ROYAL COLLEGE
OF PHYSICIANS AND SURGEONS OF CANADA
COLLÈGE ROYAL
DES MÉDECINS ET CHIRURGIENS DU CANADA

Sample Written Exam – Hematological Pathology

Question 1

a. For each deficiency listed, indicate the characteristic peripheral smear finding, the inheritance pattern and the metabolic pathway affected.

   i. Glucose-6-phosphate dehydrogenase (G6PD) deficiency

      MODEL ANSWER (0.25 marks each, 0.75 marks total)

      - Characteristic peripheral smear finding: bite cells, irregularly contracted RBC, blister cells
      - Inheritance pattern: X-linked
      - Metabolic pathway affected: hexose monophosphate shunt/pentose phosphate pathway

   ii. Pyruvate kinase (PK) deficiency

      MODEL ANSWER (0.25 marks each, 0.75 marks total)

      - Characteristic peripheral smear finding: contracted echinocytes (sputnik cells), none also reasonable
      - Inheritance pattern: autosomal recessive
      - Metabolic pathway affected: glycolysis

b. List **TWO** causes of a false-negative G6PD assay.

   MODEL ANSWER (0.5 marks each, 1 mark total)

   - Acute hemolysis eliminating affected RBC
   - Reticulocytosis
   - Leukocytosis if WBC-depleted blood is not used
   - Heterozygous females
   - Blood transfusion

c. Name **ONE** stain commonly used to detect Heinz bodies on a peripheral smear.

   MODEL ANSWER (0.25 marks)

   - Supravital staining with methyl violet
   - New methylene blue and brilliant cresyl blue are fainter (p. 315, Dacie)

   ** Note to markers - just supravital stain would be incorrect

d. Name **FOUR** clinical settings that may increase hemolysis in patients with G6PD deficiency.

MODEL ANSWER (0.25 marks each, 1 mark total)

- Neonatal period
- Infection
- Consumption of fava beans, including nursing moms
- Use of oxidative drugs: dapsone, primaquine, methylene blue, phenazopyridine, cotrimoxazole, sulfadiazine (sulfa-containing drugs), quinolones, nitrofurantoin, rasburicase, toluidine blue, chloroquine, quinine, high dose aspirin, acetaminophen, sulfasalazine, high dose ascorbic acid, chloramphenicol, isoniazid, glibenclamide, vitamin K, isosorbide dinitrate
- Henna
- Storing clothes with moth balls (naphthalene)

Question 2

For each of the following B-cell lymphomas, specify if putative origin of the malignant cell is pre-germinal centre, germinal centre or post germinal centre.

a. Mantle-cell lymphoma

MODEL ANSWER (0.5 marks)

- Pre-germinal centre

b. Lymphoplasmacytic lymphoma

MODEL ANSWER (0.5 marks)

- Post-germinal centre

c. Chronic lymphocytic leukemia (with mutated *IGHV*)

MODEL ANSWER (0.5 marks)

- Post-germinal centre

d. Follicular lymphoma

MODEL ANSWER (0.5 marks)

- Germinal centre

e. Diffuse large B-cell lymphoma (activated B-cell type)

MODEL ANSWER (0.5 marks)

- Post-germinal centre

f. Marginal zone lymphoma

MODEL ANSWER (0.5 marks)

- Post-germinal centre

Question 3

a. For each of the hereditary bone marrow failure syndromes listed, indicate **ONE** extra-hematopoietic clinical/laboratory finding, **ONE** cytopenia typically present at diagnosis, and **ONE** diagnostic test to confirm the disorder.

i. Fanconi anemia

MODEL ANSWER (0.25 marks each, 0.75 marks total)

- Clinical/Laboratory Finding: skin colour increased pigment, short stature, limb abnormality, hypogonadism, facial changes
- Cytopenia: platelets
- Diagnostic Test: chromosome fragility, FANCD2 nonubiquination

ii. Shwachman-Diamond

MODEL ANSWER (0.25 marks each, 0.75 marks total)

- Clinical/Laboratory Finding: exocrine pancreas, metaphysial dysplasia, skeletal changes, renal tubular dysfunction, diabetes, liver enzyme elevation, short stature
- Cytopenia: neutrophils
- Diagnostic Test: mutational analysis SDS gene

iii. Dyskeratosis congenita

MODEL ANSWER (0.25 marks each, 0.75 marks total)

- Clinical/Laboratory Finding: skin pigment changes, nail changes, mucosal leukoplakia, ocular tearing
- Cytopenia: platelets or RBC
- Diagnostic Test: short telomeres, DKC1 gene mutation

b. Name the **SINGLE** MOST significant future risk for patients with the above hereditary bone marrow failure syndromes, excluding risk of pancytopenia, infection or transfusions.

MODEL ANSWER (0.25 marks)

- Predisposition to AML/MDS later on in life.

Question 4

a. List **TWO** defining properties of cryoglobulins.

MODEL ANSWER (0.5 marks each, 1 mark total)

- Immunoglobulins that precipitate in vitro at temperatures below normal body temperature (<37°C) and redissolve upon rewarming.

b. For each type of cryoglobulinemia listed, specify if the characteristics of immunoglobulin is monoclonal, polyclonal, mixed monoclonal-polyclonal and provide **ONE** causative disease.

i. Type I

MODEL ANSWER (0.5 marks each, 1 mark total)

- Characteristics of immunoglobulin: Monoclonal
- One causative disease: MGUS, MM, WM, CLL

ii. Type II

MODEL ANSWER (0.5 marks each, 1 mark total)

- Characteristics of immunoglobulin: Mix of monoclonal and polyclonal
- One causative disease: HepC, HIV, HBV, B cell LPD

iii. Type III

MODEL ANSWER (0.5 marks each, 1 mark total)

- Characteristics of immunoglobulin: Polyclonal
- One causative disease: Connective tissue disorders, Secondary to infection (Hep C), B cell LPD

Question 5

a. Name **ONE** function of ferroportin.

MODEL ANSWER (0.5 marks)

- Increases iron eggress from macrophages and intestinal cells.

b. What molecule is MOST important in determining the localization and function of ferroportin?

MODEL ANSWER (0.25 marks)

- Hepcidin

c. List **THREE** mutations leading to hereditary hemochromatosis.

MODEL ANSWER (0.25 marks each, 0.75 marks total)

- C282 mutation
- C63D mutation
- Hemojuvulin (HJV) mutation
- Transferrin Receptor Gene mutation (TfR2)
- HAMP mutation

d. What is the **SINGLE** MOST sensitive laboratory test for screening for hemochromatosis?

MODEL ANSWER (0.25 marks)

- Iron saturation

e. List **TWO** adverse clinical outcomes that can occur in a patient with untreated hemochromatosis.

MODEL ANSWER (0.25 marks each, 0.5 marks total)

- Cardiac dysfunction
- Liver cirrhosis
- Endocrine gland dysfunction (adrenal, diabetes, pituitary etc)
- Skin changes

Question 6

a. List **FOUR** secondary causes of aplastic anemia.

MODEL ANSWER (0.25 marks each, 1 mark total)

- Drugs (in particular chloramphenicol)
- Iatrogenic/cytotoxic
- Idiosyncratic
- Radiation-associated
- Viruses (EBV, CMV)
- Pregnancy
- Eosiniophilic fasciitis
- Hepatitis/aplastic anemia syndrome (seronegative for hepatitis)
- Pancytopenia of autoimmune diseases
- Thymoma
- Lymphoproliferative disorder

b. For each element listed, indicate the criterion for severe aplastic anemia.

i. Bone marrow cellularity (%)

MODEL ANSWER (0.5 marks)

- <25% (or<50% if <30% of BM is hematopoietic cells)

ii. Absolute neutrophil count

MODEL ANSWER (0.5 marks)

- $<0.5x10^9/L$

iii. Absolute reticulocyte count

MODEL ANSWER (0.5 marks)

- $<20x10^9/L$

iv. Absolute platelet count

MODEL ANSWER (0.5 marks)

- $<20x10^9/L$

c. What is the prognostic significance of the presence of a paroxysmal nocturnal hemoglobinuria clone in aplastic anemia?

MODEL ANSWER (0.5 marks)

- Aplastic patients with a PNH clone have fast response to immunosuppressive therapy, 64% failure-free survival
- Aplastic patients without a PNH clone have slow response to immunosuppressive therapy, 12% failure-free survival

Question 7

Provide **TWO** possible causes for each of the following results on an automated CBC analyzer:

a. falsely high WBC counts

MODEL ANSWER (0.25 marks each, 0.5 marks total)

- NRBCs
- Failed RBC lysis
- Platelet clumps
- Cryoglobulins
- Fibrin strands
- Malarial parasites

b. falsely low WBC counts

MODEL ANSWER (0.25 marks each, 0.5 marks total)

- WBC lysis due to prolonged storage
- Leukocyte aggregation (antibody-mediated)
- Potent cold agglutinin

c. falsely high hemoglobin values

MODEL ANSWER (0.25 marks each, 0.5 marks total)

- Poorly mixed sample
- High WBC
- Hyperlipemia
- Paraprotein
- Non-lysis of red cells
- Hyperbilirubinemia and high CarboxyHb

d. falsely high MCV values

MODEL ANSWER (0.25 marks each, 0.5 marks total)

- Storage of blood at room temperature
- Cold agglutinins
- Very high WBC count
- Excess K2EDTA (or use of K3EDTA)

e. falsely low MCV values

MODEL ANSWER (0.25 marks each, 0.5 marks total)

- Hypochromia
- Increase in ambient temperature
- Hypoosmolar states

f. falsely high platelet counts

MODEL ANSWER (0.25 marks each, 0.5 marks total)

- Microcytic RBC fragments
- Microspherocytes
- HbH disease
- Cryoglobulinemia
- Lipemia
- Fungus/malaria/bacteria in the blood

g. falsely low platelet counts

MODEL ANSWER (0.25 marks each, 0.5 marks total)

- Clotted specimen
- Activation of platelets during venipuncture/in the tube
- Platelet clumping
- Platelet satellitism
- Giant platelets

Question 8

a. For each hemoglobin listed, indicate the structure of the 2 hemoglobin chains. Hemoglobin A has been provided as an example.
Example: Hemoglobin A
Structure of Chains:
- 2 alpha
- 2 beta

i. Hemoglobin A2

MODEL ANSWER (0.25 marks each, 0.5 marks total)

- 2 alpha
- 2 delta

ii. Heterozygous hemoglobin Lepore

MODEL ANSWER (0.25 marks each, 0.5 marks total)

- 2 alpha
- 2 deltabeta fusion

iii. Hemoglobin Gower-2

MODEL ANSWER (0.25 marks each, 0.5 marks total)

- 2 alpha
- 2 epsilon

iv. Hemoglobin F

MODEL ANSWER (0.25 marks each, 0.5 marks total)

- 2 alpha
- 2 gamma

b. List **THREE** causes of a left shift to the hemoglobin-oxygen dissociation curve.

MODEL ANSWER (0.5 marks each, 1.5 marks total)

- Hypothermia
- Alkalosis
- Reduced 2,3 DPG
- High oxygen affinity

c. State the point mutation that gives rise to hemoglobin S.

MODEL ANSWER (0.25 marks)

- Valine for glutamic acid substitution at position 6 of the beta chain.