**Disorders of Leukocytes**

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1. A young child with consanguineous parents has developmental delay and a history of multiple recurrent bacterial infections and short stature. He presents to the emergency department following trauma and requires a blood transfusion. Blood work identifies leukocytosis, neutrophilia, and the Bombay blood group (absent H antigen as well as absent A and B antigens). What is this patient’s diagnosis?
2. Chediak-Higashi syndrome
3. Leukocyte adhesion deficiency (LAD) Type II
4. CD18 deficiency
5. Griscelli syndrome

**Explanation**

This scenario is consistent with leukocyte adhesion deficiency (LAD) Type II, caused by pathogenic biallelic variants in *SLC35C1*. As a result, fucosylation of macromolecules is defective, resulting in no SLeX (CD15) on myeloid cells and the red blood cell phenotype (Bombay) described above. Infections typically are not as severe as they are in LAD-I, though patients have associated severe mental deficits, short stature, and distinctive facial appearance. XLP and Griscelli syndrome are associated with defects in vesicle trafficking with risk of hemophagocytic lymphohistiocytosis (HLH). CD18 deficiency is associated with LAD-I.

1. A 4-year-old male child presents to the emergency department with his fourth invasive *Staph* infection. CBC consistently identifies moderate neutropenia. Sophisticated lab testing identifies lack of Toll-like receptor responses. The patient undergoes whole exome sequencing and is found to have pathogenic variants in *IRAK4.* What does *“IRAK4”* stand for?
2. Interferon gamma receptor-associated kinase 4
3. Inducible RAS activating kinase 4
4. Interleukin-1 receptor-associated kinase 4
5. Immune response activating kinase 4

**Explanation**

*IRAK4* is interleukin-1 (IL1) receptor-associated kinase 4 and plays critical roles in initiating innate immune responses against pathogens. Patients with *IRAK4* dysfunction have frequent bacterial infections but rarely experience abnormal viral or parasitic infections. This is due to the role of IL1 and Toll-like receptors (TLR) in inducing innate immune responses to bacteria. Deficiency of MyD88 has a clinically identical phenotype. TLR signaling (except TLR3) and most IL1R require functional *IRAK4* and MyD88.

1. An avid 16-year-old triathlete was in a bike accident and developed cellulitis, which was treated with Bactrim. While still on antibiotics, he moved with his family from Houston to Denver, and during the car trip he developed fever, pharyngitis, and malaise. Upon arriving in Denver he presented to the emergency department and was noted to have significant lymphocytosis with some atypical lymphocytes. What is the most likely cause of the white blood cell abnormalities?
2. Drug reaction
3. Altitude higher than 5,000 ft above sea level
4. GATA2 mutation
5. Epstein-Barr virus infection

**Explanation**

This patient most likely has acute primary Epstein-Barr virus infection (mononucleosis), which frequently is associated with elevated lymphocyte count as well as atypical lymphocytes. Many drugs, including sulfonamides, and living at high elevations can be associated with neutropenia. GATA2 can be associated with loss of monocytic populations with risk of infections and myeloid malignancies.

1. A 10-year-old child presents to his primary care physician with a several-week history of bruising and fatigue with some difficulty sleeping. He is afebrile with CBC results demonstrating platelets 25,000/mcl and ANC 50. His spleen is palpable 4 cm below costal margin. What test would you prioritize next?
2. Glucocerebrosidase assay
3. Ferritin
4. Liver/spleen ultrasound
5. Chest x-ray

**Explanation**

Splenomegaly in this case is most likely due to leukemia or lymphoma. Glucocerebrosidase tests for Gaucher disease, which is unlikely in this case due to rapid onset. Ferritin to screen for hemophagocytic lymphohistiocytosis (HLH) is less likely given the absence of fever. Liver/spleen ultrasound is reasonable to evaluate possible mechanical causes of splenomegaly and to characterize liver and/or spleen masses. However, chest x-ray is the most urgent to rule out the possibility of mediastinal mass.

1. A 2-year-old girl presents to the emergency department with her third life-threatening bacterial or fungal infection. The treating team is increasingly concerned about a primary immune deficiency. Deficiencies/defects in which of the following would lead to defective innate immunity?
2. Major histocompatibility complex (MHC) class I
3. MHC class II
4. *p67phox*
5. *RAG2*

**Explanation**

Defects in *p67phox* would result in dysfunctional oxidative burst, a mechanism of innate immunity associated with chronic granulomatous disease. The other complexes/genes are specific to lymphocyte function, which contribute to adaptive immunity.

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**

Answer D is correct. 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**

Answer C is correct. 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**

Answer C is correct. 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**

Answer E is correct. 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**

Answer D is correct. 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. Anti-neutrophil antibodies

**Explanation**

Answer E is correct. 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**

Answer C is correct. 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**

Answer D is correct. 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**

Answer E is correct. 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**

Answer B is correct. 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**

Answer C is correct. 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**

Answer B is correct. 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 re-exposure 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**

Answer B is correct. 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**

Answer E is correct. 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. Pathogenic variant in which germline gene is identified by whole exome sequencing?

A. *GATA2*

B. *PRF1*

C. *P53*

D. *BRAF-V600E*

**Explanation**

Answer A is correct. 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.