Autoimmune and other cytopenias in primary immunodeficiencies: pathomechanisms, novel differential diagnoses, and treatment

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Autoimmunity and immune dysregulation may lead to cytopenia and represent key features of many primary immunodeficiencies (PIDs). Especially when cytopenia is the initial symptom of a PID, the order and depth of diagnostic steps have to be performed in accordance with both an immunologic and a hematologic approach and will help exclude disorders such as systemic erythromatosus, common variable immunodeficiency, and autoimmune lymphoproliferative syndromes, hemophagocytic disorders, lymphoproliferative diseases, and novel differential diagnoses such as MonoMac syndrome (GATA2 deficiency), CD27 deficiency, lipopolysaccharide-responsive beige-like anchor (LRBA) deficiency, activated PI3KD syndrome (APDS), X-linked immunodeficiency with magnesium defect (MAGT1 deficiency), and others. Immunosuppressive treatment often needs to be initiated urgently, which impedes further relevant immunologic laboratory analyses aimed at defining the underlying PID. Awareness of potentially involved disease spectra ranging from hematologic to rheumatologic and immunologic disorders is crucial for identifying a certain proportion of PID phenotypes and genotypes among descriptive diagnoses such as autoimmune hemolytic anemia, chronic immune thrombocytopenia, Evans syndrome, severe aplastic anemia/refractory cytopenia, and others.

A synopsis of pathomechanisms, novel differential diagnoses, and advances in treatment options for cytopenias in PID is provided to facilitate multidisciplinary management and to bridge different approaches. (Blood. 2014;124(15):2337-2344)

Introduction

Primary immunodeficiencies (PIDs) are classified into nine subclasses, depending on their underlying immunologic defect or predominant symptom. The current view of PIDs includes an increasing number of syndromes that are associated with immune dysregulation and autoimmunity as a predominant feature rather than an overt pathologic risk of infections. Cytopenia, defined as the reduction of one or more mature blood cell types (eg, neutropenia, anemia, or thrombocytopenia) in the peripheral blood, may be a typical first symptom of such an immunodeficiency. Possible causes of cytopenia in PIDs comprise cellular or humoral autoimmunity, immune dysregulation in form of hemophagocytosis or lymphoproliferation with or without splenic sequestration, bone marrow failure and myelodysplasia, or secondary myelosuppression. In some patients, cytopenia may be detected as an incidental finding, whereas other patients may be severely ill. Because primary defects in the number or function of phagocytes are classified under their own group of PIDs, the syndromes of severe congenital neutropenia (based on defects in ELANE, GFI1, HAX1, G6PC3, VPS45, and CSFR3 genes, or activating mutations in the Wiskott-Aldrich syndrome [WAS] gene) and cytopenia-linked metabolic diseases are not included in this overview. Similarly, isolated lymphopenic syndromes are excluded if they present without neutropenia, anemia, or thrombocytopenia; also excluded are non-PID inherited bone marrow failure syndromes such as Fanconi anemia, congenital amegakaryocytic thrombocytopenia, bone marrow failure with radionuclarin synostosis, and others (Table 1 and footnotes). These syndromes are beyond the scope of this review because they do not represent a concurrence of immunodeficiency with cytopenia nor do they harbor an underlying defect of the immune system.

Like the self-limited benign forms of post- or parainfectious autoimmune cytopenia or acquired autoimmune neutropenia of childhood that typically occur independently of a (recognized) underlying PID, many but importantly not all cytopenias in patients with underlying PIDs are mediated by autoantibodies. Thus, it is essential that clinicians take an underlying PID into account in patients with clear antibody-mediated cytopenia and also in other situations as described. This review provides a conceptual synopsis of cytopenias in PIDs and aims to increase the awareness of hematologists as well as immunologists for this manifestation of PID.

Pathomechanisms of cytopenia in PID

Cytopenia in PID may have a variety of causes. In some instances, it is a primary feature of the immunodeficiency, and in others, it is a secondary phenomenon. This review will focus on the clinical relevance of cytopenias and suggest the following grouping: (1) classic autoimmune cytopenias, further subdivided into autoantibody-mediated and cellular autoimmunity; (2) cytopenias in the context of immune dysregulation, lymphoproliferation, and inflammation in PID; (3) PID with bone marrow failure; and (4) toxic or infectious myelosuppression secondary or concomitant to PID (Figure 1).
Autoimmune-mediated cytopenia in PID

According to the causal involvement of autoantibodies against hematopoietic cells or predominant cellular cytotoxicity, the autoimmune-mediated cytopenias may be further subgrouped into antibody-mediated and cellular autoimmunity (Figure 1, upper left quadrant).

Autoantibody production may occur in B-cell–intrinsic defects or in disorders with disturbed T-cell–B-cell interaction and regulation. When B-cell maturation is impaired, vital mechanisms of B-cell interaction and regulation.

Figure 1. Synopsis of cytopenias in PID. Conceptual overview, excluding primary defects of phagocyte number or function, inherited non-PID bone marrow failure syndromes, and disorders of isolated lymphopenia (without other cytopenia). *Includes hypomorphic mutations in SCID genes, CD40, CD40L, and other combined immunodeficiencies such as radioresponsive disorders, defects in the Ca2+ channel, and activating PI3K syndrome. AHI-A, autoimmune immune deficiency; AIN, autoimmune neutropenia; CHH, cartilage hair hypoplasia; CHS, Chediak-Higashi syndrome; DKC, dyskeratosis congenita; FRH-L, familial hemophagocytic lymphohistiocytosis 1-5; HPS-2, Hermansky-Pudlak syndrome 2; ITK, IL-2–inducible T kinase deficiency; LRBA, lipopolysaccharide-responsive beige-like anchor deficiency; PNH, paroxysmal nocturnal hemoglobinuria, RCC, refractory cytopenia of childhood; RD, reticular dysgenesis; SCN1, severe congenital neutropenia 1; SDS, Shwachman-Diamond syndrome; WHIM, WARS, hypogammaglobulinemia; XIP, WAS protein-interacting protein; WIP, WAS protein-interacting protein; XLP-1,2, X-linked lymphoproliferative syndrome. CD4, CD40, CD40L, and other combined immunodeficiencies such as activating mutations of PI3K, PI3K-gamma, PI3K-delta, and activating PI3K syndrome.

An example of impaired T-cell–B-cell interaction is CD40/CD40L deficiency, in which the missing signal from T cells causes humoral autoimmunity as well as other severe immunologic symptoms; the phenotype for this deficiency is classified as combined immunodeficiency (CID).

In addition to these primary or secondary humoral defects, intrinsic defects in T-effector cells may lead to cellular autoimmunity. The simplified principle is similar to that of B-cell maturation defects described above, namely that impaired T-cell development may lead to a lack of functional effectors against non-self or dangerous antigens and simultaneously yield “uneliminated” autoreactive clones directed against self-antigens. Defects in signaling or in T-cell receptor recombination or editing may result in both a deficit of FOXP3-positive regulatory T cells (Tregs) and an incomplete development of autoimmune regulator transcription factor–expressing medullary thymus epithelial cells that result in peripheral and central tolerance defects. Thus, many classic T-cell disorders such as combined immunodeficiencies (CIDs) that lack naive T cells based on hypomorphic mutations in genes usually associated with severe CID (SCID); ie, leaky SCIDs such as RAG1, RAG2, adenosine deaminase, artemis, and purine nucleoside phosphorylase and well-known syndromes with immunodeficiency such as WAS, WAS protein-interacting protein deficiency, and 22q11 microdeletion syndrome may show some extent of autoimmunity as a result of autoreactive T cells and reduced T-cell regulation. Furthermore, certain T-cell signaling defects that may cause SCID or CID, such as ORAI-1, STIM-1, MAGT1, STK4, or LCK deficiencies as well as activating mutations of PI3K, predispose to autoimmunity including cytopenias. Recently, loss of function of tripeptidyl peptidase 2 was demonstrated to cause...
CID with autoimmune cytopenia (manuscript by Polina Stepensky, Anne Rensing-Ehl, Ruth Gather, Shoshana Revel Vilk, Ute Fischer, Cohen syndrome (MIM# 301000); WHIM, warts, hypogammaglobulinemia, immunodeficiency, myelokathexis (CXCR4 gain-of-function, MIM# 193670); WIP, WAS protein-interacting protein (MIM# 602357); XLP, X-linked lymphoproliferative syndrome; MEN, X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia (MAGT1 deficiency, MIM# 300715).

Type

Antibody-mediated autoimmunity

Cellular autoimmunity

Immune dysregulation

Bone marrow failure, myelodysplasia

Myelosuppression

Antibody-mediated autoimmunity

CVID, ALPS, [cITP, Evans syndrome] [SLE], CID,

Good syndrome, LRBA deficiency

CID,§ PCID,§ WAS, WIP, 22q11, [SAA, RCC/MDS RC]

IPEX(-like), XLP, CD27, ITK, XEN, ALPS, HLH, FHL, Griscelli syndrome, CHS, HPS

DKC, CHH, Schimke syndrome, RD, SDS, Monomac syndrome, PNH, other

Various, WHIM syndrome

Disorders*

May be asymptomatic, bacterial infection, multiorgan autoimmunity, thrombosis, inflammatory bowel disease

May be asymptomatic, opportunistic infection, eczema, atopy, sydromic features, pancytopenia, autoimmunity

Often severely ill patient, fever, organomegaly, lymphoma, positive family history, partial albinism

May be asymptomatic, syndromal features, skin, bones, deafness, maladigestion, hemolysis, dystonia

Viral infection, toxic, malignant (nutritional) deficiency

Possible symptoms

Hyppogamaglobulinemia, csBm cells reduced, DNT cells increased, vitamin B12, sFasL, IL-10, IL-18

Empty bone marrow, lack of naive T cells, microplatelets, MLPA, B-cell and NK-cell deficiency, T cells nonfunctional

Stat5b-P, EBV viremia, hyperferetinemia, sIL2R, genetic testing, DNT cells increased, INKT cells reduced, vitamin B12, sFasL, NK/CTL cytotoxicity

Telomere length, genetic testing, lymphopenia, pancreatic insufficiency, altered pDC/mDC ratio

Ectrombopag, G(M)CSF, HSCT,‡ ecucluzumab

Pancytopenia, myelokathexis

Treatment options

IVIG, corticosteroids, MMF, plasmapheresis/exchange, anti-CDO2, † CY, purine analogs, TPOR agonists, ‡ HSCT‡

Calcineurin inhibitors, ATG, altemutzamab, MMF, mTOR inhibitors, CY, MTX, purine analogs, Vcr, Vbl, HSCT‡

corticosteroids, calcineurin inhibitors, † etoposide, ‡ ATG, † altemutzamab, ‡ anti-CDO2, M TOR inhibitors, MMF, HSCT‡

Treatment options

Table 1. Possible clinical presentation (apart from symptoms of cytopenia), laboratory parameters of PID with cytopenia, and treatment options

<table>
<thead>
<tr>
<th>Type</th>
<th>Disorders*</th>
<th>Possible symptoms</th>
<th>Typical laboratory parameters</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody-mediated autoimmunity</td>
<td></td>
<td>May be asymptomatic, bacterial infection, multiorgan autoimmunity, thrombosis, inflammatory bowel disease</td>
<td>Hyppogamaglobulinemia, csBm cells reduced, DNT cells increased, vitamin B12, sFasL, IL-10, IL-18</td>
<td>IVIG, corticosteroids, MMF, plasmapheresis/exchange, anti-CDO2, † CY, purine analogs, TPOR agonists, ‡ HSCT‡</td>
</tr>
<tr>
<td>Cellular autoimmunity</td>
<td>CID,§ PCID,§ WAS, WIP, 22q11, [SAA, RCC/MDS RC]</td>
<td>May be asymptomatic, opportunistic infection, eczema, atopy, sydromic features, pancytopenia, autoimmunity</td>
<td>Empty bone marrow, lack of naive T cells, microplatelets, MLPA, B-cell and NK-cell deficiency, T cells nonfunctional</td>
<td>Calcineurin inhibitors, ATG, altemutzamab, MMF, mTOR inhibitors, CY, MTX, purine analogs, Vcr, Vbl, HSCT‡</td>
</tr>
<tr>
<td>Immune dysregulation</td>
<td>IPEX(-like), XLP, CD27, ITK, XEN, ALPS, HLH, FHL, Griscelli syndrome, CHS, HPS</td>
<td>Often severely ill patient, fever, organomegaly, lymphoma, positive family history, partial albinism</td>
<td>Stat5b-P, EBV viremia, hyperferetinemia, sIL2R, genetic testing, DNT cells increased, INKT cells reduced, vitamin B12, sFasL, NK/CTL cytotoxicity</td>
<td>corticosteroids, calcineurin inhibitors, † etoposide, ‡ ATG, † altemutzamab, ‡ anti-CDO2, M TOR inhibitors, MMF, HSCT‡</td>
</tr>
<tr>
<td>Bone marrow failure, myelodysplasia</td>
<td>DKC, CHH, Schimke syndrome, RD, SDS, Monomac syndrome, PNH, other</td>
<td>May be asymptomatic, syndromal features, skin, bones, deafness, maladigestion, hemolysis, dystonia</td>
<td>Telomere length, genetic testing, lymphopenia, pancreatic insufficiency, altered pDC/mDC ratio</td>
<td>Ectrombopag, G(M)CSF, HSCT,‡ ecucluzumab</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>Various, WHIM syndrome</td>
<td>Viral infection, toxic, malignant (nutritional) deficiency</td>
<td>Pancytopenia, myelokathexis</td>
<td>Treat underlying disease, infection intoxication/deficiency state, CXCR4 antagonist (in WHIM)</td>
</tr>
</tbody>
</table>

Square brackets indicate diseases not considered primary immunodeficiencies but representing frequent hematologic/rheumatologic diagnoses with cytopenia and immunologic pathomechanisms.

CID, with autoimmune cytopenia (manuscript by Polina Stepensky, Anne Rensing-Ehl, Ruth Gather, Shoshana Revel Vilk, Ute Fischer, Schafiq Nabhani, Sebastian Fuchs, Simon Zenke, Elke Firat, Vred Molho Pessach, Arndt Borkhardt, Mirzokhid Rakhmanov, Baerbel Keller, Klaus Warnatz, Hermann Eibel, Gabriele Niedermann, Orly Elpeleg, and Stephan Ehl, submitted August 2014; Hambleton et al13). In WAS, however, the basis of thrombocytopenia and microplatelets is the underlying cytoskeletal dysfunction.34,35 A close connection between T-cell and B-cell pathology exists (eg, in 22q11 syndrome and WAS) in which, in addition to T-cell dysfunction, there is also an altered B-cell differentiation/maturation pattern with predisposition to humoral autoimmunity.36,37 Conversely, PIDs with humoral autoimmune mechanisms that have historically been considered the principal cytopenia-linked PIDs, such as ALPS or CVID, have been shown to have have T-cell maturation18 or reduced Treg function,19,41 respectively.

Many hematologic conditions such as refractory cytopenia of childhood (RCC), myelodysplastic syndrome (MDS), severe aplastic anemia (SAA), chronic immune thrombocytopenia (cITP), Evans syndrome (ES), and/or rheumatologic diseases such as systemic lupus erythematosus (SLE) (shown in square brackets in Figure 1) are either the result of an unrecognized PID or are based on a variety of polygenic or epigenetic defects in hematopoietic stem cells or within the immune system that in turn lead to autoimmune reactions. Both SAA and RCC/MDS, if no cytogenetic aberration or clonal evolution is detected, are being treated with T-cell–directed immunosuppression or hematopoietic stem cell transplantation, indirectly confirming a primary or secondary involvement of autoreactive T cells in pathogenesis.42–45 A variety of pathomechanisms underlying the antiplatelet autoimmunity in cITP has been suggested, ranging from dysfunctional Tregs and lacking regulatory B cells to cytokine gene polymorphisms, disturbed antigen presentation, and autoreactive B cells.46–50 The detection of CVID- or ALPS-like immune phenotypical parameters in a subgroup of patients with ES has recently been reviewed.9 SLE is a descriptive symptom complex mainly ascribed to humoral autoimmunity that may arise in PIDs, typically caused by deficiencies in the classical complement pathway (eg, C1q, C1R, C1S, C4, C2, factor B, factor D, factor H).11,12

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Table 2. Genes and MIM numbers of disease entities caused by multiple different genes

<table>
<thead>
<tr>
<th>Disorder*</th>
<th>Involved genes†</th>
<th>MIM#</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVID</td>
<td>TACI, BAFF-R, CD19, CD20, CD21, ICOS, LRBA, TWEAK</td>
<td>604907, 606269, 107265, 112210, 614699, 186845, 604558, 606453, 602695</td>
</tr>
<tr>
<td>ALPS</td>
<td>TNFRSF6 (CD26/Fas: germine or somatic), TNFRSF6 (CD95L/FasL), CASP10, CASP8, FADD, CARD11, PRKCD, KINRAS</td>
<td>601859, 134638, 603908, 607271, 613759, 606445, 615559, 614470</td>
</tr>
<tr>
<td>CID</td>
<td>RAG1/2, ARTEMIS, ADA, FNP, CD40L, CD40, ZAP70, SH2D1A, RMRP, STK4, TCRA, LCK, P3Kd, ORAI1, STIM1, TPP2</td>
<td>601457, 602450, 102700, 164050, 300386, 109535, 269840, 308240, 250250, 614866, 615387, 153390, 602839, 610277, 605921, 190470</td>
</tr>
<tr>
<td>IPEX, IPEX-like</td>
<td>FOXP3, CD25, STAT5b, STAI</td>
<td>304790, 603637, 245590, 600555</td>
</tr>
<tr>
<td>XLP</td>
<td>SH2D1A, XIAP/BIRC4</td>
<td>308240, 300635</td>
</tr>
<tr>
<td>FHL with or without hypopigmentation (including CHS, HPS, GS2)</td>
<td>PRF1, UNC13D, STX11, STXB2, LYST, AP3B4, RAB27A</td>
<td>603553, 608898, 603552, 613101, 214500, 608233, 607624</td>
</tr>
<tr>
<td>DKC</td>
<td>DKC1, NHP2, NOP10, RETL1, TERC, TERT, TINF2</td>
<td>305000, 613987, 224230, 608833, 127550, 614742, 613990</td>
</tr>
</tbody>
</table>

See Al-Herz et al 3 for more detailed PID disease classification.

*In the same order of appearance as in Table 1.
†Listed unless gene name is identical with disease name and thus is mentioned in Table 1 (see also Al-Herz et al 3).

C1s, C2, C4, C5, C6, C7, C8A, and C8B).1-3 In addition to these recognized PIDs, there are SLE-CVID/SLE-CID overlap syndromes and SLE features in hyper-IgM syndromes, including constitutive mismatch repair defects.1,3,51,52 However, because the diagnostic algorithms are not standardized and because existing recommendations (such as those for cITP53 or those within RCC/SAA international treatment guidelines from the European Working Group for childhood MDS54) are often not sufficiently executed before initiating immunosuppressive treatment, a substantial number of unrecognized PIDs may be hidden among these allegedly hematologic disorders. International initiatives for prospective registries aim to establish and continuously update diagnostic, prognostic, and therapeutic approaches for immune cytopenias (eg, the intercontinental cooperation IPP study group, the Franc, et al Center for Rare Diseases and Autoimmune Cytopenias of Childhood, and the German Pediatric Hematology-Oncology Working Group ITP/ES prospective studies).35,56

Practically all conditions within this first group of diseases may lead to cytopenia without any previous history of infections or autoimmunity and may present with mild or absent clinical symptoms. However, acute hemolytic anemia, as well as newly diagnosed immune thrombocytopenia, are potentially life-threatening conditions.

Immune dysregulation underlying cytopenia in PID

One classical PID with immune dysregulation linked to cellular autoimmunity is immune dysregulation, polyendocrinopathy, and enteropathy X-linked (IPEX) syndrome, which is the result of a lack of functional FOXP3-positive Tregs that leads to a peripheral T-cell tolerance defect and often to cytopenia.57-59 In addition to the mutations in FOXP3 that cause IPEX,60,61 other components of the Treg activation pathway may be defective and may thus reduce the function and/or number of Tregs and lead to an IPEX-like syndrome (eg, deficiency of CD25 or STAT5b and gain-of-function mutations in STAT1).62-65 Interestingly, the classical central T-cell tolerance defect, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED) due to a defect of the autoimmune regulator transcription factor is not typically associated with cytopenias.66 Furthermore, immune dysregulatory processes such as hemophagocytosis or lymphoproliferation (and subsequent splenic sequestration of blood cells) may cause secondary cytopenia in critically ill patients. The underlying pathomechanisms are pathological macrophage activation, functional natural killer (NK) cell defects, and polyclonal or oligoclonal lymphoproliferation. These dysfunctions may arise as complications of certain infections, oncologic treatments including hematopoietic stem cell transplantation (often referred to as infection-associated macrophage-activation syndrome or secondary hemophagocytic lymphohistiocytosis,67 or lymphoproliferative syndrome [with unknown genetic predisposition]), or as a main symptom of PIDs that stem from monogenic communication defects between B and T cells. The manifestation of lymphoproliferative disorders is often triggered by primary Epstein-Barr virus (EBV) infection and is associated with a lack of invariant T-cell receptor NKT (iNKT) cells (eg, X-linked lymphoproliferative syndrome, CD27 deficiency, and interleukin-2 (IL-2)—inducible kinase deficiency). Likewise, interaction defects between T cells and the innate immune system are found in this category (familial hemophagocytic lymphohistiocytosis and immunodeficiencies with hypopigmentation; Figure 1, upper right quadrant) (Alkhairy O, Perez-Becker R, Driessen G, et al, manuscript submitted June 2014).67,71 Another newly identified PID with increased susceptibility to EBV-induced lymphoproliferation and development of lymphoma—the X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia syndrome, which is due to a magnesium transporter MAGT1 defect—also appears to predispose to autoimmunity cytopenia,68 most likely as a result of autoantibodies generated on the basis of the underlying T-cell defect similar to the Ca-signaling defects ORAI-1 and STIM-1 (see above). ALPS should be mentioned again in this context, because splenic sequestration contributes to cytopenia in ALPS as in other lymphoproliferative syndromes (and sometimes also in CVID).

Bone marrow failure in PID

If pancytopenia is the initial clinical symptom, diagnostic algorithms in hematology-oncology exclude malignancy, RC/MDS, acquired and inherited bone marrow failure syndromes such as paroxysmal nocturnal hemoglobinuria, and Fanconi anemia, Shwachman-Diamond syndrome, and dyskeratosis congenita, and may end up with a diagnosis of exclusion such as SAA (depending on bone marrow cellularity, morphology, and cytogenetics), but do not always consider immunodeficiencies as the underlying cause. Because rare and novel PIDs such as immune osseous dysplasias (cartilage hair hypoplasia, Schimke syndrome) or MonoMac syndrome (GATA2
Secondary myelosuppression in PID

Unspecific secondary bone marrow suppression may occur in PID as in secondary states of immunosuppression due to viral (or rarely bacterial) infections, toxic marrow damage from drugs used to treat infections or autoimmunity in PID, extrusion and/or suppression of hematopoiesis by malignant cells, or simply in states of nutritional deficiencies (eg, resulting from inflammatory bowel disease, metabolic disorders, or wasting conditions involving vitamin B12, folate, or iron; Figure 1, lower left quadrant). Myelokathexis (trapping of neutrophils in the bone marrow) is a rare condition involving pseudosuppression of the marrow in which the marrow is unable to release mature neutrophils into the periphery because of a gain-of-function mutation in CXCR4; this PID (warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis [WHIM] syndrome) is usually diagnosed based on the typical symptoms indicated in its name. X-linked agammaglobulinemia is not typically linked with cytopenia; however, it is listed here because some patients experience neutropenia, which may be an underestimated clinical concern; its mechanisms include enhanced neutrophil apoptosis and have recently been demonstrated.

Management

The following recommendations should be considered as general background information for the differential diagnostic workup and consideration of treatment options for cytopenia in the context of PIDs. They are not guaranteed to be complete for any individual situation nor are they designed for hematologic emergency situations or for managing forms of cytopenia other than those associated with PID (such as hemoglobinopathies). This review should not and cannot replace a consultation with a pediatric hematologist or hematologist-oncologist and a pediatric immunologist who can perform the differential diagnostic procedures for PIDs associated with cytopenia. Likewise, this review cannot provide a general diagnostic algorithm or therapeutic guideline because the spectrum of possible underlying diseases is too vast and heterogeneous for one tool to suffice.

Diagnostic analyses

In PID-associated cytopenia, the first question to answer is whether it is a result of the increased loss or the decreased production of blood cells. This may be an emergency situation because autoimmune hemolytic anemia may evolve into a life-threatening situation within hours. Therefore, the first laboratory analyses that should be performed are for cell lysis parameters (eg, potassium, lactate dehydrogenase, aspartate transaminase, uric acid); for anemia, additional parameters include those for hemolysis (indirect bilirubin, absolute reticulocyte count, haptoglobin) and immunologic and metabolic parameters (eg, direct and indirect Coombs test; IgG, IgA, and IgM; fluorescence-activated cell sorter analyses for T-, B-, and NK-cell counts; serum ferritin concentration; vitamin B12; and folate [soluble IL-2 receptor, IL-18, soluble Fas ligand]) (Table 1 and Sills).

Antiplatelet antibodies are of no help in the differential diagnostic process because they are present in less than two-thirds of patients with immune thrombocytopenia and are not predictive, specific, or prognostically relevant, whereas antineutrophilic (bound or soluble) and antiglucocytocytocytic antibodies have a rather high specificity for autoimmune hemolytic anemia and autoimmune neutropenia, respectively. Of note, the detection of antibodies against granulocyte surface antigens (not to be confused with antineutrophilic cytoplasmic antibodies) is a delicate analysis that depends on using specialized reference laboratories to perform tests and interpret results; it is not a test that can be performed under emergency conditions. Before an immunosuppressive treatment is initiated, at least some of the following special immunologic tests should be performed to exclude diseases that cannot be easily diagnosed under intravenous immunoglobulin or pharmacologic immunosuppression. Parameters that are impacted by intravenous immune globulin are mainly the serologic tests such as quantitative immunoglobulins, antibodies against vaccination antigens and previous infectious diseases (protein and polysaccharide antigens), and isohemagglutinins. Analyses that should be done before pharmacologic immunosuppression (including the use of corticosteroids) are immune cellular tests such as quantification of T-, B-, and NK cells, T-cell receptor α/β-positive CD4+ and CD8+ double-negative T cells, CD27+ IgD+ and CD27+IgD+ memory B cells; functional assays such as in vitro lymphocyte proliferation, NK/cytolytic T lymphocyte cytotoxicity; and CD107a degranulation assays to exclude functional T- or NK-cell defects. If a primary lymphoproliferative disorder is suspected, invariant T-cell receptor NKT (γδ T) cells should be quantified (Table 1). Infection serology should be analyzed for EBV, cytomegalovirus, parvovirus B19, and other DNA viruses, as well as HIV and hepatitis viruses; and if an antibody formation defect is suspected, a virus nucleic acid detection test may be needed. In many cases, bone marrow smears and trephine biopsies will need to be assessed and, ideally, they should be sent to reference laboratories for evaluation, as done in international treatment optimization studies. More specific laboratory tests and genetic analyses depend on the clinical situation, the immune hematologic phenotype, and patient’s history, as outlined in Table 1.

Treatment options

The main intention of this review is to increase awareness of and to classify the types of cytopenia that occur in the context of PID to facilitate correct management. Table 1 provides an overview of typical and potential treatment approaches. However, it is not feasible to provide general treatment guidelines for cytopenias in PID because of the heterogeneity of underlying causes and mechanisms, as outlined above and in Figure 1 and Table 1. Although PIDs with autoimmune-mediated cytopenia most often respond well to various degrees and modes of immunosuppression (recently reviewed by Teachey and Lambert), certain diseases might represent an indication for early hematopoietic deficiency) may cause bone marrow failure and are not widely taken into consideration, these entities need to be mentioned here (Figure 1, lower right quadrant; Table 1). In contrast to the widespread view of a PID diagnosis being dependent on compromised immunity, patients with GATA2 deficiency, as with other PID-linked cytopenias, may be asymptomatic and may lack a history of severe infections. Because of its presentation as SCID with granulocytopenia or pancytopenia and deafness, reticular dysgenesis (deficiency of AK2) is unlikely to be missed during a differential diagnosis. The deficiency of IKAROS, a zinc finger transcription factor essential during hematopoiesis, has been reported to be associated with hematologic malignancies (reviewed in Wang et al) and also with congenital pancytopenia in humans. It is known to impede B- and NK-cell development and is thus suspected to cause an immunodeficiency with antibody deficiency and cytopenia (reviewed in John and Ward).
stem cell transplantation, which should be performed according to international transplantation guidelines (such as those recommended by the European Group for Blood and Marrow Transplantation) and within well-controlled clinical trials. Rituximab is used when autoreactive CD20-expressing B-cell clones need to be eradicated and also in EBV-mediated immune dysregulation such as hemophagocytosis and lymphoproliferation (eg, in X-linked lymphoproliferative syndrome, CD27, and IL-2–inducible kinase deficiency), because B cells represent the main pool of EBV and are therefore the trigger for subsequent dysregulated immune processes. A novel group of substances for treating immune-mediated thrombocytopenia (and potentially also pancytopenia resulting from RCMDs) are thrombopoietin receptor agonists such as romiplostim and eltrombopag. Although this treatment option appears even less causal than immunosuppression, at least short-term side effects are low and response rates are promising in adults and children. The future will tell whether long-term follow-up remains acceptable and whether the spectrum for clinical use of thrombopoietin receptor agonists will be extended. In the future, other novel substances for use in antibody-mediated cytopenias may include the proteasome inhibitor bortezomib, the anti-B-cell–activating factor antibody belimumab, the anti-IL-6–directed antibody tocilizumab, the anti-CD22 antibody epratuzumab, and an anti-APRIL antibody, which are currently used only within phase 1 to 3 clinical trials against refractory autoimmunity in certain indications such as in subgroups of patients with SLE, multiple sclerosis, other severe autoimmune diseases, in antibody-mediated graft rejection, or as a treatment adjunct in certain B-cell malignancies. The recommendation to avoid splenectomy, which is still one of the widely accepted (and likely least expensive) options for treating hypersplenism—recommendation to avoid splenectomy, which is still one of the widely accepted (and likely least expensive) options for treating hypersplenism—

Acknowledgments

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Authorship

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Autoimmune and other cytopenias in primary immunodeficiencies: pathomechanisms, novel differential diagnoses, and treatment

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