375e Primary Immunodeficiencies Associated with (or Secondary to) Other Diseases

Alain Fischer

There are an increasing number of conditions in which a primary immunodeficiency (PID) has been described as one facet of a more complex disease setting. It is essential to consider associated diseases when a PID is identified as the primary manifestation and, conversely, not neglect the potentially harmful consequences of a PID that could be masked by other manifestations of a particular syndrome.

Below is a short description of these syndromes in which the PID is classified according to the arm of the immune system that is affected.

1. Primary Immunodeficiencies of the Innate Immune System

a) Several severe congenital neutropenia (SCN) syndromes can be associated with malformations. The recently described SCN disease caused by glucose-6-phosphatase deficiency (G6PC3) can be associated with heart and urogenital malformations. The related glycogenesis Ib disease combines SCN with hypoglycemia and hepatosplenomegaly. Some *HAX*-1 gene mutations lead to neurocognitive impairments as well as SCN. Barth syndrome combines SCN with cardiomyopathy. Lastly, Shwachman syndrome is a known autosomal recessive entity (caused by mutation of the *SBDS* gene) in which the defect in granulopoiesis can extend to the other hematopoietic lineages; short stature, bone metaphyseal dysplasia, and exocrine pancreatic insufficiency are known hallmarks of this condition.

b) Syndromic asplenia combines the risk of infection with heart defects and situs inversus.

c) Leukocyte adhesion deficiency (LAD) type II includes growth retardation and impairment of cognitive development.

d) A few patients with X-linked chronic granulomatous disease present with a contiguous gene deletion syndrome that can include the McLeod phenotype, which is characterized by anemia, acanthocytosis, and a severe risk of immune reaction against donor red cells because the patient's red cells do not express the Kell antigen. The McLeod phenotype also can result in a neurologic disease.

e) X-linked nuclear factor-κB (NF-κB) essential modulator (NEMO) deficiency provokes not only a variable set of deficiencies of both innate and adaptive immunity but also mild osteopetrosis, lymphedema, and, more frequently, anhydrotic ectodermal dysplasia, dysmorphic facies, and abnormal conical teeth. The last finding is often helpful in the diagnosis of that condition.

2. Primary Immunodeficiencies of the Adaptive Immune System

a) **T cell primary immunodeficiencies.** Reticular dysgenesis, a rare severe combined immunodeficiency (SCID) characterized by T lymphopenia and agranulocytosis, can cause sensorineural deafness. Coronin A deficiency is another SCID variant that can be associated with behavioral disorders because the Coronin A gene is located in a genome area known to have been deleted in some patients with this disorder. The lack of enzymes of purine metabolism (adenosine deaminase and purine nucleoside phosphorylase) provokes not only profound T cell lymphocytopenia but also neurologic impairment, including dysautonomia and abnormalities of cognitive development of variable intensity, in many patients. The neurologic impairment can persist after hematopoietic stem cell transplantation (HSCT). Mild chondrodysplasia is a common finding in adenosine deaminase (ADA) deficiency and, indeed, can help the physician arrive at a final diagnosis.

b) **Primary thymic defects.** DiGeorge syndrome is a complex embryopathy that is caused by hemizygous interstitial deletion of chromosome 22, leading to multiple developmental defects, including conotruncal defects, hypoparathyroidism, and dysmorphic syndrome. Although a profound T cell immunodeficiency is rare in DiGeorge syndrome (~1% of cases), failure to recognize this feature is likely to have a fatal outcome. Similarly, some forms of the related CHARGE syndrome (mutation of the *CHD7* gene) also cause a profound T cell immunodeficiency.

c) **T cell primary immunodeficiencies related to calcium influx defects.** Recently, rare T cell PIDs were found to be caused by defective store-operated entry of calcium ions into T and B lymphocytes after antigen stimulation. These defects (caused by ORA-1 and STIM-1 deficiencies) also lead to anhydrotic ectodermal dysplasia, abnormal teeth, and, above all, a nonprogressive muscle disease characterized by excessive fatigue.

d) **DNA repair defects.** Several genetic defects impair DNA repair pathways. Many lead to combined T and B lymphocyte PIDs in a syndromal setting of varying complexity. The most common is ataxia-telangiectasia (AT), an autosomal recessive disorder with an incidence of 1 in 40,000 live births; AT causes a B cell immunodeficiency (low IgA, IgG2 deficiency, and low antibody production) that often requires immunoglobulin replacement therapy.

AT is associated with a progressive T cell immunodeficiency. As the condition's name suggests, the hallmark features are telangiectasia and cerebellar ataxia.

These manifestations may not be detectable before age 3–4 years, and so AT should be considered in young children with IgA deficiency and problematic infections. Diagnosis is based on a cytogenetic analysis showing excessive chromosomal rearrangements (mostly affecting chromosomes 7 and 14) in lymphocytes. AT is caused by mutation of the gene encoding the ATM protein, a kinase that plays a major role in the detection of DNA lesions and the organization of DNA repair (or cell death if the lesions are too numerous) by triggering several different pathways. Overall, AT is a progressive disease that carries a very high risk of lymphoma, leukemia, and (during adulthood) carcinomas. A variant of AT (AT-like disease) is caused by mutation of the *MRE11* gene.

Nijmegen breakage syndrome (NBS) is a less common condition that also results from chromosome instability (and the same cytogenetic abnormalities as in AT). It is characterized by a severe T and B cell combined immunodeficiency with autosomal recessive inheritance. Subjects with NBS exhibit microcephaly and a birdlike face but neither ataxia nor telangiectasia. The risk of malignancies is also very high. Nijmegen breakage syndrome results from a deficiency in Nibrin (NBS1, a protein associated with MRE11 and Rad50 that is involved in checking DNA lesions) caused by hypomorphic mutations.

Severe forms of dyskeratosis congenita (also known as Hoyeraal-Hreidersson syndrome) combine a progressive immunodeficiency that can include an absence of B and natural killer cell (NK) lymphocytes, progressive bone marrow failure, microcephaly, in utero growth retardation, and gut disease. The disease can be X-linked or, more rarely, autosomal recessive. It is caused by the mutation of genes encoding telomere maintenance proteins, including dyskerin (DKC1).

Bloom syndrome (helicase deficiency) combines a typical dysmorphic syndrome with growth retardation, skin lesions, and a mild immunodeficiency that also can be found in some patients with Fanconi's anemia.

Rare forms of combined T and B cell immunodeficiencies with autosomal recessive inheritance are associated in more complex syndromes with microcephaly, failure to grow, and a variable dysmorphic syndrome. These disorders are caused by mutation of the genes that encode DNA ligase 4 and Cernunnos (XLF), both of which are members of the nonhomologous end-joining DNA repair pathway.

The Vici syndrome combines callosal agenesis, cataracts, cardiomyopathy, hyperpigmentation, and a combined immunodeficiency. It is caused by biallelic *EPG5* gene mutation that results in defective autophagy.