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CHAPTER 49

LYMPHOCYTOSIS, LYMPHOCYTOPENIA, HYPERGAMMAGLOBULINEMIA, AND HYPOGAMMAGLOBULINEMIA

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Any discussion of quantitative abnormalities of lymphocytes and immunoglobulins is necessarily linked because the B-cell compartment is responsible for immunoglobulin production, and the T-cell compartment helps provide the stimulus. Nevertheless, clinicians are often consulted when a quantitative disorder of one or the other is recognized. Thus, although overlapping, the defects are presented separately.

QUANTITATIVE DISORDERS OF LYMPHOCYTES

The normal number and distribution of lymphocyte subtypes in the peripheral blood varies with age, but no careful study has demonstrated gender or ethnic differences in lymphocyte count. In general, circulating T cells exceed B cells by a ratio of approximately four to one, with that ratio increasing slightly with age (Table 49.1). Natural killer (NK) cells are grouped with lymphocytes but comprise only about 10% of the lymphocyte population. Infants have total lymphocyte counts between 5500/μL and 7000/μL, but this number declines beginning at about 1 year of age to reach 2000/μL to 2400/μL in adults. At birth, the total number of circulating B cells is approximately 1000/μL but decreases over the first 10 years of life to approximately 200/μL to 300/μL by the age of 18 years. A slow decline in circulating B cells continues throughout adulthood and is primarily accounted for by a decline in transitional and naive B cells with a stable or mild increase in circulating memory B-cell numbers with age. Circulating naive B cells represent about two-thirds of the entire naive B-cell pool, and circulating memory B cells represent only about one third of the entire memory B-cell pool.[1]

T cells dominate the circulating lymphocyte population with approximately 3500/μL in infancy, declining to 1500/μL on average in young adults, with even lower numbers (approximately 1200/μL) in elderly adults. In both children and adults, CD4 cells outnumber CD8 cells. Naive CD4 and CD8 T cells decline with age by twofold to fourfold. In one large study, CD4 memory T cells significantly increased with age, but no such trend was seen for CD8 memory T cells.[2]

Against this background, *lymphocytosis* is defined as a lymphocyte count greater than 8000/μL in young children and greater than 4000/μL in teenagers and adults. Lymphocytopenia has been defined as a total lymphocyte count of less than 1000/μL. Given the composition of the circulating lymphocyte pool, it is critically important to define which lymphocyte subsets are over- or underrepresented when there is a quantitative disorder.[2]

Lymphocytosis

As in any clinical disorder, a careful history is critical to defining the origin of lymphocytosis. Inherited causes of lymphocytosis are rare. One recently identified inherited lymphocytosis is BENTA disease (B-cell expansion with nuclear factor kappa-B [NFκB] and T-cell anergy). Germline gain of function mutations in caspase-activating recruitment domain 11 *(CARD11)* drive this disorder, which is characterized by polyclonal lymphocytosis and splenomegaly beginning in infancy. In most cases of lymphocytosis, however, the issue is to determine whether a lymphocyte disorder is clonal/malignant or benign and related to infection, drugs, or physiologic stress. Rarely, neither a malignancy nor an underlying condition can be identified, in which case the lymphocytosis is termed *persistent polyclonal B-cell lymphocytosis*. When an excess of B cells exists, clonality can usually be defined by examining cell surface expression of κ- and λ-light chains using antibody techniques; with T-cell proliferation, it may be important to define clonality by examining T-cell receptor gene rearrangement using molecular procedures. In the case of NK cell disorders, clonality can be quite difficult to determine.

Clonal Disorders

Malignant causes of peripheral blood lymphocytosis are covered in Chapters 76–80, 84, and 86 and include chronic lymphocytic leukemia (CLL), hairy cell leukemia, splenic marginal zone lymphoma, lymphoplasmacytic lymphoma, follicular lymphoma, mantle cell lymphoma, adult T-cell leukemia or lymphoma, and Sézary syndrome. Occasionally, precursor T-cell or precursor B-cell leukemia presents with circulating small cells, which morphologically appear more similar to mature lymphocytes than blasts.

A recently identified clonal disorder causing lymphocytosis is monoclonal B-cell lymphocytosis (MBL), an accumulation of clonal B lymphocytes that does not meet the criteria for CLL (greater than 5000 clonal B cells/μL), but is nevertheless defined by the presence of a clonal population of B cells. Data demonstrate that up to 10% to 15% of patients with lymphocytosis have MBL. Three major subtypes of MBL exist: the CLL immunophenotype ($CD5^+$, $CD23^+$), which is by far the most common; the atypical CLL type ($CD5^+$, $CD23^-$); and non-CLL lymphoproliferative disorder ($CD5^-$). In a systematic study of blood donors more than 45 years of age, 7.1% had detectable MBL. Of these, the majority had the CLL immunophenotype and more than 93% were low-count MBL (B-cell clonal count less than 500 cells/μl). Similar to the relationship between monoclonal gammopathy of uncertain significance and multiple myeloma, only a small proportion of patients with CLL-type MBL (1% to 4% per year) go on to develop progressive disease requiring treatment. Epidemiologic studies of MBL patients have demonstrated strong familial risk for CLL, and the first reports of MBL came from studies of "unaffected" CLL family members. Studies of CLL families suggest that there is an inherited abnormality that increases the risk of developing CLL, and some families exhibit anticipation, with the disease occurring earlier in successive generations. The supposition that MBL is a progenitor lesion for CLL is strengthened by the observation that both low-count and high-count MBL carry the same cytogenetic aberrations observed in good-prognosis CLL. MBL has been identified in up to 30% of individuals infected with hepatitis C virus (HCV), and up to 50% of the HCV-associated cases demonstrate the atypical CLL immunophenotype. The presence of MBL correlates with more advanced liver disease, suggesting that the persistence of viral infection is crucial to development of the B-cell clone. Follow-up for MBL patients is not clearly defined, although it is probably reasonable to evaluate lymphocyte counts with complete blood counts and follow the clone with flow cytometry at periodic

TABLE 49.1 Normal Lymphocyte Subsets With Age[a]

	Cord Blood	2 Days–11 Months	1–6 Years	7–17 Years	18–70 Years
Total lymphocyte count ($\times 10^3$ cells/mL)	5.4 (4.2–6)	4.1 (2.7–5.4)	3.6 (2.9–5.1)	2.4 (2.0–2.7)	2.1 (1.6–2.4)
$CD4^+$ T cells (%)	35 (28–42)	41 (38–50)	37 (30–40)	37 (33–41)	42 (38–46)
$CD45Ra^+$ in $CD4^+$ (naive T cells)[b]	91 (82–97)	81 (66–88)	71 (66–77)	61 (55–67)	40 (32–49)
$CD8^+$ T cells (%)	29 (26–33)	21 (18–25)	29 (25–32)	30 (27–35)	35 (31–40)
B cells (%)	20 (14–23)	23 (19–31)	24 (21–28)	16 (12–22)	13 (11–16)
NK cells (%)	20 (14–30)	11 (8–17)	11 (8–15)	12 (9–16)	14 (10–19)

[a]Values are median, with ranges from the 25th to 75th percentiles.
[b]Naive T cells expressed as a percentage of $CD4^+$ T cells.
NK, Natural killer.

intervals depending on the pace of the lymphocyte rise, the clinical scenario, the family history, and the age of the patient.[3]

Infectious Causes

The most common infections causing lymphocytosis are Epstein-Barr virus (EBV) and cytomegalovirus (CMV). In young children, EBV infection frequently presents as an upper respiratory infection, but in adolescents and young adults, it can result in acute glandular fever with pharyngitis, splenomegaly, lymphadenitis, and profound reactive lymphocytosis. Lymphocytosis is less prominent in older adults. Although the B cells are targeted by EBV, the lymphocytosis consists of $CD8^+$ lymphocytes reacting to neoantigens expressed on the surface of infected B cells. The massive T-cell response usually clears the infection in a matter of days to 1 week, and the lymphocytosis resolves. CMV infection can produce a similar lymphocytosis. In the case of CMV, however, the macrophages are the target of infection, and the T-cell lymphocytosis results from a response to the macrophage neoantigen. CMV infection and lymphocytosis are more common in older adults. In both viral infections, lymphocytosis can be profound, with 50% or more of the circulating white blood cells (WBCs) identified as lymphocytes. Examination of the peripheral smear reveals that up to 10% of the circulating lymphocytes are atypical and larger than normal lymphocytes with open chromatin and increased cytoplasm. It is particularly important to recognize lymphocytosis caused by these two viruses in pregnant women because congenital infection can cause fetal death and birth defects. In addition to EBV and CMV, primary infection with human immunodeficiency virus (HIV) can cause lymphocytosis and should be suspected in the presence of a viral syndrome in the appropriate clinical circumstance. In children, infection with Coxsackie A and B6 viruses, echovirus, and adenovirus can cause a brief but profound lymphocytosis. Infections with other viruses, including human herpesvirus 6 (HHV-6) and human herpesvirus 8 (HHV-8) as well as rubella virus, varicella, human T-lymphotropic virus type 1 (HTLV-1), and hepatitis viruses, can cause a lymphocytosis, although much less frequently than CMV and EBV.

Important nonviral infections causing lymphocytosis include *Toxoplasma gondii* and *Bordetella pertussis*. In an immune-competent host, *Toxoplasma* infection is often asymptomatic, but patients can have fever, chills, and lymphadenopathy. Mild lymphocytosis with atypical lymphocytes can be observed. As in the case of EBV and CMV, infections during pregnancy can lead to adverse effects on the fetus. In children and adults, infection with *B. pertussis* can lead to lymphocytosis, with the absolute lymphocyte count frequently greater than 10,000/μL. In more severe cases, lymphocytosis is more pronounced.[4] Unlike viral infections and *Toxoplasma* infection, the lymphocytosis observed in *B. pertussis* infection is caused by increases in all lymphocyte subsets, and it appears that the pertussis toxin blocks migration of the lymphocytes from the bloodstream into lymph nodes.[4] Tuberculosis, rickettsial infection, brucellosis, and shigellosis may also cause lymphocytosis.

Physiologic Stress

Lymphocytosis related to physiologic stress is a poorly studied phenomenon. After strenuous physical exercise, subjects develop lymphocytosis, which returns to preexercise levels within 15 minutes to 1 hour of ceasing the activity. The exercise-induced rise is thought to be attributable to catecholamine and steroid hormones, and their effect on expression of cell adhesion molecules and on cardiac output and shear stress.[5] Exposure to catecholamines increases the expression of β_2-adrenergic receptors on lymphocytes influencing cell trafficking. Reports suggest that a number of other physiologic stresses increase lymphocyte counts, including surgery, trauma, cardiac conditions, sickle cell crises, abdominal pain, and obstetric emergencies. In these cases, all lymphocyte subsets appear to increase, but the increase is most profound for CD4 and CD8 memory T cells. Neutrophil counts also rise in these patients, but in most cases, the lymphocytosis resolves before the peak of the neutrophil count.[6]

Drug Reactions

Drug-induced lymphocytosis can occur as part of a hypersensitivity syndrome. In these cases, the lymphocytosis is usually part of a systemic condition that includes a fever, rash, and lymphadenopathy. Elevation in other WBC counts, including eosinophils and monocytes, is common, and atypical lymphocytes are seen. The time period between drug introduction and the syndrome is usually about 3 weeks with the most common implicated drugs being aromatic anticonvulsants and sulfonamides.[7] Some studies differentiate this syndrome from drug-induced cutaneous pseudolymphomas in which collections of nonclonal lymphocytes appear in the skin after longer periods of drug exposure, but there is no peripheral lymphocytosis.

Polyclonal B-Cell Lymphocytosis

A final entity causing lymphocytosis is persistent polyclonal B-cell lymphocytosis (PPBL). This rare disorder is seen primarily in young to middle-aged women who smoke and results in mild polyclonal lymphocytosis. The lymphocytes are medium sized with abundant cytoplasm and a variable proportion is binucleate. A polyclonal increase in serum immunoglobulin M (IgM) is also observed, and there is an association with the human leukocyte antigen (HLA) antigen D-related 7 (DR7) phenotype. Examination of the B cells reveals that most are $CD19^+$, $CD5^-$, and $CD23^-$, with a normal kappa-to-lambda ratio and a variety of heavy chain rearrangements. Adenopathy, hepatomegaly, or splenomegaly has been observed in some, but not all, patients. Genetic analysis has demonstrated the presence of isochromosome 3q in a proportion of B cells, as well as the presence of multiple B-cell lymphoma immunoglobulin *(BCL2-Ig)* gene rearrangements. Similar gene rearrangements have been identified in family members of PPBL patients along with increases in serum IgM, suggesting that there may be an underlying genetic

defect. In vitro studies have shown that PPBL cells proliferate in a CD40-CD154 culture system and secrete both IgM and IgG (isotype switching). This suggests that PPBL may arise from deregulation of the microenvironmment or from a defect in a different B-cell activation pathway resulting in extensive proliferation. Overall, the clinical course of this disorder is benign, and the lymphocytosis is not usually progressive; however, clonal B-cell disorders have been seen in a few patients with the disorder, suggesting that it may represent a preneoplastic state.[8]

Lymphocytopenia

Inherited Disorders

Although there are few inherited causes of lymphocytosis, such is not the case for lymphocytopenia, in which the genetic bases of a number of inherited immunodeficiency disorders have been identified. Chief among these disorders is severe combined immunodeficiency (SCID), which is characterized by the absence of functional T lymphocytes. T lymphocytes, B lymphocytes, and NK cells share progenitors, signaling pathways in development and function, and metabolic pathways; thus B lymphocytes, NK cells, or both are often severely affected in SCID. Moreover, in the absence of functional $CD4^+$ T-helper lymphocytes, B lymphocytes cannot function properly, and hypo- or agammaglobulinemia is observed. In most cases of SCID, the absence of T lymphocytes leads to an extremely low absolute lymphocyte count. As detailed in Chapter 49, SCID can be grouped based on the cellular pathway that is affected. In general, whereas SCID is characterized by complete loss of function of the affected gene, hypomorphic mutations of the same genes lead to quite different phenotypes (Omenn syndrome and atypical SCID). Defects in more than 30 genes are known to lead to SCID. Inheritance is primarily X-linked or autosomal recessive, but in a few cases, such as the DiGeorge anomaly and some cases of Hoyeraal–Hreidarsson syndrome (defects in telomerase), inheritance is autosomal dominant. Until the genetic diagnosis is known, it is useful to characterize SCID syndromes as $T^-B^+NK^+$, $T^-B^-NK^+$, $T^-B^+NK^-$ or $T^-B^-NK^-$ based on the presence or absence of defects affecting B and/or NK cells. SCID can be classified based on the cellular function which is lacking, including deficiency in cytokine-mediated signaling, defects in V(D)J recombination, absent signaling through the T-cell receptor, defects in antigen presentation, and defects in basic cellular processes. Defects in the interleukin-7 receptor alpha chain *(IL7RA)*, actin-regulating protein coronin 1A *(CORO1A)*, CD3 chain components *(CD3D*, *CD3E*, *CD3Z)*, and CD45 *(PTPRC)* lead to $T^-B^+NK^+$ SCID. $T^-B^+NK^-$ SCID defects include deficiencies in cytokine-mediated signaling *(IL2RG*, *JAK3)*. Defects in V(D)J recombination *(RAG1, RAG2)* or in nonhomologous end joining for repair of double-strand DNA breaks (*DCLRE1C*, *PRKDC*, *LIG4*, and *NHEJ1* mutations) lead to $T^-B^-NK^+$ SCID. Defects that lead to increased lymphocyte apoptosis (*AK2*, *ADA* gene mutations) lead to $T^-B^-NK^-$ SCID and are often associated with anomalies outside of the immune system. Defects in thymic embryogenesis and calcium flux, as well as a collection of other abnormalities, including defects in telomerase activity, can also lead to SCID and are usually associated with abnormalities of other organ systems.[9]

In addition to SCID, other inherited disorders can also perturb T- and B-cell numbers. Patients with Wiskott-Aldrich syndrome, caused by mutations in *WASP* (which encodes a cytoplasmic protein responsible for transducing cell surface signals to the actin cytoskeleton), can present with low T-cell counts early in life and become profoundly lymphopenic over time. Abnormalities in immunoglobulins are also noted in this syndrome, with low levels of IgM and high levels of IgA and IgE.[10] Immunodeficiency affects more than half of all patients with ataxia telangiectasia. Patients with ataxia telangiectasia have homozygous or compound heterozygous mutations in the ataxia-telangiectasia–mutated *(ATM)* gene, which encodes a protein kinase with functions in the cellular response to DNA damage. Lymphopenia, especially of naive CD4 cells, is observed in about half of patients with ataxia telangiectasia, with mutations leading to absent expression of ATM kinase activity.[11] Heterozygous germline mutations in *GATA2* lead to a spectrum of clinical syndromes characterized by dendritic cell, monocyte, B cell, and NK lymphoid deficiency (DCML deficiency) with elevated 3 ligand (Flt3L). Mononuclear cytopenia appears to evolve in diverse clinical groups of *GATA2* mutation including monoMAC syndrome (monocytopenia, B-cell and NK-cell lymphopenia, mycobacterial, fungal, and viral infections and alveolar proteinosis), Emberger syndrome (lymphedema, deafness, and myelodysplastic syndrome [MDS]) and familial (MDS)/acute myeloid leukemia (AML)[12]. *GATA2* mutation appears to cause loss of progenitor cells, clonal hematopoiesis and elevation of Flt3L, but the molecular mechanisms of marrow failure and transformation to MDS or AML are as yet unclear.

Infections

A variety of viral and nonviral infections can lead to lymphopenia. HIV is the most common virus associated with lymphopenia. The target of HIV is the CD4 receptor, and the virus selectively targets and infects activated expanding CD4 T cells. Large studies in HIV-infected patients have shown that peripheral blood CD4 T-cell counts fall most rapidly in the year after seroconversion (from approximately 1000/μL before seroconversion to 670/μL at 1 year after infection) and then decline more slowly by about 50/μL per year.[13] In a subset of untreated patients, viremia is absent or well controlled, and lymphocytopenia develops very slowly if at all; particular HLA class I alleles are overrepresented in this group. Lymphopenia is an early and reliable laboratory observation in adult influenza infection and is also detected in infections caused by swine influenza (H1N1) and the highly pathogenic avian influenza (H5N1).[14] Lymphopenia has been reported in patients with severe acute respiratory syndrome (SARS) caused by the SARS-coronavirus. In children, respiratory syncytial virus (RSV) infection is associated with a reduction in lymphocyte count, which is most extreme in the sickest patients; similar effects on lymphocyte counts are seen in measles infections (also a paramyxovirus). In West Nile virus encephalitis, lymphopenia is profound and prolonged, and the initial degree of lymphopenia is predictive of outcome. A variety of other viruses can also cause lymphopenia, including herpes viruses (herpes simplex, HHV-6, HHV-8), parvovirus B19, and Dengue virus. In many viral infections, the degree of lymphopenia is correlated with the severity of the disease.[14]

A variety of nonviral infections cause lymphopenia. Infections with *Ehrlichia* (a tick-borne obligate intracellular gram-negative bacteria), *Salmonella typhi*, and *Leptospira* have all been reported to cause lymphocytopenia during the acute illness. $CD4^+$ T-cell depletion has been described in a subset of HIV-negative patients with tuberculosis and low albumin levels, low body weight, and more extensive disease. Recovery of CD4 count after treatment of tuberculosis suggests that the lymphopenia is caused by the tuberculosis infection.[15] Lymphocytopenia is often observed in sepsis and is thought to occur as a result of cytokine-mediated apoptosis of B cells, CD4 and CD8 T cells, and follicular dendritic cells. In autopsy series, most deaths from sepsis occur during the prolonged hypoimmune state, and the more prolonged the sepsis, the more profound the loss of splenic lymphocytes. In one large retrospective study, severe persistent lymphopenia (defined as an absolute lymphocyte count of less than 600 cells/μL) on the fourth day following a diagnosis of sepsis was predictive of development of secondary infections, as well as short- and long-term survival.[16]

Collagen Vascular Disorders

Autoimmune diseases frequently exhibit decreases in circulating lymphocytes. In systemic lupus erythematosus (SLE), lymphopenia (usually decreases in T cells but occasionally in B cells as well) is not only one of the diagnostic criteria but also a parameter used to assess disease activity. Lymphopenia was observed in more than 60% of

patients at diagnosis, with the cumulative incidence over the course of the disease reaching over 90%. Lymphopenia in SLE seems to be more frequent in patients of African descent, and in one study more than half of patients with lymphopenia demonstrated antilymphocyte antibodies. Antigalectin 8 antibodies have been described in patients with SLE, rheumatoid arthritis, and sepsis. In SLE, these autoantibodies are associated with lymphopenia. Apoptosis may also play a role in lymphopenia in SLE, possibly by upregulation of fas antigen on naive peripheral T cells.[17] CD4 T cells may also be decreased in rheumatoid arthritis, and increasing evidence suggests that deficiencies in DNA repair enzymes such as ATM render rheumatoid arthritis T cells sensitive to apoptosis.[18] Apoptotic loss of naive T cells results in lymphopenia-induced proliferation to preserve T-cell homeostasis; this proliferation is now thought to lead to both premature immune aging and an autoimmune-biased T-cell repertoire. In Sjögren syndrome, a minority of patients has been noted to have deficient CD4 counts, and this has been correlated with the presence of anti-CD4 antibodies. Similarly, low lymphocyte counts have been observed in patients with primary vasculitides, type 1 diabetes, and Crohn disease.[17]

Malignancies

Lymphopenia is found in a variety of systemic illnesses; chief among them are cancers. In hematologic malignancies, including Hodgkin lymphoma, diffuse large B-cell lymphoma, and peripheral T-cell lymphoma, patients with lymphopenia have a worse prognosis. Lymphopenia has also been observed in solid tumors, including breast and colon cancer, and soft tissue sarcomas, in which its presence before treatment predicts decreased overall survival. Which specific lymphocyte subsets are involved and the cause(s) of lymphopenia in these tumor types has not been described.

Systemic Disorders

End-stage renal disease (ESRD) has also been associated with lymphopenia, an observation not thought to be exclusively attributable to an effect of dialysis alone. Naive and central memory CD4 and CD8 T cells are significantly reduced in the blood of ESRD patients, apparently because of increased susceptibility of these cells to apoptosis. Lymphopenia occurs in more than 50% of sarcoidosis patients and is associated with chronic disease. Sarcoidosis patients with severe organ system involvement, including neurologic, cardiac, ocular, and advanced pulmonary disease, have lower lymphocyte counts than patients with less severe manifestations (see E-Slide VM03953). Older studies suggest that burn victims have profound decreases in T-cell counts, which may contribute to the infection risk in these patients. Interestingly, lymphopenia is a characteristic of both protein-energy malnutrition and zinc deficiency. Both of these deficiencies perturb the hypothalamic–pituitary–adrenocorticoid axis and increase glucocorticoid levels, which results in increased apoptosis of B and T cells.[19] Intestinal lymphangiectasia, which may be either congenital or secondary to processes that obstruct lymphatic drainage of the gastrointestinal tract, can cause lymphopenia as a result of loss of lymph fluid into the gut along with lymphocytes.

A rare cause of lymphopenia is idiopathic $CD4^+$ lymphocytopenia (ICL), which is defined as a CD4 count less than 300/μL or less than 20% of the T-cell count on two occasions that is not caused by HIV or HTLV infection, drug therapy, or a known immunodeficiency. Patients usually come to clinical notice when they present with opportunistic infections. CD4 T-cell counts typically remain low, but counts do not continue to drop or do not fall rapidly after diagnosis. In one large series, only about 20% of patients recovered from lymphopenia within 3 years of diagnosis. Opportunistic infections plague these patients, and autoimmune diseases occur both before and after the diagnosis of ICL. In ICL, unlike HIV infection, increased activation and turnover are observed in CD4 but not CD8 T lymphocytes.[20]

Drug Effects

A number of drugs are known to cause lymphopenia. Glucocorticoids inhibit production of a number of cytokines and rapidly deplete circulating T cells by enhancing emigration from the circulation, inducing apoptosis, interfering with growth signaling, and inhibiting release from lymphoid tissues. B cells are less affected acutely by glucocorticoid administration, but prolonged administration may result in decreased IgG levels. In clinical trials for multiple sclerosis, delayed release dimethyl fumarate resulted in a decrease in mean lymphocyte count of about 30% in the first year, but about 2% of patients had lymphocyte counts less than 500 cells/μL which persisted for 6 months or longer. Antimetabolite chemotherapeutic agents such as methotrexate, azathioprine, and 6-mercaptopurine lower lymphocyte as well as neutrophil counts, and alkylating agents such as cyclophosphamide have more profound effects on lymphocytes. Purine nucleoside analogs, including cladribine, fludarabine, pentostatin, nelarabine, clofarabine, and others, inhibit DNA synthesis and repair, and cause accumulation of DNA strand breaks. All of these agents are associated with profound lymphopenia, which may persist for several years after completion of treatment. In general, T cells are more affected than B cells. Nelarabine in particular is a prodrug of ara-G and is converted to ara-GTP, which accumulates at higher levels in T cells.[21]

Monoclonal and polyclonal antibodies directed against lymphocytes are useful in clinical practice and can induce profound and long-lasting lymphopenia. Whereas antithymocyte globulin and alemtuzumab produce depletion of both T and B cells, the monoclonal antibodies OKT3, daclizumab, and basiliximab produce a more pronounced decrease in T cells. The drugs rituximab and ofatumumab are monoclonal antibodies directed against distinct epitopes on B cells. These drugs deplete peripheral B cells but do not routinely produce lymphopenia.

Finally, radiation exposure commonly results in lymphopenia, which occurs before depression of other cell counts. In fact, lymphopenia can develop within the first 24 hours of exposure if the dose of radiation is great enough, and a drop of 50% or more predicts an increased risk of death. B cells are more sensitive to radiation than T cells and recover more slowly than T-cell numbers.[22]

QUANTITATIVE DISORDERS OF IMMUNOGLOBULINS

In practice, as there are several methods for determining serum immunoglobulin levels it is critical that age-adjusted normal reference ranges are provided by the laboratory when evaluating immunoglobulin level results. Children first achieve adult levels of IgM around 2 years of age, IgG by 6 years of age, and IgA during puberty. Hypogammaglobulinemia is defined as an IgG less than 2 standard deviations from normal, and agammaglobulinemia is usually defined as an IgG level less than 100 mg/dL. Low levels of IgA, IgG, and IgM are characteristic of most forms of SCID.

Hypogammaglobulinemia

Causes of hypogammaglobulinemia can be divided into primary causes related to genetic deficiencies and secondary causes related to malignancies or their treatment, infections, medications, and protein-losing states that deplete antibody.

Secondary Causes

Before embarking on a search for a primary disorder causing hypogammaglobulinemia, it is important to rule out secondary causes. Malnutrition, malabsorption, and any disease state in which large amounts of protein are lost, such as nephrotic range proteinuria, severe burns, lymphangiectasia, or protein-losing enteropathy, can overwhelm the capacity of the B cells to provide adequate immunoglobulin to

maintain normal serum levels. Aside from chemotherapeutic agents, a number of medications can produce hypogammaglobulinemia; these include captopril, antiseizure medications (carbamazepine, phenytoin), gold salts, antimalarials, fenoclofenac, penicillamine, and sulfasalazine, as well as glucocorticoids. Infection with HIV and EBV, and congenital infection with rubella, CMV, and *T. gondii* can produce very low immunoglobulin levels and should be ruled out as appropriate. A host of lymphoid malignancies produce hypogammaglobulinemia, but the defect is most profound in CLL, in which up to 85% of patients are said to possess hypogammaglobulinemia even in the absence of treatment.[23]

Primary Immunodeficiencies

The International Union of Immunological Societies has classified the primary immunodeficiency diseases into nine groups, including one class called *predominantly antibody deficiencies*.[9] These disorders present in both adults and children, although some are very rare. Table 49.2 provides a simple grouping of these antibody disorders, some of which are discussed in greater detail in Chapter 49.

The first group is characterized by a severe reduction in all serum immunoglobulin isotypes, with absence or profound reduction in B cells. Patients with these disorders, particularly those with a well-defined genetic basis, present with severe bacterial infections, most commonly in the respiratory tract (pneumonia, sinusitis, and otitis media), as well as diarrhea caused by bacteria, parasites, and viruses. The prototypic member of this group is X-linked agammaglobulinemia (XLA) caused by a mutation in the Bruton tyrosine kinase *(Btk)* gene, which produces a block in B-cell maturation. Female carriers of a *Btk* mutation are generally asymptomatic, but most boys with XLA come to clinical attention by the age of 1 year. In addition to low-serum immunoglobulins, a clue to the diagnosis is the absence of lymphoid tissue, including tonsils. Autosomal recessive mutations in the μ heavy chain as well as defects in *λ5*, *Igα*, *Igβ*, and *BLNK* produce a similar phenotype. Phosphatidylinositol 3-kinase deficiency *(PIK3R1)* and heterozygous mutation of the E47 transcription factor deficiency *(TCF3)* can cause severe reduction in all serum immunoglobulin isotypes. In a small percentage of patients, no clear molecular defect can be identified. Also included in this group are thymoma with immunodeficiency (Good syndrome) and myelodysplasia. Good syndrome is a poorly understood disorder that presents primarily in middle-aged adults. Immunodeficiency can precede or follow the diagnosis of thymoma and does not resolve with thymectomy. In addition to infections, patients experience autoimmune phenomena, including myasthenia gravis, immune thrombocytopenia purpura, pure red blood cell aplasia, and pernicious anemia. Myelodysplastic syndromes can also mimic XLA and

TABLE 49.2 Predominant Antibody Deficiencies

	Disease	Mode of Inheritance/Genetic Locus	Clinical Features
Severe reduction in all serum immunoglobulin isotypes with absent B cells	Bruton tyrosine kinase deficiency	XL/Xq21.3–22	Severe bacterial infections (especially of the respiratory tract), absent lymphoid tissue
	μ heavy chain deficiency	AR/14q32.3	Severe bacterial infections
	λ5 deficiency	AR/22q11.21	Severe bacterial infections
	Igα deficiency	AR/19q13.2	Severe bacterial infections
	Igβ deficiency	AR/17q23	Severe bacterial infections
	BLNK deficiency	AR/10q23.2	Severe bacterial infections
	SP110 deficiency	AR/2q37.1	Hepatic veno-occlusive disease, some with frequent infection
	LRRC8A deficiency	AD/9q34.11	Facial anomalies
	PIK3R1	AR/5q13.1	Recurrent bacterial infection
	Thymoma with immunodeficiency (Good syndrome)	None	Recurrent infection with encapsulated bacteria and diarrhea, autoimmune phenomena
	Myelodysplasia	Variable/monosomy 7, trisomy 8, dyskeratosis congenita	Recurrent infections and pancytopenia
Severe reduction in at least two serum immunoglobulin isotypes with low or normal B-cell numbers	Common variable immunodeficiency syndromes	≈10% with family history AR or AD	Recurrent respiratory tract infections leading to chronic sinusitis, hearing loss, bronchiectasis, autoimmune disease, lymphoproliferation, malignancy (especially non-Hodgkin lymphoma and gastric carcinoma)
	TACI alterations	AD and AR/17p11.2	
	BAFFR alterations	AR/22q13	
	MSH5 alterations	Unk/6p22.1-p21.3	
	ICOS deficiency	AR/2q33	Recurrent infections
	CD19 deficiency	AR/16p11.2	Recurrent infections
	X-linked lymphoproliferative disease (mutation in SH2 domain protein 1A)	XL/Xq25–q26	Fulminant infection with EBV, lymphoma, dysgammaglobulinemia
	CD81 deficiency	AR/11p15.5	Recurrent infections
	CD20 deficiency	AR/11q12.2	Recurrent infections
	CD21 deficiency	AR/1q32.2	Recurrent infections
	LRBA deficiency	AR/4q31.3	Recurrent infections, inflammatory bowel disease, EBV infection
	TNSF12 deficiency	AD/17p13.1	Recurrent bacterial infections, thrombocytopenia, neutropenia
	NFKB2 deficiency	AD/10q24.32	Recurrent infections
	CXCR4 activation	AD gain of function/2q22.1	WHIM syndrome

TABLE 49.2 Predominant Antibody Deficiencies—cont'd

	Disease	Mode of Inheritance/Genetic Locus	Clinical Features
Severe reduction in serum IgG and IgA with increased IgM and normal B-cell numbers (disorders of immunoglobulin class switching)	CD40 ligand deficiency	XL/Xq26.3-Xq27.1	Recurrent infections with bacteria and opportunistic pathogens, neutropenia, autoimmune disease
	CD40 deficiency	AR/20q11-20q13.2	Recurrent infections with bacteria and opportunistic pathogens, neutropenia, autoimmune disease
	NEMO hypomorphic mutations	XL/Xq28	Recurrent infections with bacteria and opportunistic pathogens, neutropenia, autoimmune disease
	AID deficiency	AR/12p13	Recurrent bacterial infections and diarrhea, marked enlargement of lymphoid organs
	UNG deficiency	AR/12q23–q24.1	Recurrent bacterial infections and diarrhea, marked enlargement of lymphoid organs
Isotype or light-chain deficiencies with normal B-cell numbers	Ig heavy-chain deficiency	AR/14q32	Most patients are healthy
	κ-chain deficiency	AR/2p11.2	Most patients are healthy
	Isolated IgG subclass deficiency	Variable/unknown	Most patients are healthy
	IgA deficiency associated with IgG subclass deficiency	Variable/unknown	Most patients are healthy
	Selective IgA deficiency	Variable/unknown	Most patients asymptomatic, but increased prevalence of infections, autoimmune disease, atopy, and celiac disease
	PRKCδ deficiency	AR/3p21.1	Recurrent infection, autoimmunity, and chronic EBV infection
	Activated PI3K-γ	AD gain of function/1p36.22	Recurrent infection, autoimmunity, chronic EBV, and CMV infection
Specific antibody deficiency with normal immunoglobulin level and B-cell number	Inability to make antibodies to specific antigens	Variable/unknown	Recurrent sinopulmonary infection, bronchiectasis, diarrhea, autoimmune disease
Transient hypogammaglobulinemia of infancy	IgG and IgA deficiency	Variable/unknown	More likely to be male (60%–80%), mild infections and diarrhea, atopy

λ5, Immunoglobulin lambda-like polypeptide (a surrogate light chain subunit that is part of the pre–B-cell receptor); AID, activation-induced cytidine deaminase (thought to be essential for initiation of the DNA cleavage required for class-switch recombination and somatic hypermutation); BAFF-R, B-cell–activating factor receptor; BLNK, B linker (a cytoplasmic linker or adaptor protein that plays a critical role in B-cell development); CMV, cytomegalovirus; CXCR4, CXC-chemokine receptor 4 (mediates migration of resting leukocytes and hematopoietic progenitors in response to its ligand, stromal cell–derived factor 1 [SDF1]); EBV, Epstein–Barr virus; ICOS, inducible T-cell costimulator (belongs to CD28 family of costimulatory surface molecules); Ig, immunoglobulin; Igα, immunoglobulin-associated α (necessary for expression and function of the B-cell antigen receptor); Igβ, immunoglobulin-associated β (necessary for expression and function of the B-cell antigen receptor); LRBA, lipopolysaccharide-responsive, beige-like anchor protein (implicated in regulating endosomal trafficking, particularly endocytosis of ligand-activated receptors); MSH5, *mutS* homolog 5 (a protein involved with DNA mismatch repair and meiotic recombination); NEMO, NFκB essential modulator; NFκB, nuclear factor kappa-B; PRKCD, member of the protein kinase c family (involved in B-cell receptor-mediated signaling); PI3K-γ, protein kinase C family member (critical for regulation of cell survival, proliferation, and apoptosis); TACI, transmembrane activator and CAML-interactor; TNSF12, tumor necrosis factor ligand superfamily, member 12 (weak inducer of apoptosis); UNG, uracil DNA glycosylase (allows creation of single-stranded breaks essential to class switch recombination and somatic hypermutation); WHIM syndrome, warts, hypogammaglobulinemia, infections, and myelokathexis.

generally present with low B cells and pancytopenia with monosomy 7, trisomy 8, or dyskeratosis congenita.[24]

A second group is characterized by severe reduction of at least two serum immunoglobulin isotypes with normal or low numbers of B cells. Most patients in this group can be categorized as having common variable immune deficiency (CVID), a heterogeneous disorder characterized by recurrent infection and failure to make antibody to vaccine antigens. Both males and females are affected, and patients can have autoimmune and gastrointestinal disease as well as lymphoproliferative disorders. Autoimmune disease can precede the hypogammaglobulinemia. About 10% of patients with a CVID phenotype have a family history of immunodeficiency and can be shown to have mutations in one of five genes expressed in both T and B cells. Homozygous or compound heterozygous mutations in *ICOS* (inducible costimulator), which is expressed on activated T cells and plays a role in activating T-helper cells and providing B-cell help, and *CD19*, a B-cell surface molecule that participates in signaling after antigen binding to the B-cell receptor, have been shown to result in recurrent infections in childhood and hypogammaglobulinemia. Mutations in *TACI* (transmembrane activator and CAML-interactor) and *BAFF-R* (B-cell–activating factor receptor) members of the tumor necrosis factor (TNF) receptor superfamily, which play roles in B-cell survival and antibody production, and *MSH5*, a mismatch repair gene, are thought to predispose to CVID and IgA deficiency but are not sufficient to independently cause their onset. X-linked lymphoproliferative syndrome caused by mutation in the signaling lymphocyte activation molecular-associated protein SAP (gene, *SH2D1A*) can present atypically or later in life with a CVID phenotype.[25] Single-gene mutations of *TNSF12* (*TWEAK*), *NFKB2*, and *CXCR4* have also been demonstrated to cause low levels of immunoglobulins.

Class-switch recombination defects encompass a third group of antibody deficiencies and result in hyper-IgM syndrome characterized by reductions in serum IgG and IgA with normal or elevated IgM. Mutations in the gene for CD40 ligand make up about 30% of these syndromes. CD40L on the surface of T cells interacts with CD40 on B cells, which is required for immunoglobulin class switching, and CD40 on monocytes, which is required for T-cell response. Patients with *CD40L* mutations and rarer mutations in *CD40* itself and in nuclear factor kappa-B (NFκB) and essential modulator (*NEMO*), required for CD40-induced signaling, have combined antibody and cellular immune deficits, resulting in hypogammaglobulinemia and

recurrent bacterial infection, as well as opportunistic infections with organisms similar to those observed in acquired immune deficiency syndrome (AIDS). Defects in the activation-induced cytidine deaminase gene *(AID)* produce hypogammaglobulinemia with recurrent bacterial infections and diarrhea, as well as enlarged lymphoid organs filled with proliferating B cells. A similar clinical picture is produced by homozygous defects in uracil-DNA glycosylase (*UNG*). AID is thought to deaminate cytosine to uracil, and UNG subsequently deglycosylates and removes the uracil residue, creating an abasic site, which allows for creation of single-stranded DNA breaks. Deficiencies in these enzymes result in defective class switching and somatic hypermutation. Patients with similar phenotypes but without defects in *AID* or *UNG* have been described and probably have mutations in other essential genes involved in class switching.[26]

Additional groups of antibody deficiencies exist in which overall antibody levels are normal, but there are defects in specific isotypes, light chains, or specific antibodies with normal numbers of B cells; the majority of patients with these deficiencies are healthy. The most common member of these groups is selective IgA deficiency, which occurs in about 1 in 500 white individuals. The molecular mechanisms underlying this deficiency are unknown, but there is an association with CVID. Finally, an entity termed *transient hypogammaglobulinemia of infancy* has been described in which the normal decline in immunoglobulins after maternal transfer is prolonged. This entity is poorly understood and usually affects boys, who have mild infections and diarrhea. Recovery usually, but not always, occurs by 3 years of age.[27]

Hypergammaglobulinemia

Hypergammaglobulinemia results from an overproduction of immunoglobulins by plasma cells, either monoclonal and reflective of a plasma cell or lymphoproliferative disorder, or polyclonal and accompanying other disease states. The distinction between polyclonal and monoclonal disorders is made by inspection of the serum protein electrophoretic pattern. Detection of one or several monoclonal bands within a polyclonal background is not unusual, and the literature suggests that small bands frequently disappear and do not become clinically relevant. No data are available to suggest that polyclonal gammopathy drives development of monoclonal gammopathy; however, if a clonal plasmaproliferative disorder is suspected, immunofixation or immunoelectrophoresis should be performed.

Disorders Producing Polyclonal Gammopathy

Polyclonal gammopathy usually reflects one of five major disorders, including liver disease, connective tissue disorders, infections, hematologic disorders, and solid tumors.[28] Interleukin-6 (IL-6) and IL-10 have been implicated in polyclonal gammopathy, as have defects in T cells and chronic antigenic stimulation, but the exact sequence of events leading to polyclonal B-cell activation is not known. In general, treatment is directed at the underlying disease, but there are reports of polyclonal gammopathy leading to symptomatic hyperviscosity. In these cases, plasmapheresis and/or corticosteroids seem to be effective. It should also be noted that polyclonal elevations in serum immunoglobulins can sometimes interfere with the direct Coombs test, possibly via nonspecific antibody binding to red blood cells. The degree of gamma globulin elevation does not seem to be helpful in defining the underlying disease state.

In the largest recent review of polyclonal gammopathy, the majority of patients had liver disease, which covered the spectrum from autoimmune disorders (autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis) to viral hepatitis, and alcoholic liver disease. In fact, elevation of serum gamma globulins is a distinguishing characteristic of autoimmune hepatitis, and the levels usually correlate with activity of disease. The most common etiology for polyclonal gammopathy related to liver disease in the United States is likely infection with HCV, but in any particular clinical setting, the exact distribution likely depends on the population demographic. Other diseases affecting the liver, such as α-1 antitrypsin deficiency and hemochromatosis, are also accompanied by increases in serum immunoglobulins.

Connective tissue diseases, including Sjögren syndrome, SLE, ankylosing spondylitis, and rheumatoid arthritis, are also accompanied by polyclonal gammopathy. In many of these diseases, the degree of gamma globulin elevation may reflect disease activity, although a causative link between the autoimmune phenomena and immunoglobulin levels has not been determined. Several of the periodic fever syndromes, which are sometimes classified with the connective tissue disorders, have elevated immunoglobulin levels as a part of their manifestations. Hyperimmunoglobulinemia D is one such syndrome and is linked to mutations in the mevalonate kinase gene. Patients with this disorder present in the first year of life with febrile attacks, lymphadenopathy, abdominal symptoms, arthritis, and oral and genital ulcers. Most, but not all, patients have elevated levels of polyclonal IgD during and between episodes often accompanied by elevated IgA levels. TNF receptor 1-associated periodic syndrome (TRAPS) results from mutation in the gene (*TNRFRSF1A*) for the TNF receptor 1 and can cause prolonged febrile attacks with abdominal pain, arthralgias, and myalgias. During attacks, polyclonal elevation of immunoglobulins (primarily IgA) is observed.[29]

Infections, usually chronic in nature, are frequently accompanied by polyclonal gammopathy. HIV infection is a common cause, and immunoglobulin levels tend to increase slowly until the diagnosis of AIDS and then decline over the ensuing 6 to 18 months. Polyclonal gammopathy can be a clue to occult infections such as subacute bacterial endocarditis, tuberculosis, perinephric abscess, Lyme disease, and a variety of parasitic infections.

Malignant B- and T-cell disorders can cause polyclonal hypergammaglobulinemia. These diseases include CLL; large granular lymphocytic leukemia; hairy cell leukemia; and angioimmunoblastic T-cell lymphoma (AITL), a rare disease characterized by rash, widespread lymphadenopathy and extranodal involvement, autoimmune phenomena, and polyclonal gammopathy. Interestingly, despite the elevated levels of immunoglobulins observed in AITL, patients exhibit immunodeficiency and a propensity to develop opportunistic infections. Patients with myeloid disorders can also have polyclonal gammopathies; in one large series, nearly 40% of patients with myelodysplastic syndrome had hypergammaglobulinemia, and patients with immunologic abnormalities had inferior survival.[30] The incidence of hypergammaglobulinemia is reported to approach 50% in chronic myelomonocytic leukemia (CMML). Hypergammaglobulinemia has been reported in AML both in adults and children, but it appears to be a rare phenomenon. Among solid tumors, ovarian and hepatocellular cancers are most commonly associated with polyclonal gammopathy. There are case reports of cancers, particularly lung and breast tumors, producing and releasing the secretory component of IgA into the bloodstream with the binding of SC to polyclonal IgA, producing hypergammaglobulinemia of serum sIgA.

A variety of other diseases, including asbestos exposure and several subtypes of hypersensitivity pneumonitis and idiopathic interstitial pneumonia, are associated with polyclonal gammopathy. In general, these disorders represent diffuse activation of B cells.

Disorders Producing Monoclonal Gammopathy

The differential diagnosis of monoclonal gammopathy includes monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, solitary plasmacytoma of bone or extramedullary plasmacytoma, Waldenström macroglobulinemia, lymphoma, CLL, and primary systemic amyloidosis. These individual disorders are described elsewhere in this text; however, there are a few points to be made about the M protein itself and MGUS. These disorders can produce intact immunoglobulins (IgG, IgM, IgD, or IgE), κ-, or λ-light chains alone or in combination with intact immunoglobulins and rarely heavy chains only. The monoclonal protein is usually detected as a discrete band in the γ or β region in serum or urine

TABLE 49.3 Diseases Associated With Monoclonal Gammopathy

Plasma cell and related disorders	MGUS	See Chapters 85–87
	Solitary plasmacytoma:	
	Bone	
	Soft tissue	
	Multiple myeloma	
	Waldenström macroglobulinemia	
	Primary amyloidosis	
Lymphoid disorders	Non-Hodgkin lymphoma	Monoclonal protein observed in CLL (>20% of cases with IgM, ≈50% with IgG, light chains also observed), extranodal marginal zone lymphomas (>30% of cases and correlated with BM involvement), follicular, mantle cell, and diffuse large B-cell lymphomas also reported with serum M proteins as has AITL
	Hodgkin lymphoma	Rare but reported
	Castleman disease	<2% with monoclonal gammopathy
Other hematologic disorders	Acquired von Willebrand disease	IVIG more effective than factor concentrate in increasing factor VIII coagulant and VWF levels
	Gaucher disease	Observed in 25% in one study; M protein declined after splenectomy
	Pernicious anemia, pure RBC aplasia, hereditary spherocytosis, MPD, MDS	
Connective tissue disorders	SLE	IgG, IgM, and IgA have been observed, no difference in disease activity or outcome
	Inclusion body myositis	80% with IgG M protein
	Polymyositis, RA, scleroderma	
Neurologic disorders	POEMS syndrome	Most have M-protein of λ light chain
	Peripheral neuropathy	Most common is IgM followed by IgG and IgA
		In half, IgM protein binds to myelin-associated glycoprotein
		Size of M protein not correlated with severity of neuropathy
		Some benefit from plasma exchange for those with IgG and IgA
		Fludarabine and rituximab with some benefit for IgM
	Myasthenia gravis, ALS, Alzheimer disease	
Dermatologic disorders	Schnitzler syndrome	Neutrophilic urticarial dermatitis, monoclonal IgM protein, and two of: lymphadenopathy, fever, hepatosplenomegaly, joint pain, increased ESR, increased neutrophils, or abnormal bone imaging
	Scleredema	
	Pyoderma gangrenosum	Frequently an IgA protein
Infections	HIV	Both IgG and IgM M proteins observed
	HCV	M protein present in up to 10% of patients
Immunosuppression	Renal transplant	In children CMV infection associated with M protein
	Liver and heart transplant	Most patients with posttransplant lymphoproliferative disorders have M proteins
	BM transplant	Observed in both autologous and allogeneic transplants
		Appearance of M protein correlated with GVHD

AITL, Angioimmunoblastic T-cell lymphoma; ALS, amyotrophic lateral sclerosis; BM, bone marrow; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; ESR, erythrocyte sedimentation rate; GVHD, graft-versus-host disease; HCV, hepatitis C virus; HIV human immunodeficiency virus; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; MGUS, monoclonal gammopathy of uncertain significance; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; RA, rheumatoid arthritis; RBC, red blood cell; SLE, systemic lupus erythematosus; VWF, von Willebrand factor.

protein electrophoresis (M spike), and then characterized and confirmed by immunofixation electrophoresis (IFE). Monoclonal antibodies have been associated with a wide variety of bacterial antigens as well as various other antigens, including thyroglobulin, von Willebrand factor, and lactate dehydrogenase; however, for most M proteins, the antigen is not recognized. A variety of other disorders are also associated with an M protein (Table 49.3), including connective tissue disorders, neurologic disorders (including POEMS [polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes] syndrome), renal disorders, and some infections such as HCV and HIV. Patients undergoing bone marrow and solid-organ transplants in which there is immune suppression are also occasionally observed to have M proteins, but these are usually transient and disappear with recovery of the immune system. Acquired immune disorders such as acquired C1 inhibitor deficiency, type 2 acquired angioedema, and acquired von Willebrand syndrome have also been associated with M proteins.

REFERENCES

1. Morbach H, Eichhorn EM, Liese JG, et al: Reference values for B cell subpopulations from infancy to adulthood. *Clin Exp Immunol* 162(2):271–279, 2010.
2. Erkeller-Yuksel FM, Deneys V, Hulstaert F, et al: Age-related changes in human blood lymphocyte subpopulations. *J Pediatr* 120(2 Pt 1):216–222, 1992.

3. Lanasa MC, Weinberg JB: Immunologic aspects of monoclonal B-cell lymphocytosis. *Immunol Res* 49(1–3):269–280, 2011.
4. Hudnall SD, Molina CP: Marked increase in L-selectin-negative T cells in neonatal pertussis: The lymphocytosis explained? *Am J Clin Pathol* 114(1):35–40, 2000.
5. Walsh NP, Gleeson M, Shephard RJ, et al: Position statement. Part one: Immune function and exercise. *Exerc Immunol Rev* 17:6–63, 2011.
6. Karandikar NJ, Hotchkiss EC, McKenna RW, et al: Transient stress lymphocytosis: an immunophenotypic characterization of the most common cause of newly identified adult lymphocytosis in a tertiary hospital. *Am J Clin Pathol* 117(5):819–825, 2002.
7. Choi TS, Doh KS, Kim SH, et al: Clinicopathological and genotypic aspects of anticonvulsant-induced pseudolymphoma syndrome. *Br J Dermatol* 148(4):730–736, 2003.
8. Cornet E, Lesesve JF, Mossafa H: Long-term follow-up of 111 patients with persistent polyclonal B-cell lymphocytosis with binucleated lymphocytes. *Leukemia* 23(2):419–422, 2009.
9. Al-Herz W, Bousfiha A, Casanova J-L, et al: Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. *Front Immunol* 5:1–33, 2014.
10. Notarangelo LD, Miao CH, Ochs DH: Wiskott-Aldrich syndrome. *Curr Opin Hematol* 15:30–36, 2008.
11. Staples ER, McDermott EM, Reiman A: Immunodeficiency in ataxia telangiectasia is correlated strongly with the presence of two null mutations in the ataxia telangiectasia mutated gene. *Clin Exp Immunol* 153:214–220, 2008.
12. Dickinson RE, Milne P, Jardine L, et al: The evolution of cellular deficiency in GATA2 mutation. *Blood* 123(6):863–874, 2014.
13. Stein DS, Korvick JA, Vermund SH: $CD4^+$ lymphocyte cell enumeration for prediction of clinical course of human immunodeficiency virus disease: a review. *J Infect Dis* 165(2):352–363, 1992.
14. Yuen KY, Chan PK, Peiris M, et al: Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet* 351(9101):467–471, 1998.
15. Turett GS, Telzak EE: Normalization of $CD4^+$ T-lymphocyte depletion in patients without HIV infection treated for tuberculosis. *Chest* 105(5):1335–1337, 1994.
16. Drewry AM, Samra N, Skrupky LP, et al: Persistent lymphopenia after diagnosis of sepsis predicts mortality. *Shock* 42(5):383–391, 2014.
17. Fayaz A, Igoe A, Kurien BT, et al: Haematological manifestations of lupus. *Lupus Sci Med* 2(1):e000078, 2015.
18. Shao L, Fujii H, Colmegna I, et al: Deficiency of the DNA repair enzyme ATM in rheumatoid arthritis. *J Exp Med* 206(6):1435–1449, 2009.
19. Prasad AS: Zinc in human health: effect of zinc on immune cells. *Mol Med* 14(5–6):353–357, 2008.
20. Zonios DI, Falloon J, Bennett JE, et al: Idiopathic $CD4^+$ lymphocytopenia: natural history and prognostic factors. *Blood* 112(2):287–294, 2008.
21. Robak T, Lech-Maranda E, Korycka A, et al: Purine nucleoside analogs as immunosuppressive and antineoplastic agents: mechanism of action and clinical activity. *Curr Med Chem* 13(26):3165–3189, 2006.
22. Fuks Z, Strober S, Bobrove AM: Long term effects of radiation of T and B lymphocytes in peripheral blood of patients with Hodgkin's disease. *J Clin Invest* 58(4):803–814, 1976.
23. Hamblin AD, Hamblin TJ: The immunodeficiency of chronic lymphocytic leukaemia. *Br Med Bull* 87:49–62, 2008.
24. Conley ME, Dobbs AK, Farmer DM, et al: Primary B cell immunodeficiencies: comparisons and contrasts. *Annu Rev Immunol* 27:199–227, 2009.
25. Jolles S: The variable in common variable immunodeficiency: a disease of complex phenotypes. *J Allergy Clin Immunol Pract* 1(6):545–556, 2013.
26. Qamar N, Fuleihan RL: The hyper IgM syndromes. *Clin Rev Allergy Immunol* 46(2):120–130, 2014.
27. Moschese V, Graziani S, Avanzini MA, et al: A prospective study on children with initial diagnosis of transient hypogammaglobulinemia of infancy: results from the Italian Primary Immunodeficiency Network. *Int J Immunopathol Pharmacol* 21(2):343–352, 2008.
28. Dispensieri A, Gertz M, Therneau T, et al: Retrospective cohort study of 148 patients with polyclonal gammopathy. *Mayo Clin Proc* 76(5):476–487, 2001.
29. Ozen S, Bilginer Y: A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin. *Nat Rev Rheumatol* 10(3):135–147, 2014.
30. Mosalpuria K, Bociek RG, Vose JM: Angioimmunoblastic T-cell lymphoma management. *Semin Hematol* 51(1):52–58, 2014.