**Disorders of Leukocytes**

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1. A 3-year-old girl with no significant past medical history is urgently referred to your office after her pediatrician noted an ANC of 270/µL on a routine CBC. She was being seen after several days of fever and upper respiratory infection symptoms. She has been taking Augmentin and acetaminophen. In your office, she is tired-appearing and has shotty cervical lymphadenopathy but no other unusual findings on exam. Peripheral smear identifies WBC 5,000/µL with some atypical lymphocytes.

What is the most likely diagnosis for this child?

A. Acute leukemia

B. Drug-induced neutropenia

C. Kostmann disease

D. Cyclic neutropenia

E. Intercurrent viral syndrome

**Explanation**

Viral infections are the most common cause of neutropenia. The neutropenia may be transient or last up to weeks (but usually no more than 3 months). The other conditions are associated with neutropenia, but viral infections are the most common cause.

2. A 6-year-old boy with a 5-day history of vomiting and diarrhea was transferred to your medical center from a rural hospital. Several other family members have been hospitalized. All were eating fresh ice cream made with raw eggs from their farm. The patient arrived with a high fever and was in shock. He had no lymphadenopathy or hepatosplenomegaly. His CBC showed a Hb 13.1 g/dL, Hct 40%, WBC count of 22,000/μL with 7% segmented neutrophils, 36% bands, 7% promyelocytes, 10% myelocytes, 1% blasts, 20% lymphocytes, and 4% monocytes. Platelet count was 135,000/μL.

What is the most likely diagnosis?

A. Chronic myelogenous leukemia

B. Acute myelogenous leukemia

C. Acute promyelocytic leukemia

D. A severe leukemoid reaction with a left shift associated with bacterial infection

E. Acute lymphoblastic leukemia

**Explanation**

With strong evidence for an acute infectious process, no hepatosplenomegaly, and leukocytosis with mild thrombocytopenia, a leukemoid reaction is most likely.

3. A 3-year-old boy with a history of recurrent bacterial infections presents to your office. His CBC shows neutropenia, and his blood smear shows giant granules in the cytoplasm of his neutrophils, monocytes, and lymphocytes.

What additional features would be part of this disorder?

A. Coarse facies and delayed dentition

B. Delayed separation of the umbilical cord and poor wound healing

C. Severe dermatitis

D. Partial albinism and photophobia

E. Telangiectasias

**Explanation**

Neutropenia and giant granules in leukocytes are pathognomonic for Chédiak-Higashi syndrome (CHS). The syndrome also includes partial albinism, bleeding diathesis, peripheral neuropathy, changes in skin and hair, and retinal abnormalities characterized by photophobia. The other abnormalities listed in answers A, B, C, and E are not features of CHS but might suggest other immunological abnormalities.

4. You follow a 3-year-old who has had intermittent neutropenia during the past 4 months. Three blood tests show an ANC of 300 to 600/µL, and one blood test shows an ANC of 1,600/µL. You are considering the diagnosis of cyclic neutropenia and are preparing to order twice-weekly CBCs for 8 weeks.

Which of the following time cycles will help establish the diagnosis?

A. 7 ± 3 days

B. 10 ± 2 days

C. 12 ± 1 days

D. 21 ± 3 days

E. 29 ± 3 days

**Explanation**

Patients with cyclic neutropenia have periodic alterations in neutrophil counts and monocytes and, in some patients, platelet counts and absolute reticulocyte counts. The cycles are different from patient to patient, but most are 21 ± 3 days; a few may be as short as 14 days or as long as 28 to 36 days, with the duration of neutropenia lasting 4 to 5 days.

5. A 2-year-old presents for evaluation of progressive and persistent lymphadenopathy and a WBC of 30,000/µL. He is generally well appearing but has notable splenomegaly on physical exam. Evaluation of peripheral blood indicates elevated IL-10 and vitamin B12 and an elevated T-cell population with absent CD4/CD8.

What inherited gene defect is most likely for this patient?

A. *RAG1*

B. *GATA2*

C. *GATA1*

D. *FAS*

E. *BRAF-V600E*

**Explanation**

This scenario describes a patient with autoimmune lymphoproliferative syndrome. As the name implies, patients often have autoimmune manifestations along with clinical signs of lymphoproliferation. This clinical syndrome can arise from inherited or acquired defects in genes regulating apoptosis, including *FAS, FASLG,* or *CASP10*. *RAG1* regulates V(D)J recombination of differentiating B and T cells, and functional mutations result in severe immune deficiency (Omenn syndrome). Somatic *GATA1* mutations are associated with transient myeloproliferative disorder in children with Down syndrome. *GATA2* also plays a role in early hematopoiesis, and mutations are identified in children and adults with monocytopenia and mycobacterial infections as well as in patients with myelodysplasia and vascular and lymphatic abnormalities. *BRAF-V600E* is a somatic mutation of *BRAF* that constitutively activates *MAPK* pathway signaling in Langerhans cell histiocytosis, melanoma, and many other cancers.

6. The neutrophils of a 4-year-old boy demonstrated failure to kill *S.* *aureus* and generate superoxide anion or H2O2. His older brother died at 3 months of age due to a fungal infection. His mother is well but had two brothers who died of bacterial infections in childhood.

What is the most likely diagnosis?

A. Autosomal recessive p22phox deficiency

B. Autosomal recessive p47phox deficiency

C. Autosomal recessive p67phox deficiency

D. X-linked recessive gp91phox deficiency

E. Dominant negative *Rac2* mutation

**Explanation**

The pattern presented is one of male patients affected by a sex-linked recessive disorder. gp91phox-deficient chronic granulomatous disease (CGD) is the only X-linked mutation of oxidase components and the most common cause of CGD, followed by the autosomal recessive p47phox deficiency (7q11.23, *NCF1* gene).

7. Severe congenital neutropenia (SCN) syndromes may be associated with mutations in the neutrophil elastase gene (*ELA-2* or *ELANE*).

Which of the following is true about SCN due to *ELA-2*/*ELANE* mutations?

A. *ELANE* mutation is a cause of autosomal dominant SCN.

B. It is the primary mutation in autosomal recessive Kostmann syndrome.

B. *ELANE* most commonly causes specific granule defects.

C. The cytoplasmic inclusions of Chédiak-Higashi syndrome are caused by *ELANE* mutations.

D. The neutropenia associated with Shwachman-Diamond syndrome is associated with *ELANE* point mutations.

**Explanation**

Defects in elastase genes have been documented in cyclic neutropenia and autosomal dominant SCN. Kostmann syndrome is associated primarily with *HAX-1* mutations and demonstrates autosomal recessive inheritance. Chédiak-Higashi syndrome is associated with *CHS1* or *LYST* mutations, and *ELANE* does not have a role in the development of cytoplasmic inclusions. Specific granule deficiency is associated with *C/EBPε* mutations and not *ELANE* mutations. Shwachman-Diamond syndrome is associated with mutations in the *SBDS* (Shwachman-Bodian-Diamond gene).

8. You are referred a 14-year-old African American girl who was noted to have an ANC of 1,000/µL on a sports physical. She had appendicitis when she was 4 years old and occasional upper respiratory infection symptoms but no other hospitalizations. On physical exam she is well appearing, without lymphadenopathy, splenomegaly, or oral lesions. At this visit, her ANC is 890/µL, Hb 14 g/dL, and platelets 334,000/µL, with a peripheral smear otherwise normal.

What is your advice?

A. HIV screen

B. Bone marrow biopsy and aspirate

C. Whole exome sequencing

D. Signed release for volleyball and repeat CBC in 1 month

E. Treatment with G-CSF

**Explanation**

This scenario describes a healthy teenager with chronic benign familial (ethnic) neutropenia. In the absence of episodes of severe infection, other cytopenias, or development of more severe neutropenia, no interventions are necessary. Serial CBC may be helpful to rule out progressive cytopenias and establish a baseline ANC range.

9. A college student comes home for Thanksgiving. She is febrile and tired. Her pediatrician notes enlarged posterior cervical lymph nodes and a palpable spleen. CBC identifies highly elevated WBC, with absolute lymphocyte count 5,500/µL and atypical lymphocytes. While home she was in close contact with her 4-year-old brother, who soon became febrile, developed lymphadenopathy, and needed evaluation in the emergency department for decreased activity, where the 4-year-old boy was found to have splenomegaly, with AST 1,500 U/L, ferritin 22,000 ng/mL, ANC 250/µL, and platelets 40,000/µL. Epstein-Barr virus (EBV) qPCR is extremely elevated.

Which mutation would be most likely in the 4-year-old brother?

A. *GATA2*

B. *FASL*

C. SH2D1A

D. p47phox

E. *BRAF-V600E*

**Explanation**

This scenario describes a young boy with an extreme reaction to primary EBV infection. Primary EBV can be a general trigger for hemophagocytic lymphohistiocytosis (HLH) but is specifically associated with HLH in boys with X-linked lymphoproliferative disorder (XLP-1). *SH2D1A* encodes the signaling lymphocyte activation molecule–associated protein. XLP-2 is caused by mutations in *BIRC4* (which encodes X-linked inhibitor of apoptosis protein) and also is associated with EBV-induced HLH. XLP-1 also is associated with elevated risk of lymphoma, and XLP-2 is associated with chronic hemorrhagic colitis.

*GATA2* mutations are associated with monocytopenias and risk of myelodysplasia. *FASL* (as well as *FAS* and *CASP10*) somatic and germline mutations are associated with autoimmune lymphoproliferative syndrome. p47phox is associated with chronic granulomatous disease.

10. A 5-year-old boy with oculocutaneous albinism undergoes a CBC. The technician notes that giant granules are present in neutrophils. Which of the following genes encodes the defect?

A. *CHS1*/*LYST*

B. *C*/*EBPε*

C. Mutations of p47phox

D. Mutations in the *ETS* oncogene

E. Mutations in *ELA-2* or *ELANE* gene

**Explanation**

CHS is associated with mutation of *CHS1*/*LYST* gene. The other genes are associated with different disorders.

11. A 12-year-old black girl is referred after an episode of cervical lymphadenitis that responded poorly to antibiotic therapy and necessitated incision and drainage. Cultures grew *Klebsiella*. She has a history of pneumonia at ages 4 and 9 years and recurrent impetigo near the nares.

Which of the following is the most appropriate next step in the diagnostic evaluation?

A. T-cell subsets

B. Quantitative immunoglobulin measurements including IgE levels

C. Measurement of leukocyte NADPH oxidase activity by DHR-123 assay or nitroblue tetrazolium test

D. Hemoglobin electrophoresis

E. Evaluation of CD11/CD18 expression

**Explanation**

*Klebsiella* is an unusual cause of lymphadenitis and, in combination with a history of recurrent lung and skin infections, suggests chronic granulomatous disease (CGD), which is characterized by absent leukocyte NADPH oxidase activity. Because your patient is a girl, she most likely has an autosomal recessive defect in the p47phox oxidase subunit, which overall accounts for 25% of CGD. Severe combined immune deficiency (T-cell defects) and leukocyte adhesion deficiency (CD11/CD18 defects) typically present with severe infections at an earlier age.

12. An 8-year-old girl has a history of eczema, recurrent furuncles, and several episodes of pneumonia. She is referred to you from the dental clinic, where she is being seen for delayed eruption of permanent teeth. On physical examination, she is found to have a broad nasal bridge and mild scoliosis.

Which of the following should be included in her evaluation?

A. Assessment for a connective tissue disease

B. Measurement of leukocyte NADPH oxidase activity by DHR-123 assay or nitroblue tetrazolium test

C. Analysis for double negative T cells

D. Quantitative immunoglobulin measurements including IgE levels

E. CD11/CD18 expression on leukocytes

**Explanation**

Hyper-IgE syndrome includes eczema, staphylococcal skin infections, pneumonias, and skeletal problems that include delayed eruption of permanent teeth associated with retained primary teeth, scoliosis, and spontaneous fractures, in addition to specific facial features. This syndrome is associated with *STAT3* and *DOCK8* gene mutations. The infectious history suggests an immune disorder; answer B describes tests for chronic granulomatous disease, answer C describes a characteristic of autoimmune lymphoproliferative syndrome, and answer E describes a test for leukocyte adhesion deficiency.

13. A diagnosis of X-linked chronic granulomatous disease is made for a 2-year-old boy after a staphylococcal liver abscess. Which of the following will be in the management plan that you recommend to the family?

A. Daily vitamin C

B. Weekly G-CSF

C. Daily penicillin

D. Daily itraconazole

E. Monthly IVIG

**Explanation**

Daily itraconazole has been shown to significantly reduce the incidence of *Aspergillus* infections in chronic granulomatous disease (CGD) and is now recommended as daily prophylaxis in addition to daily trimethoprim/sulfamethoxazole. Interferon-gamma prophylaxis administered three times a week has also been shown to reduce the incidence of serious infections. The other therapies have not been demonstrated to be helpful in children with CGD.

14. A 2½-year-old girl is referred to you by her dentist for chronic gingivitis. Her pediatrician saw her 1 week ago for fever and upper respiratory symptoms; a CBC showed an ANC of 900/µL. She has 4 or 5 upper respiratory infectionsa year but no history of skin infections or pneumonia. Her parents report that she has episodes where she is irritable for several days, which occur “every few weeks.” She appears well and has a normal exam other than gingivitis. Her ANC today is 530/µL.

What would be the most appropriate laboratory studies to order as part of the initial evaluation?

A. Quantitative immunoglobulin measurement, including IgE levels

B. Bone marrow examination

C. CBCs twice a week for the next 6 to 8 weeks

D. Flow cytometry for CD11/CD18 expression on leukocytes

E. Repeat CBC and differential in 1 month

**Explanation**

Gingivitis in a toddler suggests a clinically significant chronic or recurrent neutrophil defect, in either number or function. Her falling ANC and recurrent episodes of irritability are clues to a possible diagnosis of cyclic neutropenia, which is identified by serial blood counts obtained over a 6- to 8-week period and is more likely than severe congenital neutropenia, which is more severe and, if untreated, usually has other infectious complications by age 2 years. Although leukocyte adhesion deficiency (LAD) type I due to a partial defect in CD11/CD18 expression can present at this age with gingivitis, LAD is associated with neutrophilia. The history is not suggestive of an adaptive immunologic defect or hyper-IgE syndrome.

15. A 12-year-old boy was diagnosed in infancy with severe congenital neutropenia (SCN), or Kostmann syndrome, after presenting with a perirectal abscess. He has maintained an ANC of 1,200/µL on daily G-CSF (25 µg/kg/day); his peripheral blood counts have otherwise been normal for his age. At routine follow-up, his ANC was noted to be 540/µL, with a hemoglobin concentration of 10 g/dL and platelet count of 55,000/µL. He had an episode of sinusitis 2 weeks ago, for which he was treated with antibiotics.

Which of the following would be the most appropriate course of action?

A. Order testing for *ELA-2* mutation.

B. Order a CT of the sinuses.

C. Perform a bone marrow examination with cytogenetics.

D. Order antiplatelet antibodies.

E. Increase the G-CSF to 30 µg/kg/day and repeat a CBC in 2 weeks.

**Explanation**

Bone marrow evaluation is indicated for patients with progressive pancytopenia without a clear etiology. This patient has SCN or Kostmann syndrome, which is associated with an elevated risk of myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), often with monosomy 7, other somatic mutations, or Ras oncogene mutations. Approximately 60% of SCN/Kostmann syndrome (SCN1) is associated with autosomal dominant mutations in the *ELA-2*/*ELANE* gene. Other SCN/Kostmann syndromes are associated with other genetic mutations, including SCN2 (autosomal dominant, *GFL1*), SCN3 (autosomal recessive, *HAX-1*), SCN4 (autosomal recessive, *G6PC3*), SCN5 (autosomal recessive, *VPS45*), and X-linked SCN (*WASP*). However, all genetic forms of SCN are believed to have an elevated risk of MDS/AML. This patient is already known to have SCN1 syndrome, so *ELA-2* testing is not going to inform the current problem of progressive cytopenias. Autoimmune causes of cytopenias are less likely in a patient with this history. CT of the sinuses and increasing G-CSF do not address the urgent issue of possible development of MDS/AML.

16. You are seeing an 11-year-old boy with neutropenia (ANC 500 to 700/µL), recurrent warts and upper respiratory infections, and hypogammaglobulinemia. His mother, uncle, and brother have similar problems.

Which of the following is the most likely diagnosis?

A. Fanconi anemia

B. Leukocyte adhesion deficiency type II

C. X-linked agammaglobulinemia

D. Chédiak-Higashi syndrome (CHS)

E. Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM syndrome)

**Explanation**

WHIM syndrome presents with a distinctive combination of warts, hypogammaglobulinemia, infections, and myelokathexis (*kathexis* = retention), with granulocyte hyperplasia and degenerating neutrophils in the marrow and peripheral neutropenia. These patients are susceptible to papilloma-induced acuminata warts, condyloma, and carcinoma. They also have a decrease in B-lymphocytes. WHIM syndrome is caused by autosomal-dominant mutations in the *CXCR4* receptor gene. Leukocytes have increased responses to SDF-1, the ligand for *CXCR4* receptor. Increased activity (gain of function mutations) of *CXCR4* receptor delays release of mature neutrophils from the marrow and apoptosis of these neutrophils. The immunologic abnormalities probably reflect abnormally increased responses to SDF-1 by other leukocytes. A, B, C, and D are disorders with different clinical presentations.

17. A dendritic cell has phagocytosed a virus and displays viral antigen on the cell surface to CD4+ T cells through which structure?

A. CD3

B. CD28

C. CD163

D. Major histocompatibility complex class II

E. CD19

**Explanation**

Dendritic cells are professional antigen-presenting cells that can activate CD4+ T cells through interactions with antigen-loaded MHC class II on the cell surface. CD3 and CD28 are T-cell costimulatory proteins. CD163 is a high-affinity scavenger receptor expressed on macrophages. CD19 is a protein on the surface of B cells involved in regulation of antigen stimulation.

18. A 5-day-old girl is being evaluated for jaundice but is otherwise doing well. She has a CBC that shows an ANC of 160/µL. The mother reports that her previous child, a boy who is healthy, also had “low white blood cells” after he was born, but this resolved.

Which of the following tests will most likely enable you to diagnosis the underlying cause of the neutropenia?

A. HIV testing

B. Quantitative immunoglobulins

C. Bone marrow examination

D. *ELA-2*/*ELANE* gene mutation

E. Antineutrophil antibodies

**Explanation**

The most likely diagnosis is neonatal alloimmune neutropenia (NAN), caused by the passage of maternal IgG antibodies across the placenta. Fetal neutrophil antigens, which are foreign to the pregnant mother but are inherited from the father, can elicit the production of maternal antibodies. Unlike Rh disease, NAN can occur in a firstborn child. Antibodies are often directed to the HNA1 or HNA2 antigens, isotypes of the neutrophil FcγIIIb receptor, and can be detected in both maternal and infant serum. The neutropenia lasts from several weeks to as long as 6 months. Infants can be asymptomatic, but some develop bacterial infections. NAN has been treated with IVIG or G-CSF. The other tests are not indicated in this clinical setting.

19. A 7-year-old girl presents with a history of recurrent skin abscesses and two episodes of lobar pneumonia. Her CBC shows a mild anemia (Hb 10.5 g/dL) with a borderline low mean corpuscular volume and normal platelet count. Her WBC is 7,000/µL and differential is normal except for an ANC of 700/µL. The morphology of her neutrophils shows most are bilobed or band forms, and cytoplasm appears washed out or hypogranular. Her family history is negative for other members with infections, neutropenia, or nuclear abnormalities.

What is the most likely diagnosis for this patient?

A. Chédiak-Higashi syndrome

B. Pelger-Huet anomaly

C. Specific granule deficiency

D. Myelokathexis

E. Severe congenital neutropenia

**Explanation**

The presence of bilobed polymorphonuclear leukocytes or band forms associated with neutropenia and severe infections is most likely specific granule deficiency. This condition is related to defects in a transcription factor, CEBPε. Bilobed neutrophils without infection inherited as an autosomal dominant trait is Pelger-Huet anomaly.

20. A 12-year-old girl with type 1 diabetes presents in very poor glycemic control, with severe sinusitis associated with mucormycosis that is eroding into her brain. WBC and differential are appropriately elevated and show a left shift.

What is the most likely leukocyte disorder associated with this scenario?

A. Leukocyte adhesion defect

B. Autosomal (recessive) chronic granulomatous disease (CGD)

C. Excessively lyonized X-linked CGD carrier

D. Myeloperoxidase (MPO) deficiency

E. Chédiak-Higashi syndrome

**Explanation**

Clinically significant fungal infections in the presence of diabetes may be associated with MPO deficiency. This is a classic presentation. Other leukocyte defects (answers A, B, C, and E) have different clinical presentations.

21. A 6-year-old boy was well until a family outing at a nearby lake. Within the next week, the patient began having intermittent fevers and a diffuse macular skin rash. His WBC is 9,500/µL, with an absolute eosinophilia of 1,100/µL. Morphologic assessment of the smear shows no immature or malignant cells. Biopsy of the skin rash shows eosinophilic infiltrate. IgE level is 950 mg/dL. The patient is on no medications and has no allergies.

What is the next step in your investigation?

A. Neutrophil chemotaxis

B. Lymphocyte stimulation to mitogens

C. Quantitative immunoglobulins

D. IL-5 levels

E. Parasite evaluation

**Explanation**

The most common causes of eosinophilia include drug reactions, allergies or allergic asthma, and parasite infection. With the onset of symptoms so closely related to possible exposure at the lake, parasite evaluation seems like the next best approach.

22. An 8-month-old boy is referred to you from the GI clinic with hepatosplenomegaly. Hemoglobin and WBC are normal for age. Platelet count is 124,000/µL. The liver biopsy shows storage cells consistent with Gaucher disease.

Which of the following is the best next step?

A. Administration of M-CSF

B. Evaluation of glucocerebrosidase activity and analysis of the glucocerebrosidase gene mutations

C. Administration of glucocerebrosidase

D. Administration of GM-CSF

**Explanation**

Confirmation of enzyme activity and documentation of the mutation in the gene for glucocerebrosidase allows classification into the type of Gaucher disease and its complications. It also will help establish the need to treat with enzyme replacement therapy.

23. A 12-year-old African American boy presents for a physical for football, and his pediatrician orders a CBC. The results are WBC 7 × 103/µL, Hb 12.5 g/dL, platelets 228 × 103/µL, and ANC 890/µL. He has a history of appendectomy at 7 years old, and he gets a “cold” once or twice a year, but he has no other problems and takes no medications. Physical exam, including careful evaluation of oral mucosa, is normal.

What is the next step in the investigation ?

A. Bone marrow biopsy and aspirate

B. G-CSF injection

C. Repeat CBC in 3 months

D. HIV screening

E. Parasite evaluation

**Explanation**

In an otherwise healthy child without a history of unusual infections or recent viral illness, a likely cause of mild neutropenia (500 to 1,000/µL) is benign ethnic neutropenia (BEN). The US National Health and Nutritional Examination Survey (NHANES) identified neutropenia in 4.5% of healthy African Americans, compared with less than 1% of white and Mexican American participants. Repeat CBC is reasonable to determine whether neutropenia is chronic or reactive and to ensure that this result does not reflect the initial stages of a progressive pathologic process. However, additional evaluations or interventions are not necessary in an otherwise healthy patient.

24. A 9-year-old with recent-onset seizures (started phenytoin 3 months ago) presents to the emergency department with fever, maculopapular rash, and lymphadenopathy. A CBC reveals WBC 14 × 103/µL, Hb 12.5 g/dL, platelets 94 × 103/µL, ANC 1,200/µL, absolute eosinophil count 1.9 × 103/µL, and atypical lymphocytes on peripheral smear. Transaminases are elevated, with normal total bilirubin.

What virus is likely to be identified in blood or lymph node qPCR?

A. HIV

B. Human herpesvirus 6 (HHV6)

C. Adenovirus

D. Hepatitis B virus

**Explanation**

Drug reaction with eosinophilia and systemic symptoms is a rare, potentially life-threatening drug-induced hypersensitivity reaction that includes maculopapular rash, hematologic abnormalities (eosinophilia, atypical lymphocytosis, lymphadenopathy, and internal organ involvement [liver, kidney, or lung dysfunction]). Typically, symptoms begin months after drug exposure, with relapses on reexposure to the same drug. Reactivation of latent human herpesviruses (HHV6, HHV7, EBV) often is identified.

25. A 2-year-old has recurrent infections, low IgG, warts, and severe neutropenia. What does the bone marrow biopsy and aspirate demonstrate?

A. Hypoplasia

B. Increased myeloid precursors

C. Hemophagocytosis

D. More than 5% lymphoblasts

**Explanation**

WHIM syndrome presents with a distinctive combination of warts, hypogammaglobulinemia, infections, and myelokathexis (*kathexis* = retention), with granulocyte hyperplasia and degenerating neutrophils in the marrow and peripheral neutropenia. These patients are susceptible to papilloma-induced acuminata warts, condyloma, and carcinoma. They also have a decrease in B-lymphocytes. WHIM syndrome is caused by autosomal-dominant mutations in the CXCR4 receptor gene. Leukocytes have increased responses to SDF-1, the ligand for CXCR4 receptor. Increased activity of CXCR4 receptor delays release of mature neutrophils from the marrow and apoptosis of these neutrophils. The immunologic abnormalities likely reflect abnormally increased responses to SDF-1 by other leukocytes.

26. A 2-year-old has recurrent skin infections, had delayed umbilical cord separation, and has abscesses lacking pus, with poor wound healing and elevated ANC. Which gene is mutated?

A. *PRF1*

B. *LYST*

C. *BRAF-V600E*

D. *CD52*

E. *ITGB2* (encoding CD18)

**Explanation**

Leukocyte adhesion deficiency type 1 is caused by autosomal recessive defects in *ITGB2* (encoding CD18), resulting in absent or significantly decreased expression of the B2 integrins. Severity of disease is associated with the degree of CD18 deficiency.

27. A 15-year-old patient presents with 2 weeks of fever and cytopenias. The patient has massively elevated CMV by blood qPCR. Flow cytometry of bone marrow aspirate reveals absent B cells and decreased monocytes, with cytogenetics identifying the presence of monosomy 7. Which gene is mutated?

A. *GATA2*

B. *PRF1*

C. *P53*

D. *BRAF-V600E*

**Explanation**

Germline mutations in *GATA2* leading to haploinsufficiency have been identified in patients with familial myelodysplastic syndrome and immune deficiencies. *GATA2* mutations are particularly associated with decreased monocytes, natural killer cells, and B cells. Penetrance is variable, with significant clinical heterogeneity.