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Approach To Leucocytosis

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ABSTRACT

Leukocytosis means elevation of WBC count for the patient's age. Leukocytosis might be because of lymphoid or myeloid series of cells. There is usually wide spectrum of causes starting from benign diseases including infections and chronic inflammation or it might indicate an underlying malignancy. So the approach in diagnosis should be very systematic starting from meticulous peripheral smear examination and then proceed to further tests for clinching the diagnosis. So we therefore discuss the approach to various types of leukocytosis in this article.

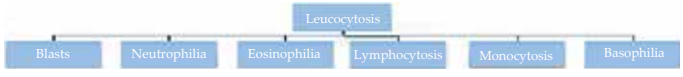
INTRODUCTION

Leukocytosis is defined as an elevation of the WBC count for the patient's age. WBC count of 30 X 10^9 /L is considered elevated in an adult, but this value is normal in the early neonatal period, so an appropriate reference value is critical. So reference intervals for WBC counts and relative percentages and absolute cell counts vary by patient age and hospital population. Leukocytosis is a common finding with a broad differential diagnosis, encompassing both benign and malignant entities. The newer generation of hematology analyzers can examine thousands of leukocytes using flow cytometry–based methodology, some in combination with cytochemistry or fluorescence or conductivity, so they could elucidate different types of WBCs, including neutrophils, lymphocytes, monocytes, basophils, and eosinophils. Spurious elevations of the WBC count can also be seen, including platelet clumps, nucleated RBCs, incomplete lysis of RBCs, cryoglobulins, and cryofibrinogen. Hyperleukocytosis refers to a WBC count greater than 100,000/mL, and is seen almost exclusively in leukemias and myeloproliferative disorders. Leukostasis, or sludging of WBC in small vessels of the brain, lungs, and kidneys, is an oncologic emergency that may cause life-threatening cerebral infarcts, cerebral hemorrhage, or pulmonary insufficiency caused by impaired blood flow. Leukostasis is more common in acute myelogenous leukemia than in acute lymphoblastic leukemia, because myeloblasts are larger and more adhesive than lymphoblasts; it is rarely seen in chronic leukemias, even with extremely high WBC counts (Table 1)

Table 1: Causes of Leucocytosis

Primary hematologic etiology :
Hereditary neutrophilia
Chronic idiopathic neutrophilia
Myeloproliferative disorders (eg, CML, PV,ET)
Familial myeloproliferative disease
Congenital anomalies and leukemoid reaction
Down syndrome
Leukocyte adhesion factor deficiency
Familial cold urticaria and leukocytosis
2. Secondary to other disease entities:
Infection
Chronic Inflammation
Cigarette smoking and Stress
Drug induced (Corticosteroids, beta agonists, lithium, G-CSF etc)
Heat Stroke
Marrow stimulation and Post splenectomy status
3. Spurious
Platelet clumping
Mixed cryoglobulinemia

WHAT MIGHT BE THE CAUSES OF LEUKOCYTOSIS?



Blasts

Blasts can be morphological identified by its atypical morphology, but its not always reliable to distinguish between myeloid and lymphoid blasts. There are some blast equivalents described by WHO for hematololymphoid malignancies 2008 which includes promonocytes, megakaryoblasts and atypical promyelocytes. The further characterization of the blast is done using immunophenotyping by flow cytometry or immunohistochemistry. Blast count more than or equal to 20 % is defined as acute leukemia. There are lower than 20% circulating blast count seen in chronic myeloid neoplasms, including myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), and overlap MDS/MPN. Iatrogenic or endogenous excess granulocyte colony-stimulating factor (G-CSF) stimulation can cause a left shift of the myeloid lineage to the blast stage. Bone marrow infiltration by fibrosis, malignancy, or infection can be associated with circulating immature cells (leukoerythroblastosis), including blasts and nucleated red blood cells.

Myeloid Leukocytosis

Myeloid leukocytosis may represent granulocytosis (ie, neutrophilia, eosinophilia, and basophilia) or monocytosis

Neutrophilia (Figure 1)

Neutrophilia is defined as an elevated circulating neutrophil count (>7.7 X 10^9/L in adults).

Leukemoid reactions represent exaggerated leukocytosis (typically 50,000– 100,000/mL) and may include in the peripheral blood all recognizable stages of neutrophil maturation, that is, from myeloblasts to mature granulocytes. Leukemoid reactions typically last hours to days and may be caused by either benign or malignant conditions. A leukoerythroblastic reaction caused by myelophthisis is similar (but the total WBC does not need to be high) and also includes nucleated RBCs.

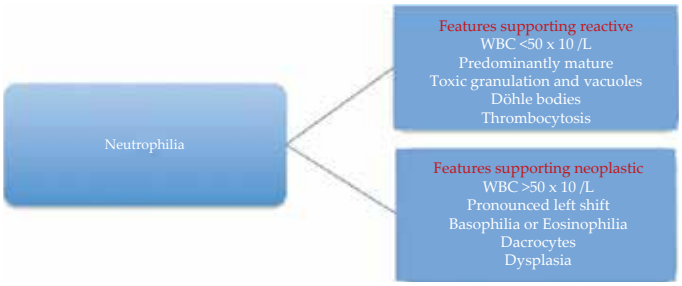


Fig. 1: Causes of Nuetrophilia

Causes of Neutrophilia

A 65 yr old female presented with low back pain and pallor for last 6 months, on examination she had no other significant findings apart from mild pallor. Peripheral blood examination showed Hb – 7 g/dl, total leukocyte count – 62 X 10^9cells/L and platelet count – 94 X 10^9 cells/L, Peripheral smear examination shows Rouleaux formation with neutrophilic leukocytosis (ANC – 41 X 10^9cells/L) and occasional nRBCs with myelocytes and metamyelocytes. Biochemistry evaluation showed S.Urea – 64 mg/dl and S.Cr – 2.6 mg/dl, Liver function showed normal bilirubin and enzymes, but Total protein – 7.2 g/dl, S. Albumin – 3.2 g/dl and S. Globulin- 4g/dl. How to proceed? (Figure 2)

1. Digital rectal examination
2. Stool for occult blood
3. LDH

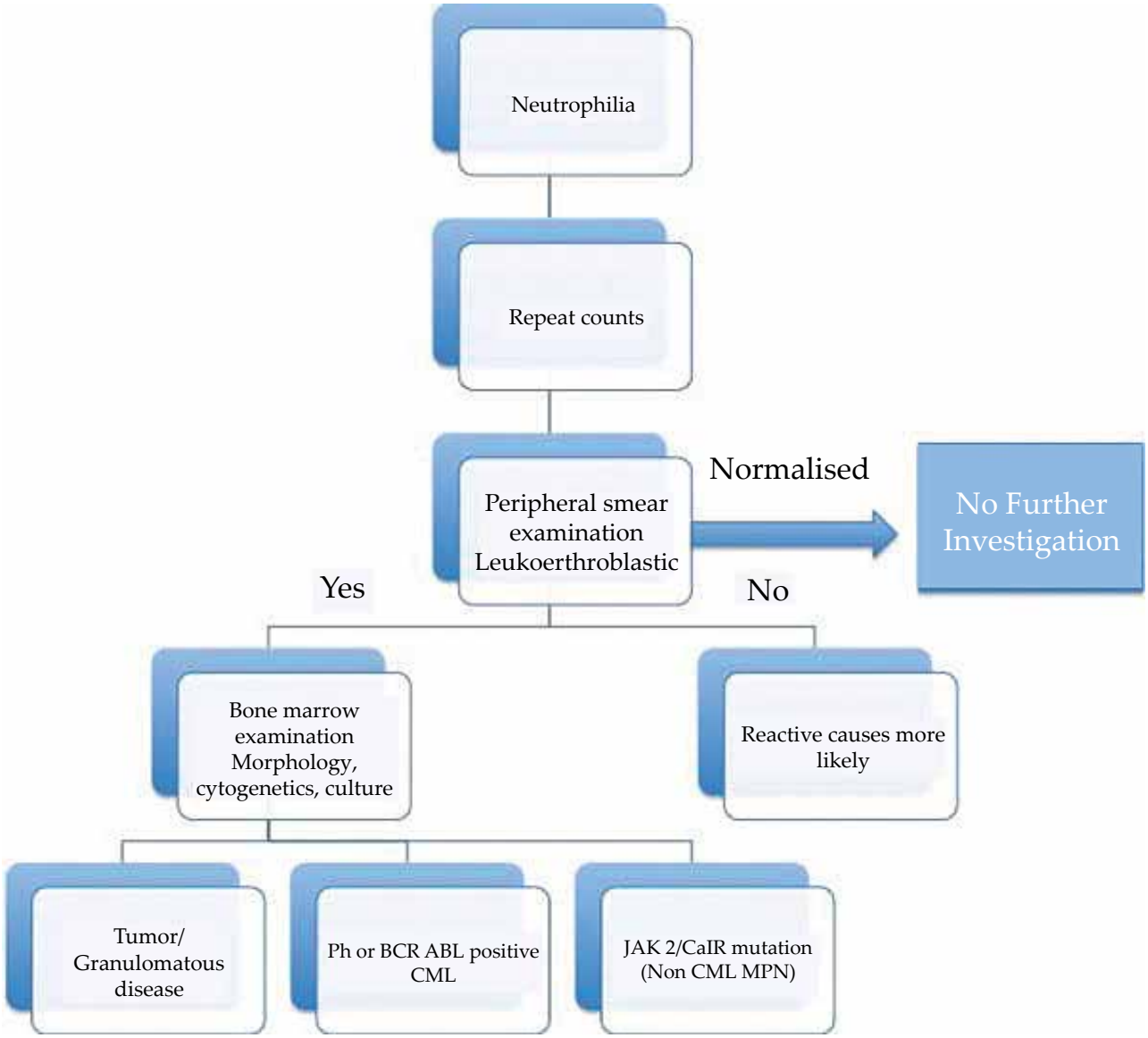


Fig. 2: Approach to Neutrophilia

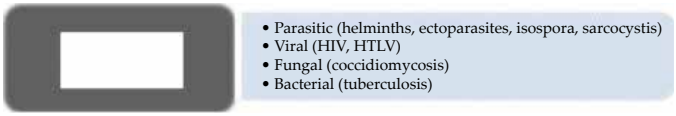


Fig. 3: Cases of Eosinophilia

4. Urine R/E and microscopic examination
5. Serum protein electrophoresis
6. USG whole abdomen and pelvis
7. S. PSA and CEA
8. Upper GI endoscopy and colonoscopy
9. S. Calcium
10. Bone marrow aspiration and biopsy

GENERAL APPROACH TO NEUTROPHILIA

Neutrophilia in Childhood

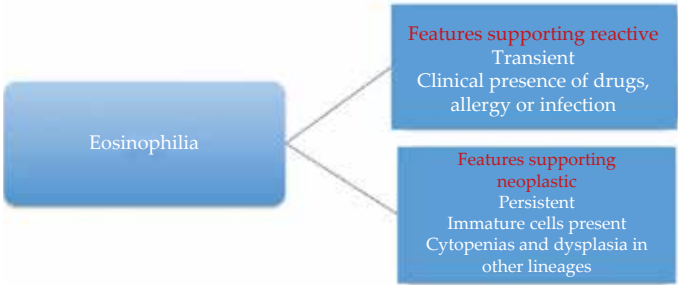
During the first few days of life the upper limit of the normal neutrophil count ranges from 7000 to 13,000 cells/μL for neonates born prematurely and at term gestation, respectively, and is followed by a decrease to adult levels within the first few weeks of life.

Congenital primary neutrophilia is rare. Autosomal dominant neutrophilia kindred of 12 patients in three generations had an activating mutation in the CSF3R gene leading to constitutive activation of the G-CSF receptor and increased proliferation and differentiation of neutrophil precursors. One of the patients progressed to MDS.

Marked neutrophilia is a hallmark of functional disorders of neutrophils that are caused by impaired adhesion or motility, such as in patients with leukocyte adhesion deficiencies or actin dysfunction.

Eosinophilia

The normal absolute eosinophil count (AEC) is 350 to 500/mm^3. The severity of eosinophilia has been arbitrarily divided into mild (AEC 500–1500/mm^3), moderate (AEC 1500–5000/mm^3), and severe (AEC >5000/mm^3).



Causes of Eosinophilia

AD familial eosinophilia has been reported in several families in which individuals displayed marked eosinophilia, but few had pulmonary, cardiac, or neurologic involvement.The disorder has been mapped to chromosome 5q31-q33, a region that contains a cytokine cluster including genes encoding IL-3, IL-5, and GM-CSF.

A 15 yr old boy presented with low-grade fever, pruritus and multiple swelling over the neck for last 2 months. On

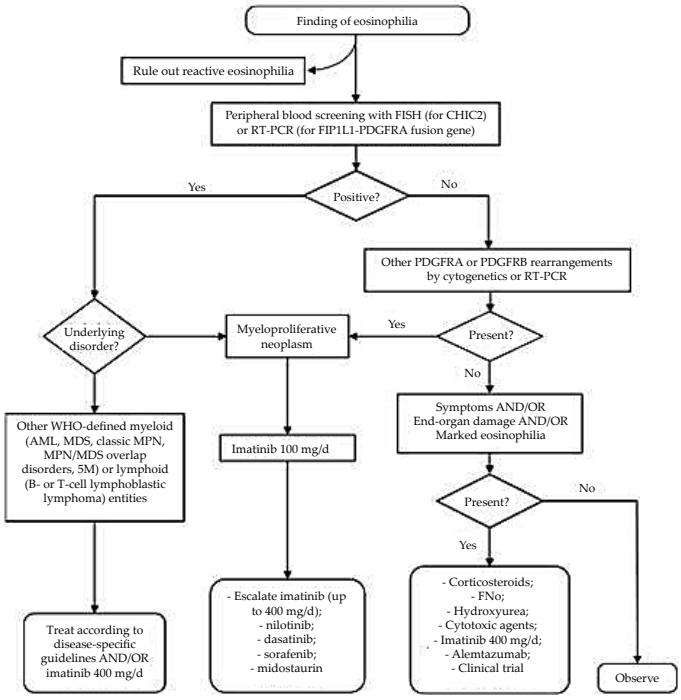


Fig. 4: Approach to Eosinophilia

examination mild pallor, scratch marks over the body and enlarged bilateral cervical, axillary and inguinal lymphnodes with maximum size of 3X3 cms . There was mild hepatomegaly and mild splenomegaly. Peripheral blood examination revealed Hb – 9g/dl, Total leucocyte count of 45 X 10^9 cells/L with prominent eosinophilia (Absolute eosinophil count – 13 X 10^9 cells/L) and platelet count of 164 X 10^9 cells/L. Biochemistry evaluation showed mildly elevated liver enzymes with normal bilirubin and renal parameters were within normal limits. How to proceed? (Figure 4)

1. Lactate dehydrogenase
2. S. Uric acid
3. Stool for parasite
4. Chest X ray and USG whole abdomen and pelvis
5. Lymph node biopsy including histopathological examination by H&E and Immunohistochemistry
6. CECT whole abdomen & pelvis and CECT thorax including neck
7. Bone marrow aspiration and biopsy
8. Molecular studies for PDGFR alpha and beta & FGFR1 mutation
9. Echocardiography

Monocytosis

An absolute monocytosis is defined as >1 X 10^9/L monocytes. A reactive monocytosis may be seen with malignancy (ie, carcinoma, plasma cell myeloma, or lymphoma), subacute bacterial endocarditis, chronic infections like tuberculosis, syphilis, Rocky mountain spotted fever, and kala-azar, autoimmune disorders, and splenectomy.

The persistence of an absolute monocytosis should prompt examination of the BM with flow cytometric immunophenotyping and cytogenetic studies, because persistent monocytosis raises a differential diagnosis, including chronic myelomonocytic leukemia (CMML), acute monoblastic/monocytic leukemia, CML, juvenile myelomonocytic leukemia, atypical (BCR-ABL negative) CML, and myelodys- plastic/myeloproliferative neoplasms, unclassifiable.

Basophilia (Figure 6)

Basophilia, defined as > 0.3 X 10^9/L in adults, is extremely rare. Isolated basophilia is extremely uncommon. Reactive basophilia has been linked to hypersensitivity disorders, iron deficiency, chronic inflammation, and rarely infection, including influenza and chicken pox.

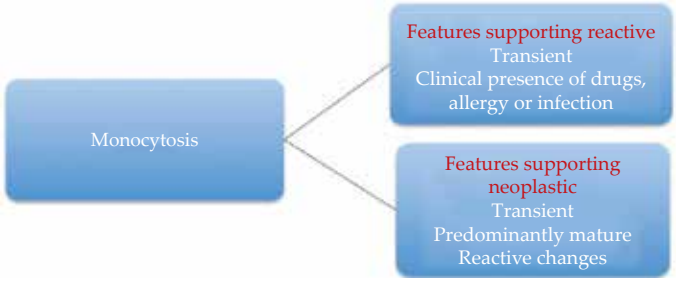


Fig. 5: Differentiating features of Reactive Vs Neoplastic Monocytosis

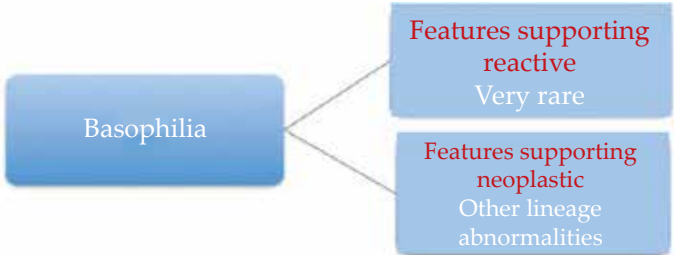


Fig. 6: Basophilia

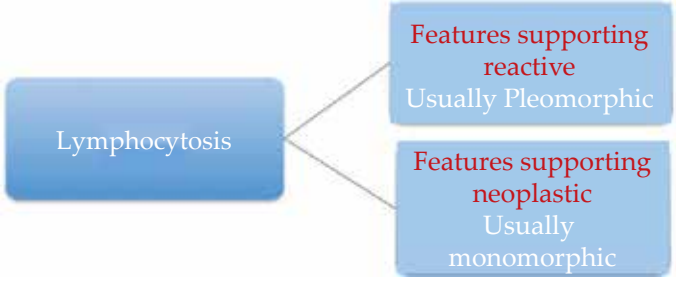


Fig. 7: Lymphocytosis

Myeloproliferative neoplasms like chronic myeloid leukemia and polycythemia vera can have basophilia. In CML, quantification of eosinophilia is very important to distinguish chronic phase from accelerated phase (>20%). Increased numbers of marrow basophils may occur in MDS and sideroblastic anemia. Peripheral blood or bone marrow basophilia may also accompany acute myeloid leukemias, usually in association with 6p or 12p chromosomal abnormalities, or juvenile myelomonocytic leukemia.

Lymphocytosis

In adults, an absolute lymphocyte count of > 3.5 X 10^9/L can be considered lymphocytosis. Absolute lymphocyte counts are higher in children and infants compared with adults, so the appropriate reference intervals must be used.

Causes of Lymphocytosis

Reactive lymphocytosis - Viral infections, some bacterial infections, toxoplasma, malaria, Babesiosis, Drug hypersensitivity, autoimmune disease, cytokines, vaccination, smoking, stress, endocrine disorders and secondary to malignancy (lymphoma, leukemia).

A 80 yr old male presented with swellings all over the body including neck, axilla and inguinal region for last 2 yrs. On examination he had generalised lymphadenopathy and moderate hepatosplenomegaly. Peripheral smear examination showed Hb – 8g/dl, TLC – 124 X 10^9 /L, There are 90% small mature lymphocytes with small round nuclei and plenty of smudge cells and platelet count of 123 X 10^9/L. No comorbidities and his biochemistry reports were unremarkable.

How to proceed?

1. Reticulocyte count
2. Direct Coombs Test
3. LDH
4. S. Uric acid
5. Chest X ray and USG whole abdomen and pelvis
6. Immunophenotyping from peripheral blood

Neoplastic lymphocytosis based on peripheral blood morphology can be as follows: (Figure 8)

To summarize

In conclusion, leukocytosis in a patient should prompt

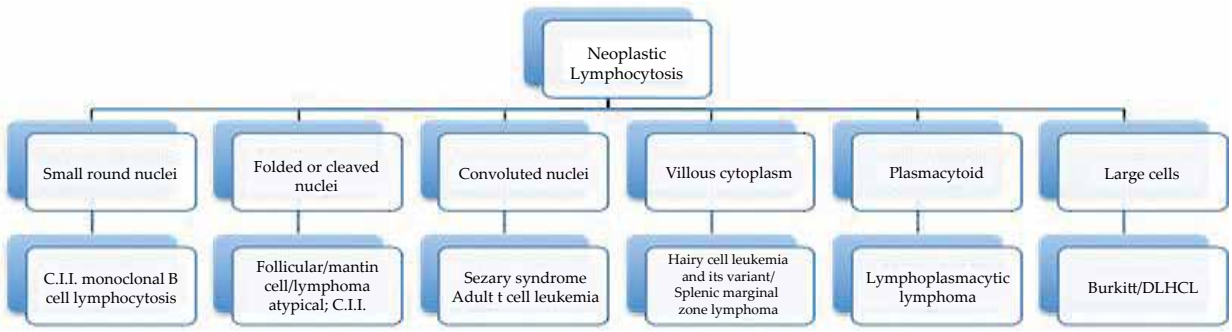


Fig. 8: Lymphocytosis

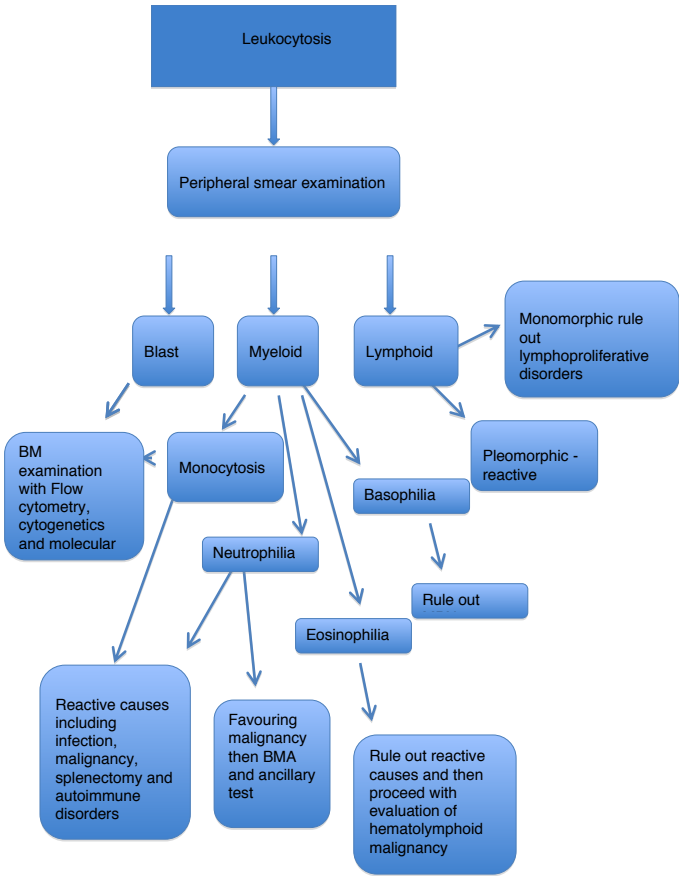


Fig. 9: Approach in a Case of Leukocytosis

confirmation of the CBC and WBC differential. Examination of the blood smear should be performed to establish a manual differential or to confirm the automated differential. This will allow the distinction of myeloid from lymphoid disorders. Distinguishing myeloid leukemoid reactions from myeloid malignancies is difficult, with features such as dysplasia, basophilia, WBC count >50 X 10^9/L, a pronounced left shift, and increased blasts favoring a myeloid malignancy with recommended BM examination and appropriate ancillary testing.

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