.1°C, conjunctival infection, and irritability. She was admitted to a tertiary care children's hospital with a presumptive diagnosis of Kawasaki disease. Physical exam on admission was notable for a well-developed, well-nourished child with tachycardia, scattered lymphadenopathy, hepatosplenomegaly, and multiple erythematous, blanchable macules, and patches of an urticarial nature, mostly involving the face, torso, and extremities with relative sparing of the palms and soles. Clinical laboratory evaluation revealed elevated inflammatory markers, leukocytosis with neutrophilia, and thrombocytosis. Her infectious workup was negative and multiple echocardiograms were normal. Her fever and rash did not improve, despite high dose intravenous immunoglobulin (IVIG). A skin biopsy was performed which demonstrated a mixed perivascular inflammatory infiltrate comprised of lymphocytes, neutrophils, and rare eosinophils, without evidence for vasculitis, suggesting a diagnosis of cryopyrin-associated periodic syndrome (CAPS).[10]

Cryopyrin-associated periodic syndromes (CAPS)

Cryopyrin-associated periodic syndromes include a spectrum of autoinflammatory diseases caused by autosomal dominant mutations in *NLRP3* which encodes the NLRP3 protein.[11] Mutations in *NLRP3* lead to increased activity of the cryopyrin protein with over-production of the inflammatory mediator IL-1b.[12,13] The CAPS spectrum consists of familial cold autoinflammatory syndrome (FCAS) on the mild end,[10] Muckle-Wells syndrome as moderate disease,[14] and neonatal-onset multisystem inflammatory disease (NOMID) on the severe end.[15] Common symptoms include an urticaria-like rash, intermittent fevers, conjunctivitis, arthralgia, headache, and fatigue but certain

phenotypic features may suggest mild vs. moderate vs. severe disease.[16] Patients with the milder FCAS, tend to have 12-24 hour attacks, with urticaria-like rash, polyarthralgia, and conjunctivitis, often triggered by cold temperatures. The moderate Muckle-Wells syndrome episodes tend to be longer in duration (2-3 days) and have the addition of sensorineural deafness, often presenting in the second decade of life.[14] Finally, NOMID, also known as chronic infantile neurologic cutaneous articular (CINCA) syndrome, is characterized by continuous symptoms of fever, urticaria-like rash, uveitis with vision loss, sensorineural deafness, chronic aseptic meningitis, and epiphysial overgrowth. Despite the differences in severity, all result in activation of the NLRP3 sensor and release of IL-1b which drives the autoinflammatory loop.[16] Three different biologic therapies are currently available to treat patients with CAPS: a recombinant IL-1 receptor antagonist (anakinra [Kineret]), a fusion protein of IL-1 receptor and IL-1 receptor accessory protein (rilonacept [Arcalyst]), and a humanized monoclonal antibody to IL-1b (canakinumab [Ilaris]). For patients with CAPS, IL-1 blockade has consistently led to a reduction of symptomatic periods and inflammatory markers (reviewed in Booshehri and Hoffman, 2019[16]). In addition, early diagnosis and initiation of anti–IL-1 therapy has often shown substantial improvement in progressive and long-term complications of CAPS, including hearing loss and renal disease, as well as improvement in quality of life measures.[17,18]

Inflammasomes and the molecular mechanisms behind CAPS

NLRP3 is part of the NOD-like receptor (NLR) family of innate immune receptors. These proteins have a similar domain structure consisting of an effector, switch, and sensor domain.[19,20] Together, they act as intracellular sensors of pathogens and danger signals. In a two-signal process, cells respond to PAMPs or endogenous cytokines to increase transcription of pro-cytokine forms of IL-1b and IL-18, as well as the molecules of the inflammasome. The second signal, mediated by extracellular ATP, pore-forming toxins, or crystals (including urate, silica, asbestos, or cholesterol), leads to oligomerization of the NLRP3 sensor with an adaptor protein (ASC) and an enzyme effector (caspase-1) to form a multimeric cytosolic protein. This process ultimately leads to cleavage of caspase-1 which acts to cleave pro-cytokines to their mature, active forms.[12,13] In CAPS, a mutation in *NLRP3* results in inflammasome activation in the absence of the second signal.[21,22] However, the varied nature of the stimuli leading to activation of the NLRP3 inflammasome has led to implications for its involvement in numerous more chronic diseases including gout, pseudogout, asbestosis, silicosis, atherosclerosis, and type 2 diabetes (reviewed in Broderick et al., 2015[23]).

Since the identification of the NLRP3 inflammasome, several additional sensor proteins, including NLRP1, NLRC4, AIM2, and pyrin, and their associated inflammasomes, have been identified that respond to other innate immune pathways, though their triggers seem to be less varied than those for NLRP3. The NLRP1 inflammasome is activated by anthrax toxin. NLRC4 is triggered by type III/IV bacterial secretion systems and flagellin.[24,25] AIM2 senses cytoplasmic double-stranded DNA (of either host or microbial origin),[26] and the pyrin sensor detects Rho-GTPase modifications of host proteins mediated by bacterial toxins including *Clostridioides difficile*.[27] Subsequently, monogenic diseases have been linked to mutations in the genes for these sensors. NLRP1 variants have been linked to NLRP1-associated autoinflammation arthritis and dyskeratosis.[28] NLCR4 mutations are associated with macrophage activation syndrome and enterocolitis, as well as a CAPS-like disease,[24,25] and mutations in pyrin cause familial Mediterranean fever[29,30] and pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND).[31] A monogenic disease linked to variants in AIM2 has yet to be identified.

Case 2. Infant with prolonged fever

The patient was a 7-month-old female, ex-32-week di-zygotic twin admitted to a tertiary care children's hospital for 7 days of fever, diarrhea, emesis, and an erythematous papular rash on the torso, with no known ill contacts or travel.[32] Clinical laboratory evaluation was notable for elevated inflammatory markers, leukocytosis with neutrophilia, microcytic anemia, and thrombocytosis. Her infectious workup was negative. She was diagnosed with atypical Kawasaki disease as multiple echocardiograms demonstrated persistent borderline dilation of multiple coronary arteries despite treatment with high-dose IVIG and infliximab (Remicade, Inflectra, others).[33] During the course of her hospitalization, her fever curve was noted to be bimodal with persistent signs of systemic inflammation. Further inquiry into the family history revealed that her mother and maternal uncle had similar recurrent episodes of fever, arthritis, rash, serositis, and conjunctivitis since infancy, and were diagnosed with systemic juvenile arthritis. For them, several treatments were partially successful including etanercept (Enbrel) and anakinra, though infliximab caused severe disease flares in the mother. This new history was suggestive of an autosomal dominant autoinflammatory disease, most consistent with TNF-receptor associated periodic syndrome (TRAPS).[34,35]

In contrast to the inflammasomopathies, TRAPS is due to an accumulation of intracellular stressors which trigger pattern-recognition receptors. In TRAPS, autosomal dominant mutations in *TNFRSF1A* negatively affect the three-dimensional structure of the receptor. In the wild-type state, binding of TNF-α to the TNF receptor leads to inflammatory, apoptotic, and cellular regulation pathways. In TRAPS, the mutated protein has been proposed to result in decreased levels of circulating inhibitor soluble TNFR1, constitutive activation of the receptor, decreased TNF-mediated apoptosis, and intracellular oxidative stress due to misfolding of the receptor in the endoplasmic reticulum.[36-39] Resulting autoinflammatory flares may last from 5 days to several weeks, and may occur spontaneously or be triggered by a minor illness. Symptoms during acute attacks include fever, migrating myalgia, arthralgia or arthritis, centrifugal or urticaria-like rash, and serous membrane inflammation that manifests as chest and abdominal pain. Periorbital edema is also common and can be associated with uveitis or conjunctivitis.[34,35] The most severe complication of TRAPS is secondary AA amyloidosis with morbidity and mortality associated with nephrotic syndrome and renal failure, though other organ systems can be affected.[35,40] Treatment options include IL-1 blockade, such as anakinra, or canakinumab, as first-line therapy, though short-term glucocorticoids, with or without nonsteroidal anti-inflammatory drugs, or anti-TNF therapy with etanercept, have also been attempted.[18]

Summary

Studies in single patients, such as the cases highlighted above, have paved the way for the establishment of a causal relationship between genotype and phenotype in autoinflammatory disease.[1] Since the identification of *MEFV* and *NLRP3* in the late 1990s, more than 30 genes have been discovered as the underlying etiology behind autoinflammatory disorders, with significant benefit from increasing access to next-generation sequencing. These disorders cover all aspects of genetics from dominant to recessive inheritance, X-linked, and somatic mosaicism.[41] Understanding of the molecular pathways underlying these diseases has allowed for the creation of sub-categories of autoinflammatory disease including IL-1-mediated autoinflammatory diseases, interferon-mediated autoinflammatory diseases, autoinflammatory diseases caused by increased NF-κB signaling, and autoinflammatory diseases caused by persistent macrophage activation.[5,8] Still, a substantial portion of patients remain unclassified.[42,43] The cases above illustrate how careful clinical phenotyping and molecular genetic evaluations can guide the clinician towards an autoinflammatory diagnosis and targeted therapy.

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Immune Dysregulation – A New Facet of Primary Immunodeficiency Disease (PIDD)

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OBJECTIVES

1. **Discuss non-infectious presentations and manifestations of primary immunodeficiency.**
2. **Formulate a differential diagnosis for children with suspected immunodeficiency**
3. **Identify new rare defects of the immune system that cause immunodeficiency**

Introduction

The number of identifiable inborn errors of immunity has grown exponentially over the last several decades. The International Union of Immunologic Societies (IUIS) develops a catalog of monogenic defects of immunity every several years, with the most recent version being published in 2019. Diseases of immune dysregulation characterized by non-infectious, immune-mediated manifestations is one of the quickest growing categories of disease in the IUIS. Further, more than half of all classified PIDD's within the IUIS have symptoms of immune dysregulation among their disease characteristics.[1]

Immunodeficiency is just as its name suggests, a deficiency of the immune system in which some part is missing or deficient. Immunodysregulation means that the immune system is dysregulated or, in other words, is not functioning normally or at capacity. Dysregulation leads to a domino effect where abnormalities in one system lead to dysfunction across multiple organ systems. The term "Primary Immunodysregulatory Disease" (PIRD) has been coined to delineate diseases in which major manifestations are non-infectious but rather secondary to immune-mediated pathology. Known PIDD subcategories that are more fitting in a PIRD designation are Immunodysregulation – Polyendocrinopathy – Enteropathy – X – linked (IPEX) syndrome and IPEX-like syndromes, Autoimmune Lymphoproliferative Disease (ALPS) and ALPS-like diseases, Common variable immunodeficiency with immune dysregulation, familial hemophagocytic lymphohistiocytosis, autoinflammatory disorders, interferonopathies, congenital hypersensitivity, infant onset or very early onset inflammatory bowel disease, and certain rheumatic disorders.[2]

Clinical manifestations of PIRD are secondary to organ-specific auto-inflammation and/or autoimmunity. More commonly affected organ systems include the gastrointestinal (GI), respiratory, and hematologic systems. GI manifestations include enteropathy that is histopathologically similar to celiac disease and inflammatory bowel disease (IBD)-like colitis. Symptoms may include chronic diarrhea, failure to thrive, weight loss, and wasting malnutrition. Respiratory disease is characterized by lymphocytic or granulomatous lung disease that is chronic and can progress to chronic respiratory failure and/or fibrosis. Hematologic manifestations include immune-mediated dyscrasias (autoimmune hemolytic anemia, autoimmune neutropenia, idiopathic thrombocytopenic purpura) and/or non-malignant lymphoproliferative disease. Lymphoproliferation typically manifests as chronic lymphadenopathy and hepatosplenomegaly. Lymphoproliferation is especially concerning when present in non-lymphoid organs such as the brain, lungs, and GI tract. Endocrinopathy is another common feature of PIRD and typically manifests as early onset type 1 diabetes mellitus, hypothyroidism, growth hormone insufficiency, or gonadal failure.[2]

Understanding the pathogenesis of PIRD has also provided greater understanding of the mechanisms of genetic inheritance and variant effects on protein quantity and function. Classically, inherited diseases are considered either autosomal recessive or autosomal dominant. In autosomal recessive inheritance, a pathogenic variant is present on each maternal and paternal allele, leading to reduced or absent protein production for the protein that the gene encodes. In autosomal dominant inheritance, a pathogenic defect is present on only one allele leading to absent protein production. However, other forms of inheritance, particularly among PIDD and PIRD, have now been described. Haploinsufficiency describes a mode of inheritance in which a pathogenic variant is present on only one allele but the wild type variant on the second allele is insufficient to produce normal amounts and/or function of the protein. Dominant negative is another dominant type of inheritance in which the protein product of the mutated allele negatively impacts the protein production or function of the normal wild type allele. Lastly, the concept of gain-of-function (GOF) describes mutations that are present on one allele, inherited in an autosomal dominant manner. GOF mutations lead to hyperactivation of the protein encoded by the gene.

In PIRD, the molecular mechanisms that cause the clinical phenotype are still not well understood. In general, one or more immune perturbations may be observed: T cells have a propensity to resist undergoing apoptosis leading to elevated quantities of double-negative T cells and lymphoproliferation, T and B cells become autoreactive, B cells produce auto-antibodies against various organ specific tissues or cytokines, and in some cases, there is unrestrained production or activation of inflammatory cytokines such as interferon gamma.[2]

In 2020, Chan et al. published the hematopoietic cell transplant (HCT) outcomes of 226 PIRD patients. Despite obvious genetic differences, the phenotypic overlap between PIRDs was remarkable.[3] The most common symptoms included: autoimmunity, auto-inflammation, immunodeficiency, and lymphoproliferation. Organ systems most commonly affected were hematologic, respiratory, and gastrointestinal. Because of this phenotypic overlap, distinguishing one PIRD from another can be very difficult based on clinical symptoms alone.

CASE-BASED EXAMPLES

Activated phosphoinositide 3-kinase δ syndrome (APDS)

APDS is a combined immunodeficiency caused by GOF mutations in the genes encoding the p110δ (*PIK3CD*) catalytic subunit and the p85 (*PIK3R1*) regulatory subunit of phosphoinositide 3-kinase (*PI3K*). Clinical manifestations include recurrent infections, nonmalignant lymphoproliferation that can manifest as lymphadenopathy and/or hepatosplenomegaly, nodular mucosal lymphoid hyperplasia, developmental delay, and lymphoma. Sinopulmonary infections are the most common infectious complication. The immune abnormalities present on standard lab testing can result in low or normal IgG or high IgM levels, poor responses to vaccine antigens, and increases in transitional B cells and senescent T cells.[4]

Use of sirolimus has been successful for the treatment of lymphoproliferative disease in APDS. Targeted therapy is currently under investigation. Leniolisib is a PI3K inhibitor that has shown early success in the treatment of APDS. Patients treated with leniolisib had normalization of the immune phenotype and reduction or resolution of lymphoproliferation as measured by lymph node and spleen size.[5]

Signal Transducer and Activator of Transcription (STAT) – 3 Gain of Function

STAT3 is transcription factor activated downstream of type I, II, and III interferons, IL-6–related cytokines, and IL-21. Loss-of-function STAT3 mutations were first described as the cause of autosomal dominant Hyper IgE Syndrome or Job's Syndrome. Job's Syndrome is characterized by recurrent infections, course facies, retention of primary teeth, and immune abnormalities. In contrast, gain of function of STAT3, first reported in 2014, is characterized by early onset organ-specific autoimmunity, severe nonmalignant lymphoproliferation, and postnatal growth failure.[6] In a large international cohort, lymphoproliferative disease, autoimmune cytopenias, enteropathy, and endocrinopathy were the most common features.

STAT1-GOF

STAT1 is a transcription factor that is activated by Janus kinases after binding of type I and II interferons, IL-6, γ chain cytokines, IL-10 family cytokines, or IL-23 to their respective receptors. STAT1 GOF mutations were first described in 2011 as a cause of chronic mucocutaneous candidiasis (CMC). Over the last decade, the clinical phenotype has been expanded and includes: infection susceptibility, combined immunodeficiency, and IPEX-like disease. Infection susceptibility in STAT1 GOF includes severe viral infections, particularly with DNA viruses such as EBV and herpes simplex virus, and severe bacterial infections. Invasive tuberculous and nontuberculous mycobacterial infections and invasive dimorphic fungal infections can occur in addition to CMC.[7]

Jakinibs for Treatment of STAT1 and STAT3 GOF

Treatment of the immunodysregulatory features of STAT1 GOF and STAT3 GOF can be challenging and many patients fail conventional immunosuppression. The molecular mechanism of Janus kinase (JAK)-STAT activation provides an opportunity to apply targeted pharmacologic inhibitors as a form of treatment. Tofacitinib (Xeljanz), ruxolitinib (Jakafi), and baricitinib (Olumiant) are small molecule inhibitors of JAK-STAT activation known as jakinibs. Previous studies reported on 11 patients with STAT1 GOF and 6 with STAT3 GOF treated with a jakinib. Ten of the 11 STAT1 GOF patients and all 6 STAT3 GOF patients had substantial improvement in immunodysregulatory features.[8]

Hematopoietic Cell Transplant for PIRD

Data from 226 patients who underwent HCT for PIRD diseases showed that these patients had poor overall survival but that the underlying disease, including the symptoms that led to HCT as a therapeutic intervention, resolved with HCT.[3]

Further investigation is needed to fully understand the disease spectrum of PIRD including understanding of the molecular biology of the PIRD defect, pathogenesis of clinical manifestations, and the best forms of therapy. However, precision therapies are available for several PIRDs. Therefore, recognition and diagnostic confirmation should be made in order to make available these precision-based therapies available to our patients.

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Pulmonary complications of primary immunodeficiency

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OBJECTIVES

1. **Understand key aspects of the pathogenesis and clinical presentation of pulmonary disease in primary immunodeficiency.**
2. **Summarize our understanding of asthma and chronic obstructive pulmonary disease in primary immunodeficiency.**
3. **Recognize the physiology, clinical presentation, and therapeutic approach to bronchiectasis in primary immunodeficiency.**
4. **Identify distinct forms of interstitial lung disease occurring in primary immunodeficiency.**

Pulmonary complications occur frequently in primary immunodeficiency (PI). In the United States Immunodeficiency Network (USIDNET), the largest PI research consortium in the United States with nearly 5500 patient participants, 39.3% were reported to have a history of pulmonary disease.[1] These complications often result from increased susceptibility to recurrent or severe respiratory infections due to immune system impairment. However, in many instances the etiology of pulmonary disease may be more complex and result, at least in part, from immune dysregulation inherent to some patients with PI. The goal of this review is to present an overview of pulmonary manifestations of PI, those with either a presumed infectious or non-infectious cause, as well as outline our current knowledge gaps for which continued research efforts aim for advancements in the future.

Respiratory Infections in PI

Infection is a frequent pulmonary complication of PI. An Immune Deficiency Foundation patient survey found that 68% reported a history of sinusitis, 55% reported bronchitis, and 51% reported a history of pneumonia. Along with ear infections (51%), these respiratory infections were by far the most common infectious complications of PI (https://primaryimmune.org/idf-surveys). One study of 252 patients with common variable immunodeficiency (CVID), the most frequently diagnosed symptomatic primary immunodeficiency, found 84% had a history of respiratory tract infection, 69% bronchitis, 63% sinusitis, and 58% pneumonia, with gastrointestinal tract involvement the next most common infection at 27% of subjects.[2] Similarly, in another form of severe primary antibody deficiency, X-linked agammaglobulinemia (XLA), a study leveraging the Italian Primary Immunodeficiency Network registry found respiratory infections to be the most frequent clinical feature.[3] Respiratory infections are also frequent in those with PIs that are not predominately antibody deficiencies, with viral respiratory infections reported in 56% of those with severe combined immunodeficiency and organisms identified from the respiratory tract accounting for 80% or more of infections in patients with chronic granulomatous disease (CGD).[4, 5]

Severe pulmonary infections, including pneumonia, lung abscess, and/or empyema, account for 29% to 44% of deaths in those with PI.[6] In those with autosomal dominant hyper IgE syndrome due to loss-of-function mutations in STAT3 in the USIDNET registry, 19.5% have a history of lung abscess.[7] Collectively, pneumonia and pulmonary abscesses are likely to be the greatest cause of death in those with CGD.[8] One study of over 400 CGD patients reported lung abscess in over 5%.[9] Thus, severe pulmonary infections are a major concern in those with PI, accounting for much of the morbidity and mortality affecting these patients.

Medical interventions are available to limit or prevent pulmonary infections in PI. Immunoglobulin replacement therapy (IRT) has been shown to reduce the incidence of pneumonia in PI patients with antibody deficiency, including one study focusing on CVID patients.[10, 11] IgG trough levels may need to be higher for some patients in order to achieve optimal efficacy.[12] In addition to IRT, or instead of this therapy in those for which it is not indicated, prophylaxis with antimicrobial agents can aid with management of respiratory infections. Prophylaxis with 250 mg of azithromycin daily three times weekly for two years was found to reduce respiratory exacerbations and hospitalizations in CVID and XLA patients with chronic infection-related pulmonary disease (asthma, bronchiectasis, and chronic obstructive pulmonary disease).[13] While this study did not find an increase in patients colonized by macrolide-resistant strains of bacteria as a result of azithromycin prophylaxis, they did report high levels of macrolide resistance in bacteria isolated from sputum, including 86% of *Streptococcus pneumoniae* and 79% of *Hemophilus influenzae* isolates. Together, IRT and antibiotic prophylaxis form the basis of respiratory infection management in PI.

Asthma and Chronic Obstructive Pulmonary Disease in PI

Asthma and chronic obstructive pulmonary disease (COPD) are frequent respiratory complications of PI. This is particularly the case for patients with CVID, the type of PI in which most of the research on respiratory disease has been conducted. Obstructive lung disease or bronchial hyperresponsiveness has been reported in 15% to 50% of CVID patients in numerous studies.[14] However, it is important to note that many cases of obstructive lung disease or other pulmonary complications may be misdiagnosed as asthma. In one study of 29 CVID patients with obstructive lung disease, only 9 were confirmed to have asthma.[15] Further complicating the evaluation of obstructive lung disease in PI, airway bronchoconstriction in response to allergens can occur even when allergy testing is negative.[15, 16] Moreover, there is frequently no difference in peripheral eosinophil counts or serum IgE in PI patients with or without airway hyperreactivity, limiting the utility of these measurements for diagnosis of asthma in these patients.[17] Notably, there is increased incidence of asthma in CVID patients compared with XLA, highlighting the fact that factors other than antibody deficiency underlie the pathogenesis of respiratory complications in PI.[18]

There have been strikingly few studies of mechanisms and treatment of asthma and COPD in PI despite the fact that such respiratory complications are common. Primary antibody deficiency is associated with more frequent COPD exacerbations, and low levels of IgA have

been proposed to underlie COPD exacerbation and/or progression.[19-21] Asthma has been associated with lower levels of IgA and IgM in CVID.[18] Other than provision of immunoglobulin replacement therapy, management of asthma and COPD in CVID follows standard diagnostic treatment guidelines. However, it is unknown whether there should be alterations to the clinical approach of PI patients with asthma and COPD. No studies have been conducted to determine whether changes in conventional management of asthma or COPD are warranted in CVID, or whether specific biologic therapies have more or less efficacy in these patients.

There can be significant overlap of features often thought of as distinct to asthma or COPD, such as elevation of eosinophils in COPD or neutrophilic asthma.[22] This asthma-COPD overlap may be more pronounced in PI given the immunological complexity of these patients. Furthermore, asthma and COPD exist in distinct forms or endotypes with specific immunological characteristics. Asthma can present with an eosinophilic endotype that renders it more susceptible to therapies targeting eosinophil biology.[23] COPD can manifest as chronic bronchitis, in which thick and narrow bronchioles are filled with excess mucus, or emphysema, defined by destruction of the alveolar walls. How the clinical and immunological complexity of asthma and COPD is shaped by PI remains a major knowledge gap.

There are several key concepts of COPD pathogenesis particularly relevant to PI. Tobacco smoking is the key risk factor for COPD, however, about one-third of those with COPD are nonsmokers.[24] This demonstrates that there are other key determinants of COPD susceptibility which may include infection or chronic pulmonary inflammation resulting from PI. COPD is thought to result from an imbalance of protease and antiprotease activity. The cardinal example of this being that α1-antitrypsin deficiency due to mutation of *SERPINA1* predisposes to COPD.[25] However, supported by studies identifying genetic polymorphisms associated with COPD, additional mechanisms can contribute, including apoptosis, oxidative stress response, and inflammation, which may be of particular relevance to PI.[26] B cell infiltration of terminal bronchioles and alveolar tissue with formation of lymphoid follicles has been described in COPD.[27] Similar pulmonary pathology also occurs in CVID patients, even in the absence of apparent COPD.[28] Study of respiratory complications, like COPD, in PI patients will not only provide insight for pulmonary disease in these patients, but may provide model human systems to elucidate pathogenic mechanisms relevant to broader patient populations.

Bronchiectasis

PI patients are particularly susceptible to developing bronchiectasis and this pulmonary complication may develop as a consequence of delayed diagnosis or inadequate treatment of immune deficiency. Patients with bronchiectasis will often present with chronic cough associated with mucus hypersecretion that is exacerbated by infection. Bronchiectasis is defined as permanent airway dilation due to chronic inflammation, recurrent infection, and/or mucus hypersecretion.[29] Bronchiectasis can be a complication of recurrent pneumonia and PI can increase the frequency of pulmonary infections that drive the inflammation and fixed changes of the airway that define bronchiectasis.[30, 31] Chronic or recurrent damage to the bronchial epithelium results in what is considered to be the vicious cycle of bronchiectasis: airway inflammation, alteration of the microbiome, and failure to resolve the infection.[32] Unsurprisingly, PI causes alterations in all three aspects of this bronchiectasis cycle. Bronchiectasis is often divided into disease that is associated with cystic fibrosis or disease that is not. Immune deficiency is among the most typical causes of non-cystic fibrosis bronchiectasis, along with aspiration, primary ciliary dyskinesia, and recurrent lung infections due to other causes.

There is evidence for numerous ways by which PI can predispose to bronchiectasis. In addition to being associated with recurrent pneumonia, as already mentioned, other respiratory infections may promote bronchiectasis. In a large study of 900 bronchiectasis patients at a United States tertiary care center, chronic rhinosinusitis was found in nearly half of subjects and was significantly associated with antibody deficiency.[33] In CVID patients, bronchiectasis has been associated with diagnostic delay, older age, pneumonia, and reduced levels of CD4+ T cells as well as IgM.[34-37] Other forms of primary antibody deficiency also predispose to bronchiectasis, including IgG subclass deficiency, selective IgA deficiency, and specific antibody deficiency.[38-42] IgA and IgM at mucosal surfaces are thought to be key aspects of pulmonary immunity, and reduced IgA and/or IgM are associated with bronchiectasis in primary antibody deficiency.[43, 44] Time is also a factor in bronchiectasis pathogenesis as this complication is more common in older PI patients.[34, 35] Clinical approaches targeting these determinants of bronchiectasis may improve care of PI.

Diagnosis of bronchiectasis may employ imaging and pulmonary function testing (PFT). Airflow obstruction is often evident on PFT. Regarding imaging, chest radiographs are often inadequate and CT scan of the chest is usually needed to confirm the diagnosis. Chest CT scan also has the sensitivity to pick up precursors of bronchiectasis, such as early bronchial wall thickening. Sputum culture is often included as part of the clinical evaluation of bronchiectasis as it can help with antibiotic selection as well as identify colonization with nontuberculous mycobacteria or *Pseudomonas* species. It is useful to rule out bacterial colonization when selecting antibiotics to reduce antimicrobial resistance.[45]

Bronchiectasis treatment in PI is multi-faceted. The first major component of management is optimization of IRT (if indicated in the particular form of PI). This typically includes a high IgG trough goal of 1000 mg/dL. Once sputum culture rules out nontuberculous mycobacteria, extended course macrolide therapy can be initiated. Efficacy of macrolide therapy for non-cystic fibrosis bronchiectasis has been demonstrated in numerous studies from 8 weeks to 24 months in duration, typically 250 or 500 mg of azithromycin 3 days per week, though not in PI patients specifically.[46-48] Other possible treatment options for bronchiectasis include inhaled antibiotics and mucolytics, though these have only been studied on a limited basis.[49, 50] Inhaled corticosteroids and β2-agonists are used in bronchiectasis management as is pulmonary rehabilitation.[14] Other than IRT, none of these therapeutic approaches have been specifically evaluated in PI. Thus, it remains to be determined whether one of the bronchiectasis interventions is superior to another for these patients.

Interstitial Lung Disease

Interstitial lung disease (ILD) significantly impacts morbidity and mortality, but disproportionately affects certain types of PI with particularly high occurrence in CVID at an estimated 5%-20% of patients.[18, 51] Unlike bronchiectasis, which is associated with older age and improves with antibiotics and IRT, ILD occurs in younger patients (typically present at PI diagnosis) and usually does not improve with antibiotics or IRT. Though both are forms of severe primary antibody deficiency, ILD occurs about 10-fold more frequently in CVID than XLA, indicating that antibody deficiency does not tell the whole story.[18] ILD is also less common in X-linked and autosomal recessive hyper IgM syndrome compared to CVID.[52, 53] Some monogenic immune dysregulation disorders associated with immune deficiency appear to have ILD frequently, including gain-of-function mutations of *PI3KD* and *STAT3* as well as genetic deficiency of *CTLA4* and *LRBA*. Numerous factors have been postulated to promote ILD in PI, including deficiency of regulatory T cells, increased inflammatory T cells, pathogenic B-cell activation, as well as other mechanisms of

systemic immune dysregulation that drive concurrent autoimmunity, lymphadenopathy, and splenomegaly.[54]

Of all forms of PI, ILD has been most extensively studied in CVID. CT findings consistent with ILD (ground glass opacity, pulmonary nodules) were found in 64% of CVID patients with respiratory symptoms at a tertiary referral center.[35] However, not all CT findings in CVID are clinically significant as they may not be associated with clinical symptoms or compromised pulmonary function.[55] Pulmonary nodules are not infrequent findings in CVID and need not be indicative of progressive ILD.[56] When pulmonary nodules do warrant additional work-up, lung biopsy is vital to confirming a diagnosis of ILD and can rule-out malignancy.[57] PI-associated ILD typically manifests within the spectrum of benign pulmonary lymphoproliferative lung disease which includes follicular bronchiolitis, peribronchial disease, and lymphocytic interstitial pneumonia, when there is broader interstitial involvement.[35, 58, 59] Granulomatous lymphocytic interstitial lung disease (GLILD) is frequently used to describe ILD in PI, as pulmonary pathology demonstrates both granulomatous and lymphocytic inflammation in these patients.[60-62]

CVID ILD may be incorrectly diagnosed as sarcoidosis due to radiologic similarities and shared associations with granulomatous inflammation. However, there are clear distinctions between these conditions. In addition to being differentiated by biopsy, CVID ILD has larger pulmonary nodules with a more generalized lung distribution than sarcoidosis.[63] Also, clinical history that includes recurrent infections, autoimmune cytopenias, benign lymph node hyperplasia, and other cardinal features of PI can aid the diagnosis.

Management of symptomatic ILD begins with optimization of IgG replacement therapy (if appropriate for the particular form of PI), with goal troughs of 1000 mg/dL or greater being typical.[56, 64] For those with mild to moderate symptoms, inhaled corticosteroids, with or without long-acting beta agonists, and/or prophylactic macrolides may be beneficial.[65-67] Systemic corticosteroid treatment may be effective in the short-term, but is not a viable long-term answer.[68] Numerous immunomodulators have been used to manage ILD in CVID, not much data exists for ILD in other PIs.[69-72] Rituximab (Rituxan) is a staple of therapy and may not heighten immunodeficiency in those already antibody deficient as much as broader immunosuppressants, and has a preferable safety profile.[73, 74] Following rituximab with azathioprine or mycophenolate mofetil (Cellcept) may induce longer remission after B-cell depletion[75]

In PI patients with known genetic etiologies, precision therapeutic approaches may be available. In those with genetic deficiency of the immune regulatory molecule CTLA-4 or a protein involved in the surface expression of CTLA-4, lipopolysaccharide responsive and beige-like anchor protein (LRBA), provision of CTLA-4-Ig (abatacept [Actemra]) is efficacious.[76] Likewise, gain-of-function mutation of *PI3KD* can be treated with leniolisib, an inhibitor of phosphoinositide 3-kinase **δ**.[77] Amelioration of gain-of-function mutations in STAT3 with jakinibs or IL-6R antagonists (as IL-6 signals via STAT3) have also been reported.[78, 79] Continued application of genomics to PI evaluation will undoubtedly reveal more opportunities for precision therapy.

Conclusion

Pulmonary complications can be the initial and/or primary complication of PI patients. One study found that the most common presenting feature among CVID patients was respiratory tract infections (29% lower respiratory tract infection, 27% upper respiratory tract infection).[80] Another found that sinopulmonary manifestations were the presenting symptoms of more than half of PI patients.[81] Consequently, earlier diagnosis of PI may limit resultant pulmonary complications. Delay in diagnosis of Pulmonary Arterial DIsease is associated with progression to obstructive airway disease, chronic atelectasis, bronchiectasis, and pulmonary fibrosis. Importantly however, lung disease occurs in many with PI diagnoses despite usage of immunoglobulin replacement therapy (IRT). Thus, some forms of chronic lung disease occurring in PI may develop because of immune dysregulation independent of infection or deficiencies in host defense that are not alleviated by IRT and/or antibiotic prophylaxis.

Even though diagnosis and treatment of PI has improved over the years, pulmonary complications remain common in these patients. There are several fundamental concepts that form the core of clinical management of respiratory disease in PI. Of paramount importance is the fact that infections of the upper and lower respiratory tract are principal clinical manifestations of PI. Accordingly, timely diagnosis and treatment may limit the progression of certain forms of chronic lung disease. While PI may increase the risk of obstructive lung disease, asthma may be frequently misdiagnosed as patients are often incompletely evaluated for their pulmonary disease. CT is often needed to diagnose bronchiectasis and sputum culture can shape appropriate management. ILD is associated with increased morbidity and mortality in CVID and results from pulmonary lymphoproliferative pathology that is responsive to immunomodulatory therapy. Clinical surveillance, lung biopsy, and genetic evaluation can be helpful to identify patients that should be treated and aid in selection of therapy. Further research is needed to expand the impact of genomics and build upon our recent advancements in diagnosis and treatment of PI-associated lung disease.

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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.