**MCQ examples**

Question 1--Persistent Polyclonal B Cell Lymphocytosis management

A 32-year-old woman who smokes 1.5 packs of cigarettes daily presents for evaluation of persistent lymphocytosis discovered on routine laboratory testing. She reports no fevers, night sweats, weight loss, or recurrent infections. Physical examination reveals mild splenomegaly (palpable 3 cm below the left costal margin) but no lymphadenopathy. Complete blood count shows WBC 12,400/microL with absolute lymphocyte count of 6,200/microL that has been stable for 18 months based on review of prior records. Peripheral blood smear demonstrates characteristic binucleate lymphocytes. Flow cytometry reveals a polyclonal B cell population without monoclonal expansion. Serum protein electrophoresis shows polyclonal increase in IgM at 320 mg/dL. Cytogenetic analysis identifies isochromosome 3q in 40% of analyzed cells.

What is the most appropriate next step in management?

A) Initiate rituximab-based immunotherapy

B) Recommend strict smoking cessation

C) Clinical observation with periodic monitoring

D) Perform bone marrow biopsy

E) Begin oral alkylating agent therapy

Correct Answer: C

Explanation of the Correct Answer:

C) Clinical observation with periodic monitoring is the most appropriate next step. The clinical scenario describes persistent polyclonal B cell lymphocytosis (PPBL), a well-characterized syndrome occurring in young to middle-aged women who smoke cigarettes. The syndrome includes polyclonal B cell expansion, a polyclonal increase in serum IgM, and may be accompanied by splenomegaly and/or lymphadenopathy. The median ALC in PPBL is 5,500 cells/microL (range 2,000 to 21,000 cells/microL) with characteristic binucleate lymphocytes, precisely matching this patient's presentation. Despite the presence of cytogenetic anomalies (isochromosome 3q in this case), the clinical course typically remains stable for years, with one study showing 89 percent four-year event-free survival. The presence of cytogenetic abnormalities in PPBL does not indicate malignant transformation or need for treatment. The polyclonal nature confirmed by flow cytometry, the stable lymphocyte count over 18 months, and the characteristic clinical and morphologic features all support observation as the appropriate approach. The pathogenesis remains unclear, with potential mechanisms including a defect in the CD40 activation pathway, expansion of functional IgD+ CD27+ memory B cells, or undefined genetic defects, but none require specific intervention. Therefore, clinical observation with periodic monitoring of blood counts and clinical status is the most appropriate management strategy for this patient with PPBL.

Analysis of Other Options (Distractors):

A) Initiate rituximab-based immunotherapy is not the best choice because PPBL is a benign condition with stable clinical course. There is no role for immunotherapy in PPBL management. Rituximab would be considered for malignant lymphoproliferative disorders, not for this polyclonal benign process.

B) Recommend strict smoking cessation is not the best choice because while smoking cessation has general health benefits and cigarette smoking is associated with PPBL development, there is no evidence that smoking cessation alters the course of established PPBL or is the primary management strategy. The disease typically remains stable regardless of continued smoking.

D) Perform bone marrow biopsy is not the best choice because bone marrow examination is not indicated in PPBL when the diagnosis can be established by peripheral blood findings. The characteristic binucleate lymphocytes, polyclonal B cell expansion by flow cytometry, polyclonal IgM elevation, and stable course over 18 months provide sufficient diagnostic information without invasive procedures.

E) Begin oral alkylating agent therapy is not the best choice because cytotoxic chemotherapy is not indicated for PPBL. This is a benign polyclonal process, not a malignant lymphoma requiring chemotherapy. The stable nature of PPBL is emphasized, and treatment with alkylating agents would expose the patient to unnecessary toxicity without benefit.

Key Insights: Persistent polyclonal B cell lymphocytosis (PPBL) occurs in young to middle-aged female smokers and is characterized by polyclonal B cell expansion, binucleate lymphocytes, polyclonal IgM increase, and mild splenomegaly. Despite cytogenetic abnormalities (isochromosome 3q, BCL2 rearrangements), PPBL follows a benign clinical course with 89% four-year event-free survival, requiring only observation. Recognition of this specific syndrome prevents unnecessary treatment and invasive procedures in patients with this stable polyclonal lymphoproliferative condition.

Question 2--Pathophysiology of Pertussis-related lymphocytosis

A 28-year-old previously healthy man presents with 3 weeks of persistent cough and post-tussive emesis. He describes paroxysmal coughing episodes followed by an inspiratory whoop. His 4-year-old daughter had similar symptoms 4 weeks ago and was diagnosed with pertussis. Complete blood count reveals WBC 24,500/microL with absolute lymphocyte count of 9,800/microL. Peripheral blood smear shows numerous small mature lymphocytes with convoluted and cleaved nuclei. Flow cytometry demonstrates a normal T lymphocyte ratio with polyclonal expansion. His colleague with similar respiratory symptoms was diagnosed with Bordetella parapertussis infection and had an absolute lymphocyte count of 3,600/microL.

What is the mechanism underlying this patient's lymphocytosis?

A) Increased bone marrow lymphocyte production

B) Blocked lymphocyte extravasation into tissues

C) Pertussis toxin-mediated T cell expansion

D) Splenic sequestration with compensatory production

E) Cytokine-driven polyclonal B cell proliferation

Correct Answer: B

Explanation of the Correct Answer:

B) Blocked lymphocyte extravasation into tissues is the most appropriate mechanism. The clinical presentation is consistent with pertussis (whooping cough) caused by Bordetella pertussis, characterized by paroxysmal cough with inspiratory whoop and marked lymphocytosis. The lymphocytosis in pertussis is polyclonal with a normal T lymphocyte ratio and appears to be due to a block in extravasation of lymphocytes from the blood into lymph nodes, rather than an increase in lymphocyte production. This mechanism explains why lymphocytes accumulate in peripheral blood—they cannot exit the circulation to enter lymphoid tissues normally. The case also highlights an important distinguishing feature between B. pertussis and B. parapertussis infections. Lymphocytosis appears to be specific to B. pertussis infection, since it is not seen with a clinically nearly identical illness caused by B. parapertussis, with one study showing mean ALC of 7,800/microL in B. pertussis versus 3,500/microL in B. parapertussis. The patient's colleague with B. parapertussis had significantly lower lymphocytosis (3,600/microL) compared to this patient's 9,800/microL, supporting B. pertussis as the etiology. The characteristic lymphocyte morphology described—convoluted and/or cleaved nucleus—is typical for pertussis. Importantly, both B. pertussis and B. parapertussis express pertussis toxin, suggesting some other effect of B. pertussis must account for the lymphocytosis. The redistribution of lymphocytes due to blocked extravasation, rather than increased production, is the key pathophysiologic mechanism.

Analysis of Other Options (Distractors):

A) Increased bone marrow lymphocyte production is not the best choice because this mechanism is directly contradicted, as lymphocytosis in pertussis appears to be due to a block in extravasation of lymphocytes from the blood into lymph nodes, rather than an increase in lymphocyte production. The polyclonal nature and normal T ratio support redistribution rather than increased production.

C) Pertussis toxin-mediated T cell expansion is not the best choice because while pertussis toxin is produced by B. pertussis, both B. pertussis and B. parapertussis express pertussis toxin, yet only B. pertussis causes significant lymphocytosis. Therefore, pertussis toxin alone cannot explain the lymphocytosis, and the mechanism must involve another factor specific to B. pertussis.

D) Splenic sequestration with compensatory production is not the best choice because this mechanism is not consistent with pertussis-associated lymphocytosis. Splenic sequestration would typically result in decreased peripheral counts, not increased counts. The polyclonal lymphocytosis with normal T ratio and blocked extravasation is the documented mechanism.

E) Cytokine-driven polyclonal B cell proliferation is not the best choice because while the lymphocytosis is polyclonal with a normal T ratio, the mechanism is not cytokine-driven proliferation but rather redistribution due to blocked extravasation. The mechanism involves a block in lymphocyte migration from blood to lymph nodes, not increased proliferation.

Key Insights: Pertussis causes lymphocytosis through blocked extravasation of lymphocytes from blood into lymph nodes, not increased production, with characteristic convoluted/cleaved lymphocyte nuclei on peripheral smear. The lymphocytosis is specific to B. pertussis (mean ALC 7,800/microL) and not seen with B. parapertussis (mean ALC 3,500/microL), despite both organisms expressing pertussis toxin. Recognition of this redistribution mechanism distinguishes pertussis from most other bacterial infections and explains the polyclonal lymphocytosis with normal T:B lymphocyte ratio.

Question 3--Initial evaluation for modest asymptomatic lymphocytosis

A 56-year-old man with no significant past medical history undergoes routine health maintenance examination. Complete blood count shows WBC 11,200/microL with 42% lymphocytes, yielding an absolute lymphocyte count of 4,700/microL. He denies fevers, night sweats, weight loss, or recent infections. Physical examination is unremarkable without lymphadenopathy or organomegaly. Peripheral blood smear shows normal-appearing small lymphocytes without atypical features, smudge cells, or lymphoblasts. Review of records from 3 years ago shows WBC 9,800/microL with absolute lymphocyte count of 2,800/microL. He is asymptomatic and clinically stable.

What is the most appropriate next step in evaluation?

A) Immediate flow cytometry of peripheral blood

B) Bone marrow aspiration and biopsy

C) Repeat complete blood count in 1-2 weeks

D) PET-CT scan for occult malignancy

E) Empiric antibiotic trial for occult infection

Correct Answer: C

Explanation of the Correct Answer:

C) Repeat complete blood count in 1-2 weeks is the most appropriate initial step in this asymptomatic patient with modest lymphocytosis is to repeat the complete blood count to confirm the finding and assess the trajectory before proceeding to more specialized testing. The CBC can be repeated with less urgency (eg, within two to four weeks) if the patient is clinically stable, the lymphocytosis is modest, and no worrisome findings are reported on blood smear. This patient is clinically stable with ALC of 4,700/microL (only modestly elevated above the 4,000/microL threshold), and the blood smear shows normal-appearing lymphocytes without concerning features. Flow cytometry is generally recommended for specific indications, including ALC >5000 cells/microL, unless lymphocytosis can be accounted for by evidence of a recent viral infection, offending drug, or asplenia or Unexplained ALC >4000 cells/microL for >1 month. Since this patient's ALC is 4,700/microL (below the 5,000 threshold for immediate flow cytometry) and this appears to be a new finding on routine testing, confirming the result and establishing whether it persists beyond one month is appropriate before proceeding to flow cytometry. The abnormal CBC and differential count should be repeated to exclude laboratory error, and in stable patients, the CBC can be repeated with less urgency. The absence of concerning morphologic features (no blasts, smudge cells, or atypical lymphocytes), lack of adenopathy or organomegaly, and absence of cytopenias all support a less urgent approach. If the lymphocytosis persists or increases on repeat testing, flow cytometry would then be indicated based on the criteria of rising ALC or unexplained ALC >4000 cells/microL for >1 month.

Analysis of Other Options (Distractors):

A) Immediate flow cytometry of peripheral blood is not the best choice because while flow cytometry is appropriate for evaluation of lymphocytosis, it is not immediately necessary in this scenario.

B) Bone marrow aspiration and biopsy is not the best choice because bone marrow examination is not indicated as an initial diagnostic step for asymptomatic lymphocytosis. Bone marrow biopsy would only be considered after establishing clonality and in specific contexts (such as suspected acute leukemia or certain lymphomas).

D) PET-CT scan for occult malignancy is not the best choice because PET-CT is not part of the initial evaluation for lymphocytosis. Initial evaluation relies on CBC, history and physical examination, and review of the blood smear. Advanced imaging would only be considered after establishing a diagnosis requiring staging (such as lymphoma), not as an initial diagnostic test.

E) Empiric antibiotic trial for occult infection is not the best choice because there is no indication for empiric antibiotics in this case. The patient has no symptoms of infection, and infectious causes of lymphocytosis (like pertussis, infectious mononucleosis, or cat scratch disease) present with clinical manifestations. Empiric treatment without diagnostic evidence is not appropriate.

Key Insights: For modest asymptomatic lymphocytosis (ALC 4,000-5,000/microL) without concerning morphology, adenopathy, or organomegaly, repeating the CBC in 1-2 weeks is appropriate to confirm the finding before proceeding to flow cytometry. Flow cytometry is indicated for ALC >5,000/microL, unexplained ALC >4,000/microL persisting >1 month, rising ALC, worrisome morphology, cytopenias, or organomegaly/adenopathy. This stepwise approach prevents unnecessary specialized testing while ensuring appropriate evaluation of persistent or progressive lymphocytosis.

**NON MCQ examples**

Clinical Vignette 2: Reactive picture with atypical lymphocytosis

A 22-year-old college student presents with a one-week history of fever, severe sore throat, fatigue, and posterior cervical lymphadenopathy. Her CBC shows a WBC count of 13,000/microL with 60% lymphocytes (ALC 7,800/microL). The peripheral blood smear review reports numerous large, atypical lymphocytes.

Questions and Answers:

1. True/False: The presence of atypical lymphocytes on the peripheral blood smear is diagnostic of Epstein-Barr Virus (EBV) infection.  
   Answer: False  
   Explanation: While atypical lymphocytes are characteristic of infectious mononucleosis (IM), most commonly caused by EBV, they can also be seen in other viral illnesses like CMV, HIV, hepatitis, and adenovirus infections, as well as drug reactions.
2. Yes/No: Is flow cytometry generally required to evaluate this patient's lymphocytosis initially?  
   Answer: No  
   Explanation: In a young patient with classic symptoms of IM and atypical lymphocytosis, the clinical picture strongly suggests a reactive viral process. Flow cytometry is typically reserved for persistent, unexplained, or morphologically suspicious lymphocytosis.
3. Drop Down Question: The lymphocytosis seen in typical infectious mononucleosis is primarily due to expansion of:  
   B cells  
   T cells  
   NK cells  
   Answer: T cells  
   Explanation: The atypical lymphocytes seen in classic EBV-induced infectious mononucleosis are predominantly reactive cytotoxic (CD8+) T cells responding to EBV-infected B lymphocytes.
4. True/False: If this patient's symptoms and lymphocytosis resolve completely within two months, further hematologic evaluation for the lymphocytosis is usually unnecessary.  
   Answer: True  
   Explanation: Lymphocytosis caused by acute conditions like infections should resolve within one to two months. Resolution supports a reactive etiology, obviating the need for further workup like flow cytometry for the lymphocytosis itself.
5. Yes/No: Could primary HIV infection present with a similar clinical and hematologic picture?  
   Answer: Yes  
   Explanation: Primary HIV infection can cause an infectious mononucleosis-like syndrome, including fever, pharyngitis, lymphadenopathy, and lymphocytosis with atypical lymphocytes.
6. True/False: The ALC of 7,800/microL is unusually high for a reactive process like infectious mononucleosis.  
   Answer: False  
   Explanation: Reactive lymphocytoses, including infectious mononucleosis, can commonly cause ALCs to rise into the range seen in this patient, and sometimes up to 20,000-30,000/microL.
7. Drop Down Question: Besides EBV, another common viral cause of an infectious mononucleosis syndrome is:  
   Pertussis  
   CMV  
   Influenza  
   Answer: CMV  
   Explanation: Cytomegalovirus (CMV) is another infectious agent that can cause a nearly indistinguishable IM syndrome.
8. Yes/No: If the patient also had significant eosinophilia, could this suggest Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)?  
   Answer: Yes  
   Explanation: DRESS is a hypersensitivity reaction that can cause lymphocytosis, often with atypical lymphocytes, and characteristically includes eosinophilia and systemic symptoms, typically occurring 2-6 weeks after starting a drug.

Clinical Vignette 3: Lymphocytosis, cytopenias, organomegaly, smudge cells

A 75-year-old female presents with progressive fatigue and unintentional weight loss over 4 months. Examination reveals diffuse non-tender lymphadenopathy and mild splenomegaly. Her CBC shows WBC 65,000/microL with 90% lymphocytes (ALC 58,500/microL), hemoglobin 10.5 g/dL, and platelets 130,000/microL; the smear shows predominantly small, mature-appearing lymphocytes and frequent smudge cells.

Questions and Answers:

1. True/False: The combination of marked lymphocytosis (>50,000/microL), smudge cells, lymphadenopathy, splenomegaly, and cytopenias strongly suggests Chronic Lymphocytic Leukemia (CLL).  
   Answer: True  
   Explanation: This clinical presentation, including the high ALC, characteristic smudge cells, organomegaly, and associated cytopenias (anemia, thrombocytopenia), is highly typical for CLL.
2. Yes/No: Is the presence of smudge cells alone sufficient to diagnose CLL without further testing?  
   Answer: No  
   Explanation: While characteristic, smudge cells are artifacts and not diagnostic. Diagnosis of CLL requires confirmation of ≥5000 clonal B lymphocytes/microL in the peripheral blood, typically confirmed by flow cytometry demonstrating a characteristic immunophenotype (e.g., CD5+, CD19+, CD20dim+, CD23+).
3. Drop Down Question: Based on the high ALC and presence of blasts being unlikely given the description, the most appropriate next diagnostic test is:  
   Bone Marrow Biopsy  
   Peripheral Blood Flow Cytometry  
   Lymph Node Biopsy  
   Answer: Peripheral Blood Flow Cytometry  
   Explanation: For suspected CLL with a high ALC and characteristic morphology (mature lymphocytes, smudge cells), peripheral blood flow cytometry is the preferred initial test to confirm clonality and establish the immunophenotype required for diagnosis.
4. True/False: The patient's anemia and thrombocytopenia could be due to autoimmune phenomena associated with CLL.  
   Answer: True  
   Explanation: CLL can be associated with autoimmune cytopenias, including autoimmune hemolytic anemia and immune thrombocytopenia, in addition to cytopenias caused by bone marrow infiltration.
5. Yes/No: Does an ALC >50,000/microL automatically constitute a medical emergency requiring immediate hospitalization in this context?  
   Answer: No  
   Explanation: While an ALC >50,000/microL in a newly diagnosed patient warrants prompt evaluation, in a clinically stable patient with suspected CLL, the absolute count itself does not automatically necessitate emergency admission. Urgency depends on clinical stability and complications, not just the ALC.
6. True/False: Mantle Cell Lymphoma (MCL) should be considered in the differential, as it can present with marked lymphocytosis.  
   Answer: True  
   Explanation: MCL has a high prevalence of lymphocytosis among B-cell lymphomas (other than CLL), with about half of patients having lymphocytosis. It should be considered, although the morphology described is more typical for CLL.
7. Drop Down Question: If flow cytometry confirms CLL, which cytogenetic abnormality detected by FISH would be particularly important for prognostication?  
   t(11;14)  
   del(17p)  
   Isochromosome 3q  
   Answer: del(17p)  
   Explanation: FISH is used in CLL prognostication. del(17p) involving TP53 is a well-established high-risk feature in CLL. t(11;14) is characteristic of MCL, and isochromosome 3q is associated with PPBL.
8. Yes/No: Could this presentation be consistent with Acute Lymphoblastic Leukemia (ALL)?  
   Answer: No  
   Explanation: The description of predominantly small, mature-appearing lymphocytes and smudge cells is characteristic of CLL, not the lymphoblasts typically seen in ALL. ALL usually presents more acutely with blasts on the smear.

Clinical Vignette 4: Neutropenia, LGLs, autoimmune disease

A 55-year-old female with a history of rheumatoid arthritis presents with recurrent bacterial skin infections and fatigue. Her CBC shows WBC 3,000/microL, ANC 800/microL, hemoglobin 11.0 g/dL, platelets 180,000/microL, and ALC 1,800/microL. Peripheral smear review notes increased large granular lymphocytes, although the total ALC is within the normal range.

Questions and Answers:

1. True/False: The presence of neutropenia (ANC 800/microL) combined with increased large granular lymphocytes (LGLs) on smear raises suspicion for LGL leukemia, even with a normal total ALC.  
   Answer: True  
   Explanation: LGL leukemia is characterized by clonal LGLs, splenomegaly, and cytopenias (usually neutropenia). Some patients have a normal ALC but an increased percentage of cytotoxic (CD8+) lymphocytes, and the diagnosis should be considered with suggestive morphology and associated findings like neutropenia or autoimmune disease.
2. Yes/No: Is the patient's history of rheumatoid arthritis relevant to the potential diagnosis of LGL leukemia?  
   Answer: Yes  
   Explanation: Patients with LGL leukemia typically present in the fourth or fifth decade with autoimmune manifestations (like rheumatoid arthritis) and neutropenia.
3. Drop Down Question: The most appropriate next step to investigate suspected LGL leukemia is:  
   Serum Protein Electrophoresis  
   Peripheral Blood Flow Cytometry  
   Bone Marrow Biopsy  
   Answer: Peripheral Blood Flow Cytometry  
   Explanation: Flow cytometry is crucial for confirming an expanded population of LGLs, determining their lineage (T-cell or NK-cell), assessing clonality (often via T-cell receptor analysis or restricted V-beta usage for T-LGL), and defining the immunophenotype.
4. True/False: A clonal population of LGLs must exceed 2000 cells/microL to diagnose LGL leukemia.  
   Answer: False  
   Explanation: While LGL levels >2000 cells/microL can be seen, the diagnosis often relies on demonstrating a clonal population of LGLs (typically via flow cytometry or molecular studies) associated with characteristic clinical features like neutropenia or autoimmune disease, even if the absolute count is lower or within the normal range.
5. Yes/No: Could this patient's neutropenia be solely attributed to her rheumatoid arthritis or its treatment (if any)?  
   Answer: Yes  
   Explanation: Rheumatoid arthritis itself (e.g., Felty's syndrome) or medications used to treat it can cause neutropenia. However, the presence of increased LGLs warrants investigation into LGL leukemia as a specific cause or contributing factor.
6. True/False: LGL leukemia typically involves clonal expansion of B lymphocytes.  
   Answer: False  
   Explanation: LGL leukemia involves clonal expansion of either T lymphocytes (CD3+) or Natural Killer (NK) cells (CD3-), which are large granular lymphocytes.
7. Drop Down Question: The characteristic granules seen in LGLs are:  
   Basophilic  
   Eosinophilic  
   Azurophilic  
   Answer: Azurophilic  
   Explanation: The blood smear characteristically reveals large lymphocytes with abundant pale-blue cytoplasm and azurophilic granules in LGL leukemia.
8. Yes/No: If flow cytometry confirms a clonal T-LGL population, is molecular testing for T-cell receptor gene rearrangements necessary for diagnosis?  
   Answer: No  
   Explanation: While molecular testing can demonstrate clonality via T-cell receptor gene rearrangements, flow cytometry demonstrating a phenotypically aberrant or restricted T-cell population (e.g., restricted V-beta usage) is often sufficient to establish clonality in the right clinical context. Molecular testing can be confirmatory or used if flow cytometry is equivocal.