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Differential Diagnosis of Mononcytosis on Bone Marrow Examination

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ABSTRACT : Introduction-A monocyte is a type of leukocyte produced in the bone marrow from precursor monoblasts and usually circulates in the bloodstream for 1 to 3 days before clustering in the spleen as reserve or entering tissues and maturing into macrophages or dendritic cells. They usually constitute 3 to 8% of circulating leukocytes. Monocytosis is an increase in the number of monocytes circulating in the blood, with a level above 950/micro Liter usually considered elevated. In patients with a normal leukocyte count, differentials with equal to or greater than 10% monocytes can also be considered monocytosis. The differential diagnosis of an absolute peripheral monocytosis includes a reactive monocytosis and a neoplastic process that may be associated with various haematological neoplasms, that is chronic myelomonocytic leukaemia, myeloid neoplasms with eosinophilia and rearrangement of PDGFRB, juvenile myelomonocytic leukaemia, chronic myeloid leukaemia, as well as acute myeloid leukaemias with a prominent monocytic component.

AIMS: To study the differential diagnosis of monocytosis on bone marrow examination.

METHOD AND MATERIAL - Prospective study, carried out in the Department of Pathology from july 2019 to february 2021 total of 20 cases presenting with monocytosis were studied. After Bone marrow aspiration, the morphological evaluation was done.

RESULTS – In our study, bone marrow revealed monocytosis in different cases of leukemias for eg, 04 cases of AML M4 and 02 cases of AML M5 show the % of blasts/promonocytes was found to be >/= 20%. 07 cases of CMML presented with an absolute monocytosis >1000 /ml and relative monocytosis >10%. 04 cases of JMML showed peripheral blood monocyte count ≥1 x 109/L. 02 cases of CML showed monocytosis. 01 case of chronic bacterial infection showed reactive monocytosis

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CONCLUSION – Most cases of monocytosis will prove to be reactive in nature. Proper evaluation is required to exclude the minority of cases which are neoplastic . This requires the initial assessment of clinical history, laboratory data and morphology. Important clues to suggest a neoplastic process include an unexplained and persistant monocytosis, the presence of blasts/blast equivalents and neutrophil dysplasia.

Keywords: persistant monocytosis, relative monocytosis

I. INTRODUCTION

Monocytosis is defined as an absolute monocyte count greater than 1.0×10^9/L in adults and greater than 3.5×10^9/L in neonates. Monocytosis is associated with numerous conditions because of their role in acute and chronic inflammation and infections, immunologic conditions, hypersensitivity reactions, and tissue repair.

In most cases reactive monocytosis is sound to be secondary(or reactive) in nature including conditions such as chronic infections, acute stress or trauma, systemic inflammatory disorders,autoimmune disorders, drug reactions,postspleenectomy,neutropenia.

Monocytosis is often the first sign of recovery after myelosuppression. When a sustained monocytosis is detected and secondary causes have been thoroughly excluded, then a primary hematologic malignancy must be considerd, especially in the elderly por in patients who also have unexplained cytopenia.Among the entities included in the 2017 WHO classification, the top differential diagnostic consideration is liely to be MDS/MPN, specifically CMML. CMML is defined as persistent peripheral blood monocytosis greater than 1000/mm^3, absent Philadelphia chromosome, and evidence of dysplasia in one or more hematopoietic cell lineages. Juvenile myelomonocytic leukemia, a disease of children that shares pathologic features with CMML, results from defective RAS signaling. Acute myeloid leukemias (AMLs) involving the monocyte line (acute myelomonocytic and acute monoblastic leukemias) may release substantial amounts of lysozyme (muramidase), which is toxic to renal tubules.

II. MATERIALS AND METHODS

This is a prospective study done in the Department of Pathology, Mahatma Gandhi Medical College, Indore. We studied bone marrow aspirates of patients who presented to our hospital from july 2019 to february 2021. A record of examination of the patient and detailed history was made. After obtaining informed consent, bone marrow aspiration was done. Bone Marrow Aspiration was evaluated for adequacy, cellularity, morphology, and maturation of hematopoietic precursor cells and the presence of monocytes.

INCLUSION CRITERIA –All patients showing absolute monocytosis on bone marrow aspirate.

EXCLUSION CRITERIA-1)Cases having no monocytosis on peripheral smear or bone marrow.

2. Hemodiluted smears were not considered for the assessment of marrow cellularity.

III. RESULTS

STUDY	CMML	JMML	AML M4	AML M5	CML	CHRONIC INFECTIONS
MONOCYTOSIS	09	05	04	05	06	01

Table 1.1 – Showing number of cases of different etiologies presenting with monocytosis.

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	Nuclear shape	Chromatin	Cytoplasm	Comments
Monoblast	Round/oval	Delicate / lace-like Nucleolus prominent	Basophilic Rare azurophilic, Granules	Large: 20-30 µm
Promonocyte	Convoluted / indented	Delicate / lace-like Nucleolus prominent	Variably basophilic Variable azurophilic Granules	Except for nuclear shape, very similar to monoblast
Immature monocyte	Convoluted / indented	More condensed Rare nucleolus	Less basophilic than promonocyte or blast, but more basophilic than mature monocyte	Resemble monocytes but less mature and smaller
Monocyte	Lobulated/ indented	Condensed No visible nucleolus	Gray Occasional azurophilic granules. Occasional vacuole	Large : 20-25 µm

Table 1.2 -: Morphological features of monoblast, promonocytes, monocytes immature monocyte.

CASSES	MONOCYTES	PROMONOCYTES	MONOBLAST
JMML	14	6	06
JMML	12	3	04
CMML	06	04	05
CMML	07	05	04
CHRONIC INFECTION	16	02	00
AML M5	07	01	27
AML M5	05	03	24
AML M5	08	02	18
CMML	06	02	11
AML M5B	05	02	21
AML M4	12	02	23
AML M4	5	3	28
CML	8	5	04
CML	7	2	02
CML	4	3	04
CML	6	4	05
CML	16	5	03
AML M4	11	05	26
AML M4	09	06	27
CML	11	04	06
AML M5	23	05	18
CMML	08	07	02
CMML	09	03	03
CMML	06	02	04
CMML	08	03	05
CMML	07	02	04
CMML	06	03	05
JMML	12	08	04

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JMML	14	07	05
JMML	12	06	08

Table 1.3 -: Different cases showing percentage of monocytes, promonocytes, and monoblast respectively.

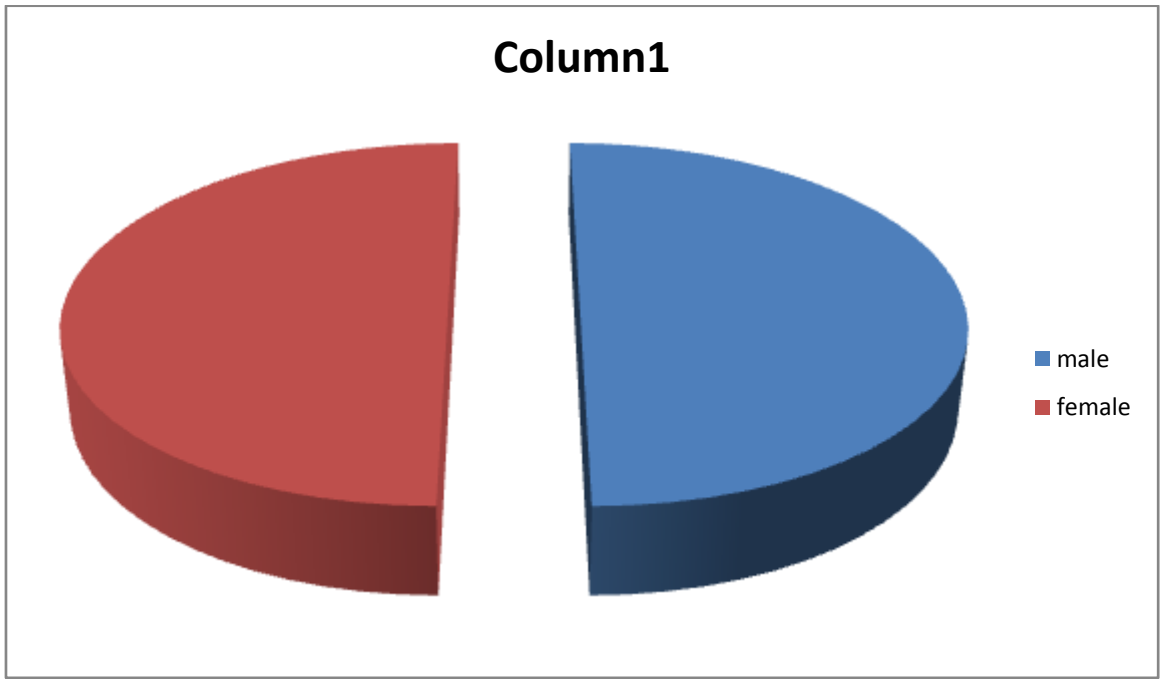

FIGURE 1.1 MALE TO FEMALE RATIO

Most cases of monocytosis will prove to be reactive in nature. Proper evaluation is required to exclude the minority of cases which are neoplastic. This requires the initial assessment of clinical history, laboratory data, and morphology. Important clues to suggest a neoplastic process include an unexplained and persistent monocytosis, the

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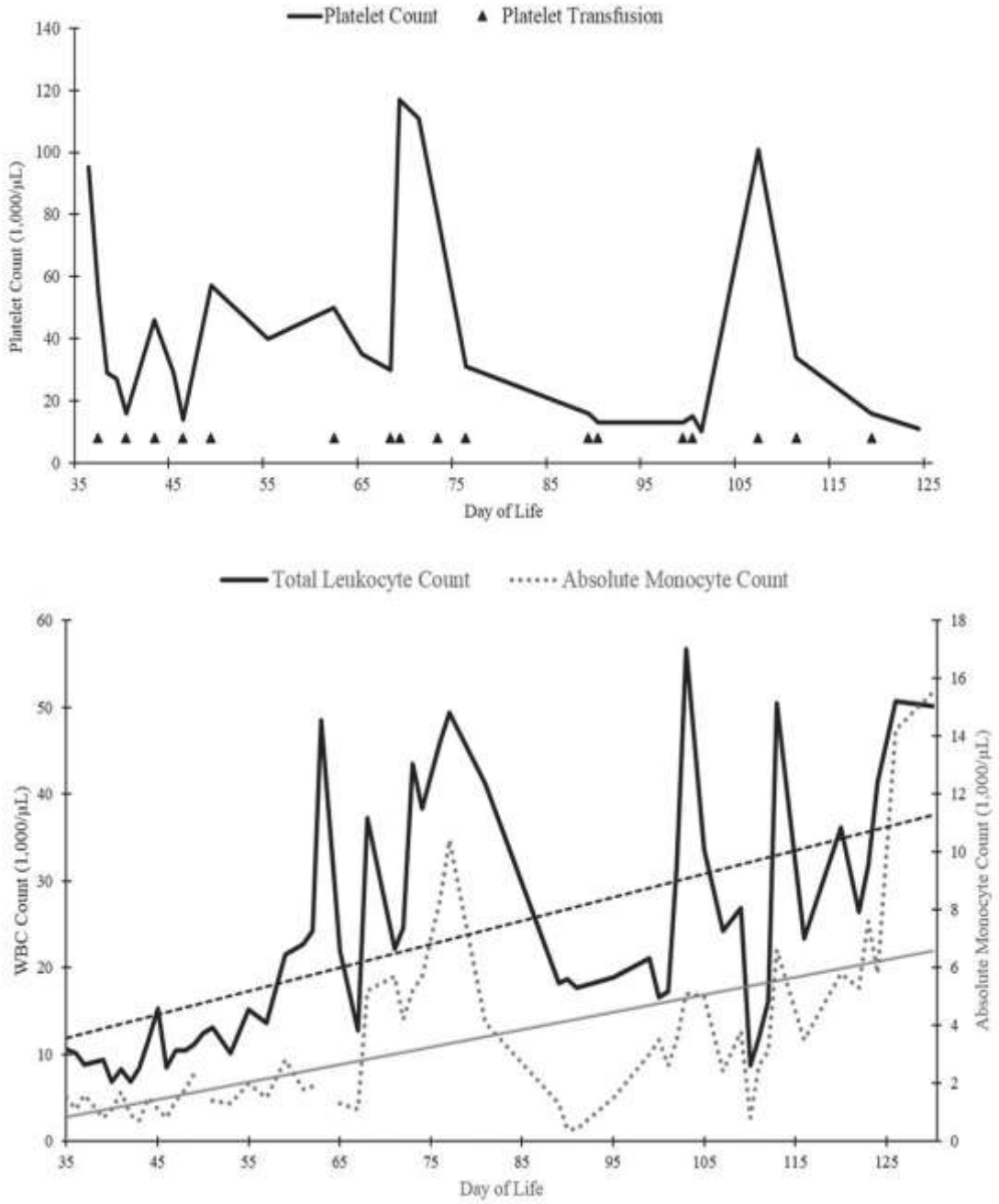

Figure 1.2 Hematologic abnormalities in the presented case. (a) Infant had severe, unremitting thrombocytopenia (solid line) which rapidly fell even after platelet transfusions (solid triangle). (b) The infant's total leukocyte count (solid line) and absolutemonocyte count (double line) steadily rose during his admission

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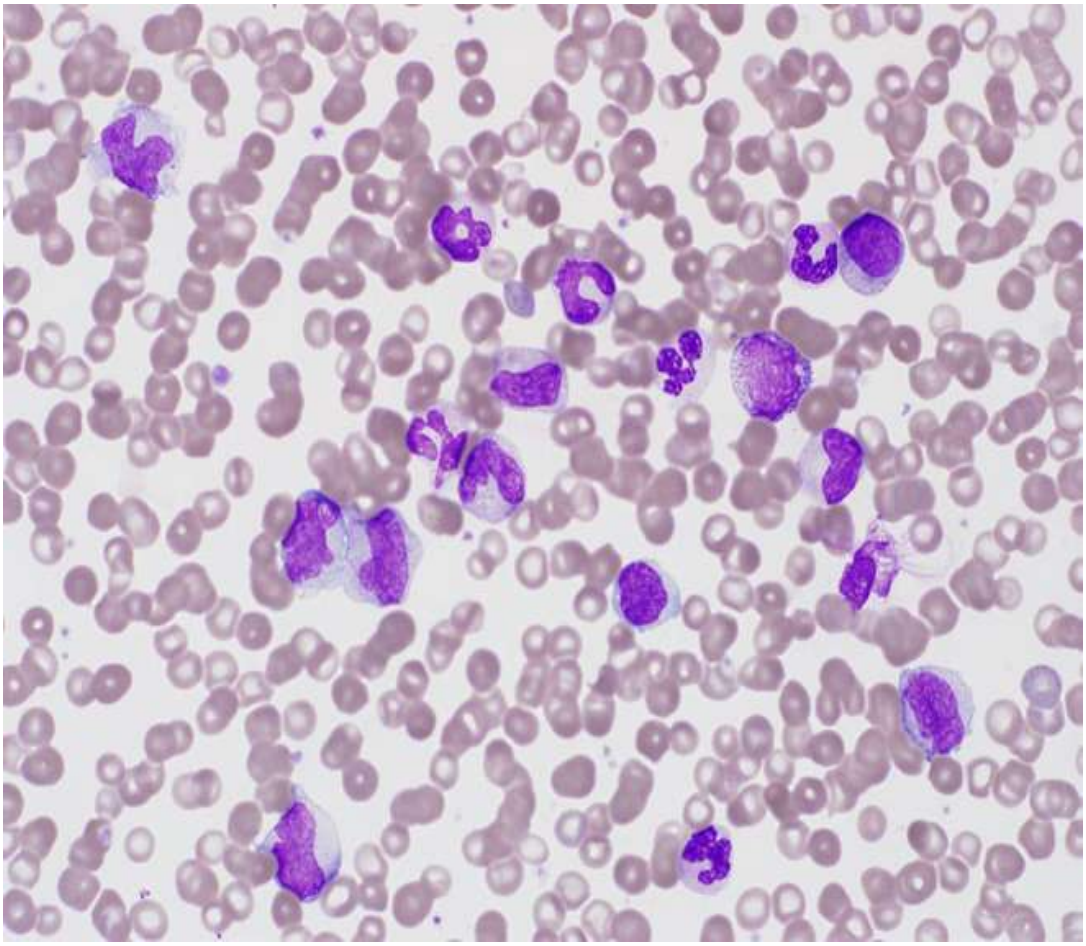

Figure 1.3 - Peripheral smear of a 54-y-old woman with leukocytosis and anemia. There are atypical monocytes with dysplastic neutrophils and only rare blasts, suggestive of CMML

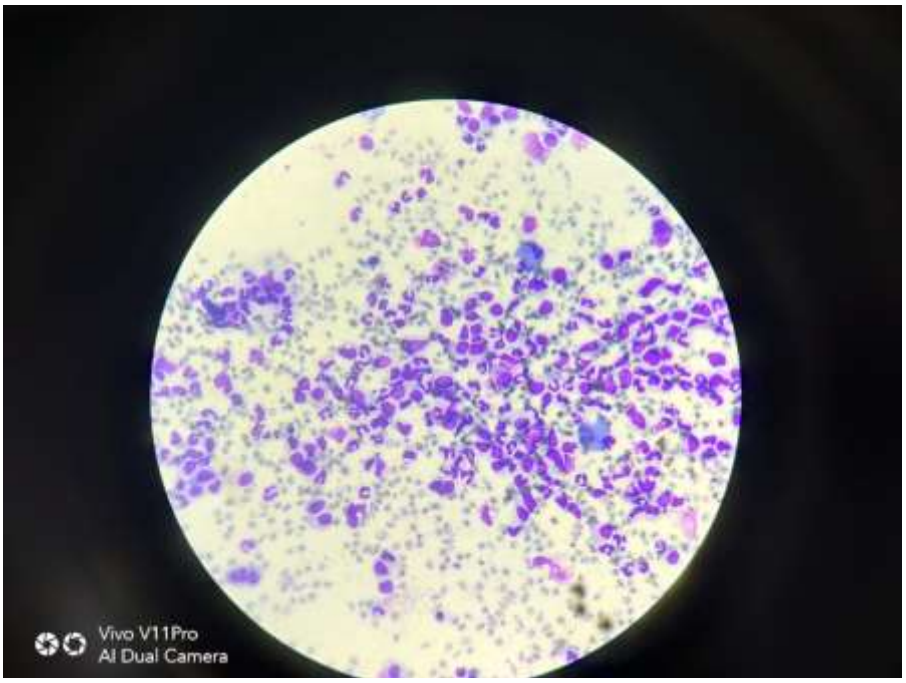

Figure-:40x picture showing increased myelooeisis with monocytosis.

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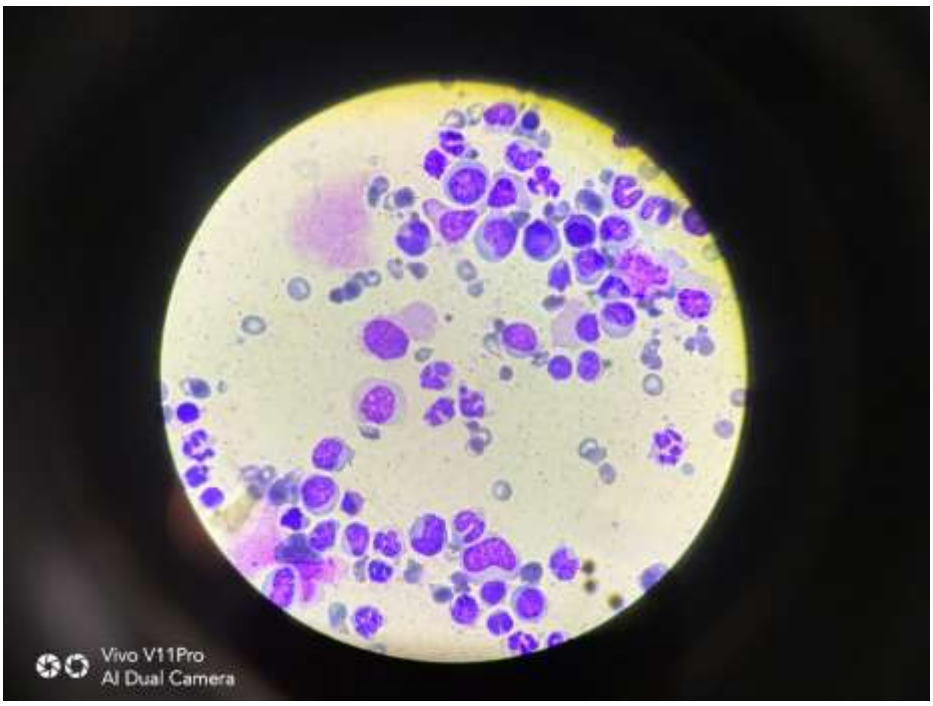
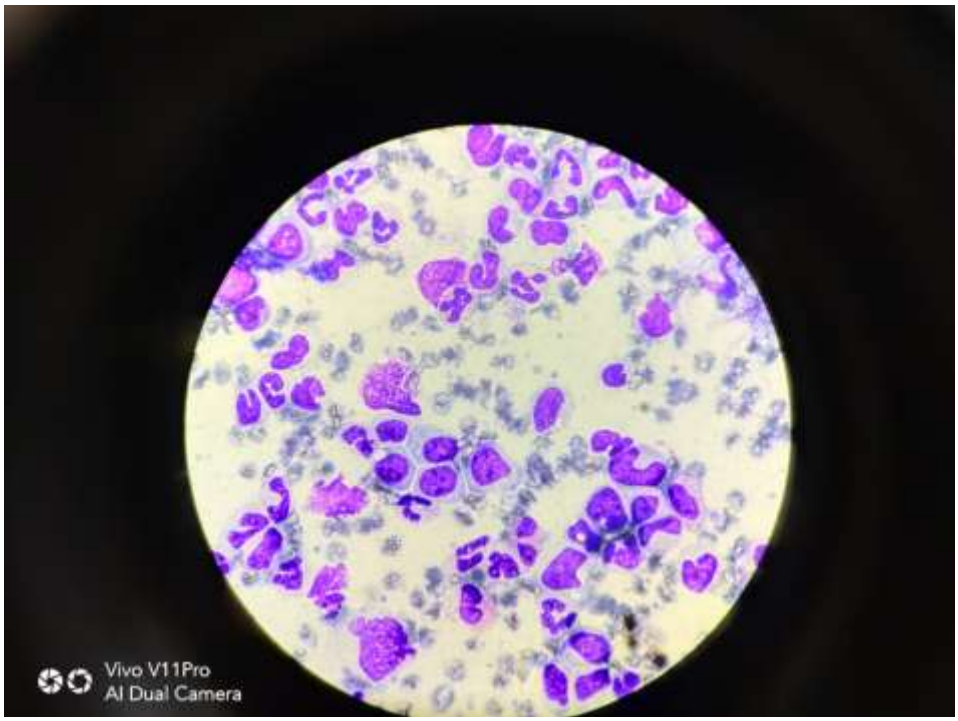


Figure-:100x showing myeloproliferation with monocytosis.



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IV. DISCUSSION-

APPROACH TO MONOCYT OSIS-

When monocytosis is recognized, steps should be taken to determine the clinical significance and need for more extensive clinicopathologic workup.

• Confirm the presence of monocytosis by blood smear review. Abnormal lymphocytes (eg, hairy cells or Sezary cells) can be misidentified as "monocytes" by automated hematology analyzers.

Certain leukemias (eg, hypogranular variant of AML with PML-RARA) can also mimic monocytic cells.

• Assess the absolute monocyte count. A relative monocytosis alone is more likely secondary or reactive (eg, in the setting of neutropenia or early bone marrow recovery/regeneration), and certain neoplasms require an AMC ≥1 × 109/L (eg, CMML or JMML in young children).

• Assess for other CBC abnormalities. Cytopenias (eg, neutropenia,anemia, or thrombocytopenia) or other cytoses (eg, neutrophilia, eosinophilia, basophilia, and lymphocytosis) may suggest an etiology or need for specific testing. Neutropenia or atypical lymphocytosis without dysplasia may suggest viral infection. Eosinophilia may prompt the need to exclude PDFGRA/B or FGFR1 rearrangement, PCM1-JAK2 fusion, mastocytosis, infection, parasite infestation, autoimmune disease, etc.

• Examine a peripheral blood smear with particular attention given to:

i) Monocyte morphology (eg, maturity and atypia). The presence
of promonocytes or monoblasts should raise concern for a myelomonocytic
neoplasm.

ii) Neutrophil morphology (eg, maturation, toxic changes, and dysplastic features including abnormal nuclear segmentation and/ or hypogranularity). The presence of significant granulocytic dysplasia and/or blasts should raise suspicion for a myelomonocytic neoplasm.

iii) Red cell morphology (eg, anisopoikilocytosis including dacrocytes, spherocytes, schistocytes, and sickle cells, Howell-Jolly bodies, Pappenheimer bodies, coarse basophilic stippling, and normoblastemia). These changes are less specific for neoplasia and may suggest other etiologies such as hemoglobin disorders, red cell membrane defects, hemolytic disorders, or splenectomy.

iv) Platelet morphology (eg, number, size, and granularity). Thrombocytosis or thrombocytopenia may indicate a reactive process such as inflammation or immune thrombocytopenia; dysplastic changes including large size and/or hypogranularity may suggest neoplasia.

v) Other features may also suggest an underlying cause (eg, the presence of microorganisms such as Plasmodium spp., atypical lymphocytosis associated with viral infections, or erythrophagocytosis due to immune-mediated hemolytic anemia).

If monocytosis is sustained, unexplained, and/or features concerning for a hematologic neoplasm are present, further worup should be done in the form of bone marrow examination, cytogenetic studies, flow cytometry, immunohistochemistry, cytochemical stains, special stains, and molecular genetic studies.

Splenomegaly, monocytosis (>1´109/L) in the peripheral blood and less than 20% of blasts in the bone marrow are the essential clinical and hematological criteria for JMML.

BONE MARROW EXAMINATION –

A bone marrow trephine biopsy and aspirate should be performed.Potential causes for monocytosis that may be detected or excluded by this route include acute and chronic hematologic malignancies, lymphoma, metastatic disease, infection, agranulocytosis, chemotherapy, and/or other drug or toxic effects. Apparent CMML based on blood findings may prove to be AML in the bone marrow.

AML-

By definition, if the percentage of blasts and/or promonocytes is 20% or more in the peripheral blood or bone marrow, then the diagnosis is AML. As previously noted, the distinction between promonocytes and abnormal or dysplastic monocytes or even dysplastic granulocytes can be quite challenging. Many AML cases with monocytic differentiation will fall under the general category of AML, not otherwise specified. This includes acute myelomonocytic leukemia, acute monocytic leukemia, and acute monoblastic leukemia. Distinction among these entities is primarily morphological and based on the percentage and specific types of monocytic precursors present. It is also worth mentioning that AML with PML-RARA, particularly the hypogranular variant, though not characterized by monocytic differentiation, can closely resemble a myelomonocytic or monoblastic neoplasm on morphologic review. In these cases, appropriate FISH or molecular genetic testing is required to further exclude an occult PML-RARA fusion.

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CMML -

Chronic myelomonocytic leukemia is the most likely of the MDS/MPNs to present with an absolute monocytosis ≥1 × 109/L and relative monocytosis ≥10%. This is important to keep in mind as BCRABL1-negative atypical chronic myeloid leukemia may meet the first criterion of absolute monocytosis, while the presence of ≥10%monocytes will exclude this diagnosis. Parameters fulfilling criteria for MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) such as ring sideroblasts ≥15%, sustained thrombocytosis ≥450 × 109/L, and SF3B1 and/or other MPN-related mutations including JAK2 mutations would be unlikely in CMML. However, as is typical for most MDS/MPNs, CMML will exhibit a combination of myeloproliferative features, such as leukocytosis including neutrophilia, marrow hypercellularity with or without reticulin fibrosis, intramedullary or extramedullary plasmacytoid dendritic cell nodules, and splenomegaly, plus features of myelodysplasia, including cytopenia(s) and morphologic dysplasia in at least one hematopoietic lineage (ie,granulocytic, erythroid, or megakaryocytic dysplasia).

JMML

The median age is 1.1-1.8 years with a male to female ratio of 2-3:1. (Hasle et al., 1999; Niemeyer et al., 1997; Passmore et al., 2003). Those with neurofibromatosis type 1 (NF-1) have a 200-fold increased risk of JMML. JMML is a rare type of childhood leukemia characterized by young age, hepatosplenomegaly, lymphadenopathy accompanied by infiltration of other organs, especially lungs, intestines and skin3. Splenomegaly invariably develops rapidly in the course of this disease, creating abdominal distension with considerable discomfort. Dry cough and tachypnea are caused by lung infiltration. WBC count is mostly elevated, but in contrast to chronic myelogenous leukemia (CML) rarely exceeds 100´109/L. Since prompt diagnosis is not always simple to make, morphological evaluation of the peripheral blood smear is often crucial. It demonstrates monocytosis with immature and dysplastic forms. An absolute monocyte count of _1000/mL is a prerequisite for the diagnosis6. Blasts may be present in the peripheral blood but their percentage is less than 20%. Typical peripheral blood findings include leukocytosis (usually less than 100 x 109/L) with variable degree of left shift, monocytosis (>1´109/L), and thrombocytopenia. Nucleated red blood cells are often identified in the peripheral blood. Myeloblasts average about 1-5% of total nucleated cells, and by definition, blasts account for <20% of cells. Bone marrow findings are not specific. The marrow is usually hypercellular with a mildly increased M:E ratio (typically 3-5:1), dispersed erythroid elements, and decreased numbers of megakaryocytes. Dysplasia is usually not prominent. Blasts are required to be less than 20%; monocytes are less prominent in the marrow than in the peripheral Bone marrow findings are not specific. The marrow is usually hypercellular with a mildly increased M:E ratio (typically 3-5:1), dispersed erythroid elements, and decreased numbers of megakaryocytes. Dysplasia is usually not prominent. Blasts are required to be less than 20%; monocytes are less prominent in the marrow than in the peripheral blood, and are usually enumerated at 5-10%

In patients fulfilling these criteria the diagnosis of JMML is further facilitated by the presence of one of the following: PTPN11/RAS/NF1 mutation, clinical diagnosis of neurofibromatosis1 (NF1) or monosomy 7. The diagnosis of JMML in patients without the PTPN11/RAS/NF1 mutation, clinica diagnosis of NF1 or monosomy 7 should be made by employing the standard criteria.

CML

Rare examples of BCR-ABL1-positive CML can present with monocytosis, particularly those with a p190 BCR-ABL1 fusion protein. A more common phenomenon is BCR-ABL1-negative myeloproliferative neoplasms (MPNs) presenting with or developing monocytosis during the disease course. One recent study reports monocytosis in 21% of PV patients.18 The identification of mutations in JAK2, CALR, or MPL is supportive of a myeloproliferative neoplasm and is not expected in CMML. Monocyte production increases during the course of Ph-positive CML, until monocytes account for as many as 10-20% of PB cells . To avoid the misdiagnosis of CML as CMML, it was proposed that the absence of relative monocytosis (a PB monocyte frequency of >8%; it was 8.5% in the present case) should be a criterion for the diagnosis of CML when the total number of leukocytes is higher than 20×109/L accompanied by prominent monocytosis and a hematological phenotype that is intermediate between those of CML and CMML.

FLOW CYTOMETRY

This can be performed on blood and/or bone marrow and may be helpful for assessing blast populations, other populations including

lymphocytes, and recognizing monocytic differentiation when morphology is equivocal.

IMMUNOHISTOCHEMISTRY/CYTOCHEMISTRY

As with flow cytometry, additional phenotyping may be necessary in tissue sections to visualize normal and abnormal populations including but not limited to myeloid cells, monocytic cells, erythroids, megakaryocytes, mast cells, lymphocytes, and plasma cells. Enumerating and assessing the distribution of blasts may also be facilitated. The utility of cytochemical staining for NSE and MPO in delineating immature monocytic and granulocytic cells has been discussed earlier.

CYTOGENETIC STUDIES

Chromosome analysis should be performed on every case when bone marrow is obtained for the workup of monocytosis. FISH studies may also be warranted, particularly when BCR-ABL1, PDFGRA, inv(16) or t(16;16), and PML-RARA must be confirmed or excluded.

MOLECULAR GENETIC TESTING

In select cases, testing for somatic mutations may be helpful for diagnosis and/or prognostication. MPN-related mutations such as JAK2,CALR, and MPL may favor an MPN with monocytosis in the appropriate context. Certain mutations may be of prognostic value (eg, ASXL1 or NPM1 in CMML). The potential for recognizing mutations in the absence of disease (eg, clonal hematopoiesis of indeterminate potential) should be kept in mind.

V. SUMMARY

Most cases of monocytosis will prove to be reactive in nature. Properevaluation is required to exclude the minority of cases which are neoplastic. This requires the initial assessment of clinical history, laboratory data, and morphology. Important clues to suggest a neoplastic process include an unexplained and persistent monocytosis, the presence of blasts/blast equivalents, and neutrophil dysplasia. Finding such clues should suggest the need for further workup to include bone marrow examination and appropriate ancillary studies such as flow cytometry, cytogenetics, and in some cases, molecular testing. Ultimately, careful and thorough integration of all available data is required for the most accurate diagnosis in this challenging area of hematopathology.