Chapter 1

Hematologic Manifestations in Human Immunodeficiency

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Abstract

Immunodeficiency disorders are usually associated with infections, autoimmune cytopenias, lymphoma and other malignancies. Primary immunodeficiencies (PIDs) are genetically determined and can be hereditary; secondary immunodeficiencies, on the other hand, are acquired and are usually related to environmental factors, diseases and medications.The three forms of PIDs in which hematologic disorders and autoimmune cytopenias are particularly common are: autoimmune lymphoproliferative syndrome (ALPS), common variable immune deficiency (CVID), and selected forms of combined immunodeficiencies characterized by “leaky” defects in T cell development. In addition, hematologic malignancies have also been reported in immunodeficiency patients, with the higher incidence being reported in PID patients. This review chapter discussed in details all these issues according to the updated literature.

Keywords: Autoimmunity; Cytopenias; Immunodeficiency; Hematologic Manifestation; Lymphoproliferative Syndrome; Malignancies; Thrombocytopenia

1. Introduction

Immune deficiencies are categorized as primary immune deficiencies or secondary immune deficiencies. Primary immune deficiencies (PID) are "primary" because the immune system is the primary cause and most are genetic defects that may be inherited. Secondary immune deficiencies are so called because they have been caused by other conditions [1]. Secondary immune deficiencies, also known as acquired immunodeficiencies, are common and can occur as part of another disease or as a consequence of environmental factors or certain medications [2]. The most common secondary immune deficiencies are caused by aging,

malnutrition, certain medications and some infections, such as human immunodeficiency virus (HIV).

Hematologic abnormalities are common in patients with immunodeficiency. Although primary immunodeficiencies (PIDs) are typically marked by increased susceptibility to infections, autoimmune cytopenias are recognized as an important component of several forms of PID [3]. Cytopenias result from the development of autoantibodies that bind to and destroy blood cells. Various mechanisms have been implied in the pathophysiology of autoimmune cytopenias in these patients, including defective negative selection of autoreactive T lymphocytes in the thymus, defects in the number and/or function of regulatory T cells, impaired apoptosis of autoreactive lymphocytes, breakage of tolerance due to increased load or decreased clearance of apoptotic cells and pathogens, and increased homeostatic lymphoid proliferation and cytokine secretion associated with lymphopenia [4,5].

2. Immunodeficiencies and Cytopenias

The three forms of primary immunodeficiencies (PIDs) in which autoimmune cytopenias are particularly common are: autoimmune lymphoproliferative syndrome (ALPS), common variable immune deficiency (CVID), and selected forms of combined immunodeficiencies characterized by "leaky" defects in T cell development [6]. While autoimmune manifestations are not typically part of the clinical features observed in patients with severe combined immunodeficiency (SCID), cytopenias have been described in some forms. Autoimmune cytopenias are also very common in patients with the Wiskott-Aldrich syndrome (WAS) and with hyperIgM syndromes, as reported in several case series studies [7-9].

3. Autoimmune Lymphoproliferative Syndrome

Autoimmune lymphoproliferative syndrome (ALPS) includes a genetically heterogeneous group of disorders characterized by lymphadenopathy, splenomegaly, autoimmune cytopenias, and increased occurrence of lymphoid malignancies associated with defective apoptosis [10]. Most often ALPS is due to genetic defects that affect the apoptosis extrinsic pathway, such as mutations in CD95 (*TNFRSF6*), or more rarely in CD95L (*TNFSF6*), caspase 8, or caspase 10 [11-14]. These defects can be inherited as autosomal-dominant or autosomal-recessive traits; however, somatic mutations in CD95 have been also reported, providing evidence that impairment in Fas-mediated apoptosis confers a selective advantage to mutated cells that tend to accumulate with time. In addition to these ALPS-causing genetic defects, a significant number of patients with clinical and immunological features of ALPS carry no known gene defects. Some of them show impaired Fas-mediated apoptosis, but others do not, suggesting that defects in other apoptosis-triggering pathways may also be involved. Indeed, one patient with an activating mutation in the *NRAS* gene, leading to a defect in IL-2 starvation-induced apoptosis, has been described [15-17].

The characteristic feature of ALPS patients is a high percentage of circulating TCRαβ^{+} CD4^{-} CD8^{-} double negative (DN) T cells that express a restricted T-cell receptor (TCR) repertoire that may possibly recognize self-antigens. It has been hypothesized that these DN T cells represent T lymphocytes targeted to Fas-mediated apoptosis. Overall, an increased proportion of DN T cells and elevated plasma levels of IL-10 and FAS-L represent useful biological markers of ALPS [18].

Autoantibodies, most commonly anticardiolipin or direct Coombs antibodies, were detected in up to 80% of patients with ALPS. Autoimmune hemolytic anemia and thrombocytopenia have been observed in 23% to 51% of the patients in different series, and autoimmune neutropenia is also common (19%–27%) [19,20]. Importantly, autoimmune cytopenias may mark the clinical onset of the disease, even in the absence of signs of lymph proliferation. Accordingly, patients with Evans syndrome should always be evaluated for ALPS [21,22].

The autoimmune cytopenias of ALPS are often severe and refractory to treatment. For these reasons, splenectomy has frequently been used in the past in the management of ALPS; however, this approach carries significant risks of sepsis. Successful results have been reported with mycophenolate mofetil (MMF) and sirolimus. Use of rituximab, with the intent to ablate autoreactive B cells, has been associated with neutropenia and persistent hypogammaglobulinemia [23,24].

4. Common Variable Immune Deficiency

Common variable immune deficiency (CVID) includes a heterogeneous group of conditions characterized by reduced levels of serum immunoglobulins and primary antibody failure [25]. Genetic defects in TACI (*TNFRST13B*), ICOS, BAFF-R and CD19 account only for a minority (15%-20%) of cases of CVID; the molecular pathophysiology of the remaining cases remains undefined and could be polygenic. Increased susceptibility to bacterial infections is a hallmark of CVID and was a prominent cause of death until immunoglobulin substitution therapy, antibiotic prophylaxis and prompt treatment of infections came into clinical practice, permitting prolonged survival and a better definition of the incidence of non-infectious complications in CVID [25, 26]. Autoimmune manifestations occur in a substantial proportion of patients with CVID, ranging from about 22% to 48% in different series from different countries. They are more frequent among patients with granuloma, with up to 50% of these patients suffering from autoimmune manifestations [26].

Among autoimmune manifestations, cytopenias are particularly common and (especially in the case of immune thrombocytopenic purpura or autoimmune hemolytic anemia) may mark the onset of the disease. The prevalence of hematological autoimmune manifestations was reported in some studies as high as 11%, with the immune thrombocytopenic purpura being the

most frequent cytopenias [27]. Compared to general population, the prevalence of autoimmune cytopenias among patients with CVID is 100 to 1000 fold higher [26]. The occurrence of autoimmune cytopenias in CVID does not correlate with organ-specific autoimmunity, but tends to correlate with splenomegaly. A reduced number of $CD4^{+}$ $CD25^{hi}$ $Foxp3^{+}$ cells, associated with lower levels of Foxp3 expression, have also been recently reported in patients with CVID with autoimmune manifestations [26].

Autoimmune cytopenias are particularly common among patients with CVID with reduced numbers of switched memory B cells and an increased proportion of $CD19^{hi}$ $CD21^{lo}$ lymphocytes [28]. The presence of TACI mutations represents another risk factor for autoimmune cytopenias. Increased serum levels of BAFF and APRIL have been observed in patients with CVID and could support expansion and antibody secretion by autoreactive B-cell clones [29]. Lower proportions of circulating $CD8^{+}$ lymphocytes were also found to be associated with autoimmunity [26].

5. Severe Combined Immune Deficiency

Severe combined immune deficiency (SCID), also known as alymphocytosis, Glanzmann–Riniker syndrome, *severe* mixed *immunodeficiency* syndrome [30], and thymic alymphoplasia comprises a heterogeneous group of genetically determined disorders that are characterized by the virtual absence of T cells and severe numerical and/or functional B-cell deficiency [30,31]. Therefore, as rule autoimmune manifestations are not parts of the clinical features observed in patients with SCID. However, genetic defects that severely compromise, but do not abrogate, T and B cell function may also result in an increased occurrence of autoimmunity, including cytopenias. The molecular and cellular mechanisms that account for autoimmunity in “leaky” forms of SCID are the focus of a series of recent studies. B-cell hyper-reactivity, with aberrant T cell-mediated immune regulation, may play a role [32]. Additional mechanisms may include impaired lymph stromal cross-talk in the thymus, with defective expression of autoimmune regulator (AIRE) protein and inadequate induction of Treg cells. Moreover, some forms of SCID reflect genetic defects that affect V(D) J recombination. Hypomorphic mutations in these genes may allow for residual T and B cell development, associated with impaired receptor editing, thus leading to accumulation of autoreactive B cells [33].

Deficiency of purine nucleoside phosphorylase (PNP) in humans causes accumulation of deoxyguanosine triphosphate (dGTP) that is toxic to lymphocytes, resulting in a progressive and severe decline in the number and function of T lymphocytes, whereas in most patients B cells are marginally affected. Although autoimmune hemolytic anemia is particularly common, Idiopathogic thrombocytopenic purpura (ITP) and neutropenia have been also reported [34]. These complications have been attributed to B-cell hyper-reactivity resulting from a loss of T-cell regulation [33].

6. Hematologic Malignancies and Immunodeficiency

In addition to the above mentioned hematologic abnormalities, hematologic malignancies have also been reported in immunodeficiency patients. Increased incidences of hematologic malignancies are reported in primary immunodeficiency (PID) patients [35]. In pediatric PID patients, the overall risk for cancer development is estimated to range from 4-25%, of which 60% of cases are lymphomas of B-cell origin with NHL being the greatest contributor [36].

Common variable immune deficiency (CVID) patients have an overall increased lymphoma incidence, suggesting that B- and T-cell function and interplay contribute to immunological surveillance against lymphoma development. A significantly increased risk of non-Hodgkin lymphoma was found in CVID patients [37]. Among relatives of patients with CVID, however, no increase in the risk was found, suggesting that the increased incidence in patients with CVID is related to the immunodeficiency itself rather than other genetic traits shared by relatives [37].

Wiskott-Aldrich syndrome (WAS) is an X-linked, combined immune-deficiency caused by mutations in the WAS protein, which is an important actin cytoskeleton regulator of hematopoietic cells [38]. A patient with WAS usually presents with thrombocytopenia from infancy, eczema and progressive immunodeficiency. In this disease, up to 90% of cancers consist of frequently EBV-positive lymphoma or leukemia. Predisposition to these malignancies very likely involves both NK-cell and T-cell activation defects [39,40]. Although SCID has been associated with malignancy, of which Non-Hodgkin Lymphoma (NHL) is again the greatest contributor, these patients usually not survive beyond 1 year without treatment due to severe infections.

The majority of cancers in patients with PID is of hematologic origin and is moreover associated with infection with oncogenic viruses; such as the human papillomavirus (HPV), human immunodeficiency virus (HIV) and the Epstein-Barr virus (EBV) results in the transduction of copies of the viral genome into cellular genes that can activate proto-oncogenes, inactivate tumor suppressor cells or stimulate growth factors. Of these viruses, EBV appears to be an important co-factor for the development of PID-associated lymphomas [41,42].

EBV infection causes polyclonal activation and proliferation of B-cells. Immunity against this virus is primarily carried out by $CD8^+$ cytotoxic T-cells and to a lesser degree by other immune mechanisms such as humoral responses or natural killer cell activity. Thus, PIDs with T-cell dysfunction are expected to be particularly susceptible to EBV-related lymphomas [41].

In HIV, it is well known that CD4 lymphocyte counts are decreased during disease progression. However, other hematologic manifestations are not well known, and these

manifestations are affected by the country and ethnicity of patients. HIV itself can cause hematological manifestations. The viral gene products of HIV can indirectly influence survival and growth of hematopoietic progenitors [43,44].

The most important malignancies associated with HIV infection are the Kaposi sarcoma (KS), aggressive B-cell NHL, and cervical cancer. These three malignancies are considered AIDS-defining conditions by the Centers for Disease Control and Prevention [44,45]. A major feature of these cancers in HIV-infected persons is their association with immune-suppression. For KS and NHL subtypes, risk increases as the CD4 count declines. This association with CD4 count has not been apparent for cervical cancer, although HIV-infected women with low CD4 counts have an elevated risk of persistent human papilloma virus infection and progression to pre-cancerous cervical lesions, compared to women with higher CD4 counts [45, 46]. In pediatric patients, HIV co-infection is a strong predisposing factors for KS development (also known as epidemic or iatrogenic KS), while classic KS in childhood is rare [36].

7. References

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