



# Differential Diagnosis and Workup of Monocytosis: A Systematic Approach to a Common Hematologic Finding

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## Abstract

**Purpose of Review** Monocytosis is a frequently encountered clinical condition that needs appropriate investigation due to a broad range of differential diagnoses. This review is meant to summarize the latest literature in the diagnostic testing and interpretation and offer a stepwise diagnostic approach for a patient presenting with monocytosis.

**Recent Findings** Basic studies have highlighted the phenotypic and functional heterogeneity in the monocyte compartment. Studies, both translational and clinical, have provided insights into why monocytosis occurs and how to distinguish the different etiologies. Flow cytometry studies have illustrated that monocyte repartitioning can distinguish chronic myelomonocytic leukemia, a prototypical neoplasm with monocytosis from other reactive or neoplastic causes.

**Summary** In summary, we provide an algorithmic approach to the diagnosis of a patient presenting with monocytosis and expect this document to serve as a reference guide for clinicians.

**Keywords** Monocytosis · Monocytes · Classical · Intermediate · Non-classical · Chronic Myelomonocytic Leukemia

## Introduction

Monocytes and their tissue-specific mature counterparts, macrophages, are key components of the mononuclear phagocyte system involved in ingestion of microorganisms and foreign material in various tissues. They also regulate inflammatory and immune responses by interacting with lymphocytes and serve as antigen-presenting cells by differentiating into dendritic cells [1]. Upon response to activating signals such as chemokines and cytokines, activated monocytes adhere and migrate to the sites of infection or inflammation through diapedesis. In addition, monocytes have a

poorly defined interaction with the coagulation cascade (Fig. 1).

Based on expression of lipopolysaccharide co-receptor, CD14, and FcγIII receptor, CD16, at least three functionally distinct populations of monocytes are known to exist in the body [2]. Classical monocytes (MO1, CD14<sup>++</sup>, CD16<sup>-</sup>) represent the largest subgroup involved in phagocytosis through the glycolytic and pentose phosphate pathway [2]. Conversely, the non-classical (MO3, CD14<sup>dim</sup>, CD16<sup>+</sup>) monocyte fraction is associated with oxidative phosphorylation pathway and protein metabolism, and the intermediate (MO2, CD14<sup>+</sup>, CD16<sup>+</sup>) subset is associated with antigen presentation to other immune cells [2, 3]. These associations with distinct pathways suggest diverse physiological roles for monocytes in healthy individuals. Recently, many groups have shown existence of transitional and intermediary subsets of monocytes with diverse functions, reflecting significant functional heterogeneity in the monocyte compartment [4, 5, 6••].

Several disease states are associated with monocytosis with diverse clinical presentations. This review is focused on how to accurately identify the underlying etiology in adult patients presenting with an elevated monocyte count. Readers are also referred to another comprehensive review on the topic [7•].

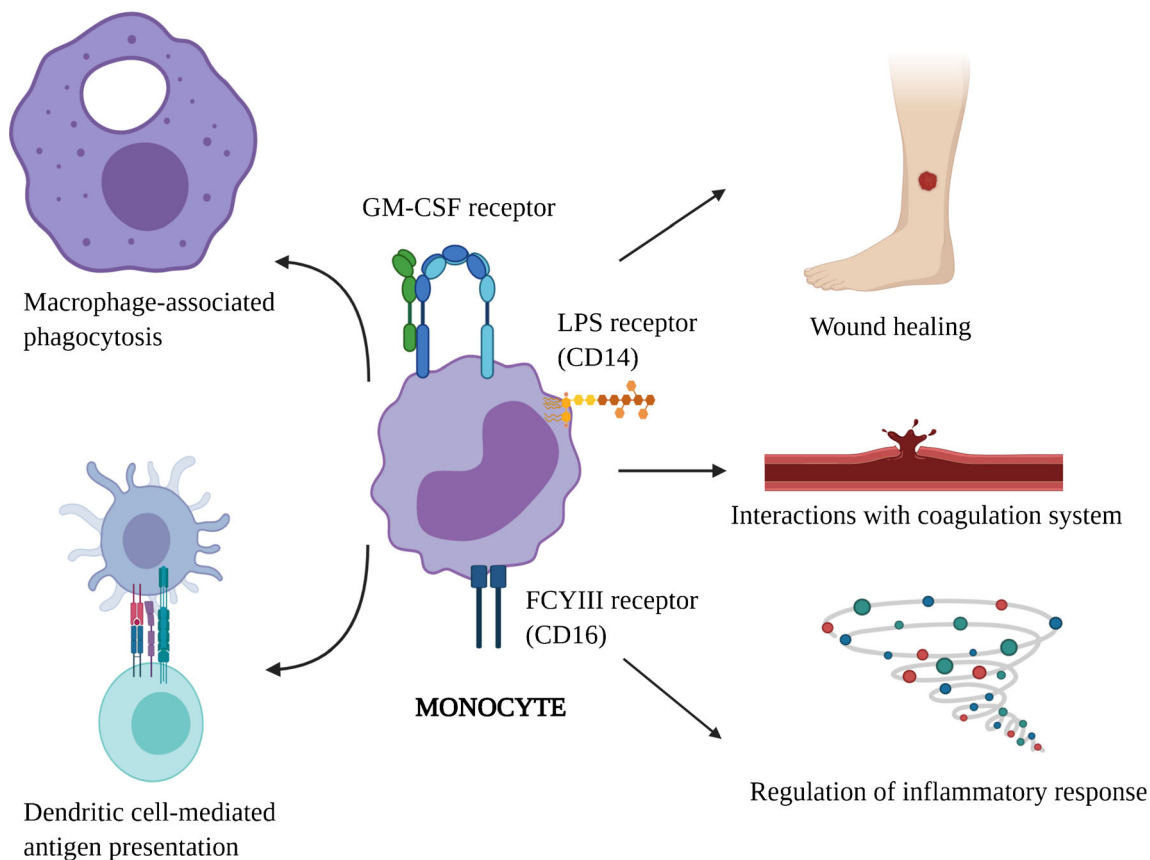
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**Fig. 1** The diverse functions of monocytes in humans. Monocytes are characterized by expression of several cell surface receptors. This figure highlights some of those receptors and the key monocyte-associated functions such as macrophage-associated phagocytosis, dendritic cell-

mediated antigen presentation, wound healing, interactions with coagulation cascade, and regulation of inflammatory responses (created with [BioRender.com](https://www.biorender.com))

## Monocytosis Definition

The normal absolute monocyte count ranges in adults ranges in between  $0.2\text{--}0.8 \times 10^9/\text{L}$ , with values varying significantly with age and sex. Under normal physiology conditions, monocyte counts are usually slightly higher in males; however total white blood cell count and other WBC types such as lymphocytes and granulocytes are not significantly different [8]. Further, monocytes are more sensitive to inflammatory stimuli in men than women likely secondary to sex hormone differences [8, 9]. Racial differences are only minimal, with some studies showing no significant differences [10], while others indicating a slightly lower absolute monocyte counts in Blacks and Asians compared to Caucasians [11, 12]. The World Health Organization defines persistent monocytosis as an absolute monocyte count  $\geq 1 \times 10^9/\text{L}$  with monocytes accounting for  $\geq 10\%$  of leukocytes persisting for  $\geq 3$  months [13].

## Differential Diagnoses of Monocytosis

The various causes of monocytosis can be divided into two broad categories: reactive or clonal (Table 1).

## Reactive Causes

*Transient causes:* Monocytosis can be seen in a patient with recovering bone marrow after cytotoxic chemotherapy [14]. Stressful events such as splenectomy [15], myocardial infarction [16], and exercise [17] can also result in monocytosis and are often transient and reversible [7•]. However, monocytosis is also a frequent occurrence in acutely ill patients, with one prospective study observing this finding in over a quarter of patients seen in a Swiss emergency department [18]. In this study, patients presenting with infections or respiratory illness were significantly more likely to present with monocytosis than other illnesses. Certain acute bacterial infections, such as leptospirosis [19] or listeriosis [20], can be classically associated with monocytosis. Recently, SARS-CoV-2-associated COVID-19 disease has been associated with increase in inflammatory  $\text{HLA-DR}^{++} \text{CD11c}^{++} \text{CD14}^{+}$  monocytes in mild cases, and dysfunctional  $\text{HLA-DR}^{\text{dim}}\text{CD163}^{++}$  and  $\text{HLA-DR}^{\text{dim}}\text{S100A}^{++}$  monocytes, disappearance of non-classical  $\text{CD14}^{\text{dim}}\text{CD16}^{+}$  monocytes in severe cases, further highlighting the important role of monocytes in regulating systemic inflammatory responses [21, 22]. However, the finding of monocytosis in the acute setting is neither sensitive nor

**Table 1** Table showing the differential diagnosis of monocytosis

Reactive	Clonal
<i>Transient</i>	<i>Acute neoplasms</i>
Bone marrow recovery	Acute monocytic or myelomonocytic leukemia
Exercise-induced	Dendritic cell leukemia
Acute infections	<i>Chronic neoplasms</i>
Splenectomy	Chronic myelomonocytic leukemia
Medication-induced	Juvenile myelomonocytic leukemia
Myocardial infarction	Myeloid neoplasms with PDGFRB rearrangement (Can mimic CMML)*
Stress-induced	Myeloid neoplasms with PDGFRA rearrangement*
<i>Persistent</i>	Myeloid neoplasms with FGFR1 rearrangement*
Chronic infections	Myeloid neoplasms with PCM1-JAK2 fusion*
Rheumatologic conditions	Chronic myeloid leukemia
Medication-induced	Myeloproliferative neoplasms with monocytosis:
	a. Essential thrombocythemia
	b. Polycythemia vera
	c. Primary myelofibrosis
	Systemic mastocytosis
	B and T cell malignancies
	Solid tumors

\*Associated with concomitant eosinophilia

specific for any particular etiology. The most appropriate and cost-effective diagnostic evaluation in the acute setting is to repeat monocyte count once the acute inflammatory response has resolved.

*Persistent causes:* A diverse group of subacute or chronic infections have been associated with monocytosis. These include syphilis [23], brucellosis [24], malaria [25], tuberculosis [26], visceral leishmaniasis [27], and rickettsial infection [28]. While these case reports and case series are intriguing, they should be interpreted with caution. Rather than suggesting a unique laboratory finding in these disparate infections, they more likely reflect a non-specific finding among a constellation of other clinical features.

Monocytosis can also be seen in chronic auto-inflammatory disorders, primarily divided into two major categories: (1) granulomatous disorders: sarcoidosis and inflammatory bowel disease (ulcerative colitis) and (2) systemic rheumatologic disorders including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and immune-mediated thrombocytopenia. Vasculitis (polyarteritis nodosa) and myositis [7•, 29], SLE and RA commonly present with leukopenia, including lymphopenia and neutropenia.

Medications can also result in monocytosis. While neutrophilia is more commonly seen with corticosteroid therapy, monocytosis has been reported [30]. Drugs such as ziprasidone [31], granulocyte colony stimulating factor (G-CSF, [32]), radiation therapy [33], and anti-thymocyte globulin [34] have all been associated with monocytosis [7•].

When evaluating for causes of a persistent reactive monocytosis, the most important approach begins with a thorough history of illness and physical examination, including an appropriate infectious diseases exposure history which includes assessment of tuberculosis risk, international travel history, and risk of zoonotic infections. Recurrent fevers, night sweats, and/or weight loss are supportive but are not specific for an occult infection since chronic inflammatory disorders and neoplastic causes can also manifest with these symptoms. Additional symptoms suggestive of a chronic systemic illness should warrant a review of systems covering features of rheumatic disorders. If clinically indicated, further testing should include auto-antibodies and imaging studies. Given the rarity of monocytosis as the presenting finding of rheumatic disease, attention may need to be focused on the differential diagnosis including infections and clonal etiologies. Additional/associated symptoms, temporal trends of the leukocyte and monocyte counts along with pharmacotherapy should be explored.

## Clonal Causes

Based on acuity of presentation, clonal causes can be divided acute and chronic neoplasms (Table 1). The acute neoplasms include acute myeloid leukemia (AML) and dendritic cell leukemia. Historically, the French-American-British (FAB) classification categorized monocytic acute leukemia into two subtypes: acute myelomonocytic leukemia (M4) and acute

monoblastic/monocytic leukemia (M5) [35]. In the 2017 World Health Organization classification, monocytic leukemias have been classified under AML, not otherwise specified (NOS) [13]. Chronic myeloid neoplasms with monocytosis include chronic myelomonocytic leukemia (CMML) and its pediatric counterpart also known as juvenile myelomonocytic leukemia (JMML), myeloproliferative neoplasms with monocytosis, myeloid neoplasms with *PDGFRB* (can mimic CMML), *PDGFRA* or *FGFR1* rearrangement or the provisional *PCMI-JAK2* fusion, and systemic mastocytosis.

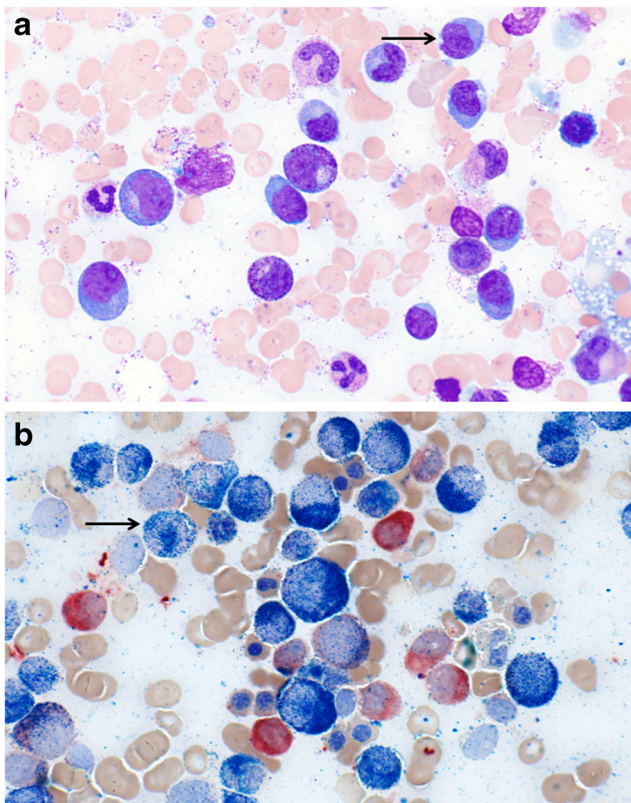
CMML is the prototypical myeloid neoplasm with monocytosis defined by the presence of monocytosis ( $\geq 1 \times 10^9/L$ ) with monocytes accounting for  $\geq 10\%$  of leukocytes in the absence of WHO-criteria for BCR/ABL1-positive chronic myeloid leukemia and myeloproliferative neoplasms, and absence of *PDGFRA*, *PDGFB*, and *FGFR1* rearrangements or *PCMI-JAK2* fusions, blast count  $< 20\%$  of cells in both bone marrow and peripheral blood, and presence of dysplasia in one or more lineages (absence of dysplasia does not exclude the diagnosis of CMML if there is evidence of clonal molecular or cytogenetic changes, and monocytosis is persistent ( $\geq 3$  months) [13, 36, 37]. Morphologically, it may be difficult to distinguish blasts from promonocytes or monoblasts and is counted together clinically when calculating total blast percentage in both peripheral blood and bone marrow assessment. Biologically, the combination of somatic variants in epigenetic (*TET2*, *ASXL1*, *IDH1/2*, or *DNMT3A*) and splicing factor genes (*SRSF2*, *ZRSR2*, or *SF3B1*) or signaling pathway genes (*RAS*, *JAK2* or *CBL*) results in monocytosis [38, 39]. The precise mechanism of monocytosis is unclear but may be at least partly explained by hypersensitivity to granulocyte-macrophage-colony stimulating factor (GM-CSF) signaling [40], which is also a relevant therapeutic target in CMML [41]. CMML is often associated by variants in the aforementioned group of genes; however it is also genetically heterogeneous, which indicates the existence of other mechanisms of monocytosis. On the contrary, JMML is more genomically homogenous and associated with *RAS* pathway genes (*PTPN11*, *KRAS*, *NRAS*, *NF1*, or *CBL*) but also characterized by GM-CSF hypersensitivity of myeloid progenitors [42]. Monocytosis can be seen in other chronic myeloid neoplasms such as myeloproliferative neoplasms (MPN), either at diagnosis or during the course of the disease. The presence of MPN features in the bone marrow or MPN-associated variants (*JAK2/CALR/MPL*) supports the diagnosis of MPN with monocytosis rather than CMML [13]. A minority of patients with myelodysplastic syndromes can also present with monocytosis (not otherwise meeting criteria for CMML); however they are likely at an early stage of evolution toward CMML [43] or can be classified as oligomonocytic CMML which is considered a pre-CMML condition due to similar clinico-pathologic and molecular features [44, 45••].

Some independent studies have assessed monocyte repartitioning as a diagnostic tool in CMML. The original study by Selimoglu-Buet D et al. established that the expansion of the classical fraction of monocytes ( $> 94\%$ ) has been shown to be associated with a sensitivity of 90.6% and specificity of 95.1% in diagnosing chronic myelomonocytic leukemia [46••]. Subsequent studies reaffirmed this finding [47, 48]. One study noted that decreased percentage of the MO3 fraction ( $< 1.13\%$  in peripheral blood,  $< 2.42\%$  in bone marrow) has a better sensitivity and specificity when compared with MO1 fraction expansion ( $> 94\%$ ) for the diagnosis of CMML [49]. However, there are some studies that advise caution when using this approach [50]. In the presence of co-existing rheumatologic or other reactive conditions, there is a preferential expansion of MO2 fraction, and therefore the aforementioned diagnostic cut-offs for the MO1 or MO3 fraction may not be as sensitive or specific for the diagnosis of CMML [50, 51]. This could be partly related to the transcriptomic heterogeneity in the monocyte compartment, especially in the MO2 compartment [6••], indicating the existence of additional functionally distinct subtypes beyond the three fractions. Although we recommend the use of this assay in distinguishing CMML from other neoplastic causes of monocytosis, caution should be exercised in patients with co-existing rheumatologic conditions or disorders. Recent techniques in cell phenotyping such as time of flight mass cytometry (CyTOF) can be potentially used to help further refine the diagnostic accuracy of monocyte repartitioning in CMML, by employing markers other than CD14 and CD16 such as CD36, CCR2, HLA-D4 and CD11c [50, 52•, 53••, 54].

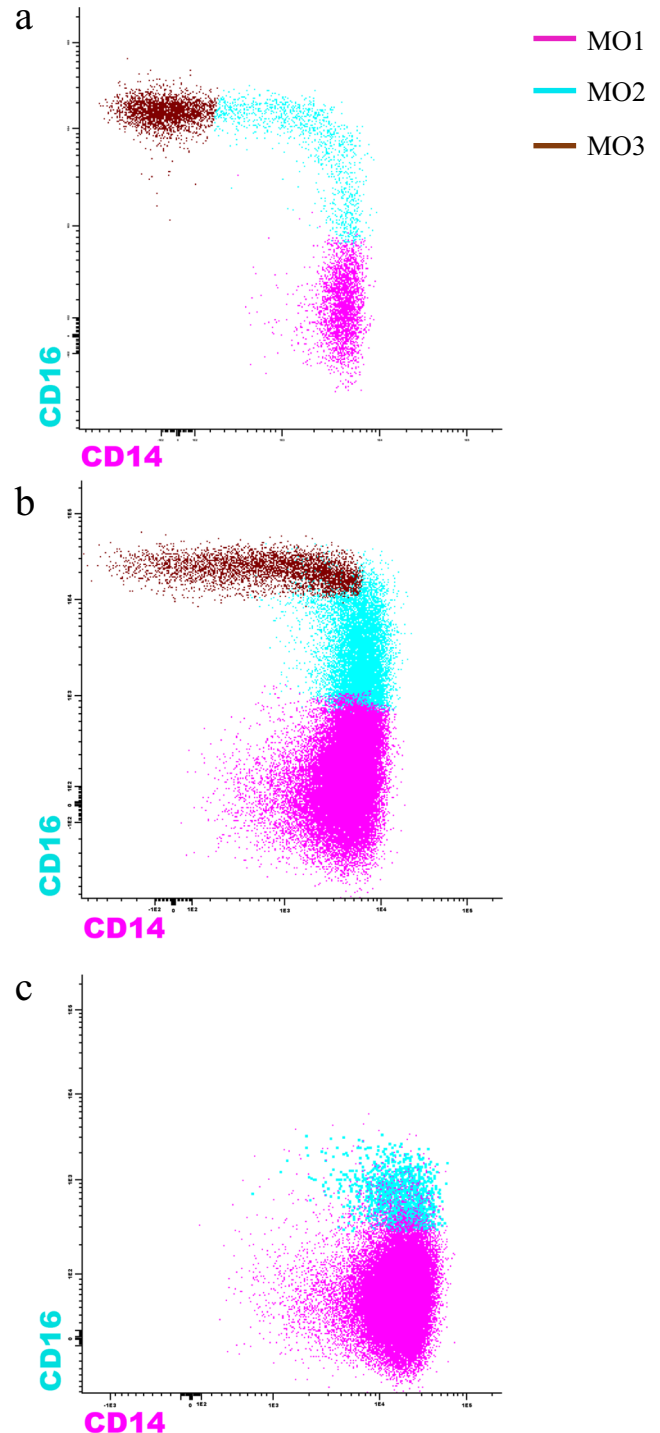
### Approach to Evaluation of a Patient with Monocytosis

When approaching a patient with monocytosis, we recommend assessing chronicity and pattern of monocytosis, along with a comprehensive history and physical exam. Morphology of the monocytes should be confirmed on a peripheral smear to assess dysplasia. Monocytosis plus dysplasia or additional complete blood count abnormalities such as anemia, thrombocytopenia, eosinophilia, or basophilia, or clinical indicators of malignancy such as splenomegaly, bone pain, or weight loss among others indicate a clonal etiology and in these cases a bone marrow aspirate/core biopsy assessment should be performed. In addition to standard morphological and cytogenetic/molecular assessment, dual staining with alpha-naphthyl butyrate-esterase and naphthol AS-D chloroacetate esterase may help in distinguishing the monocytic component and also in

distinguishing monocytes from monoblasts and/or promonocytes (Figs. 2 and 3) [55]. Dual staining with both the aforementioned dyes indicates the existence of dysmyelopoietic cells, whereas pure monocytic cells stain positive only for alpha-naphthyl butyrate-esterase [55]. In the absence of dysplasia and isolated monocytosis, a repeat complete blood count in 3 months can be considered. Resolution of monocytosis at that time-point indicates a reactive etiology. However, if the monocytosis is persistent, then a comprehensive clinical assessment for reactive causes should be undertaken, sometimes in coordination with other sub-specialist experts such as rheumatology or infectious diseases. Monocyte compartment flow cytometry assessment can be considered. However, if there are concomitant rheumatic conditions, then we recommend proceeding straight to bone marrow evaluation due to the aforementioned limitations of monocyte repartitioning. The expansion of CD16+ fraction of monocytes often indicates a non-neoplastic etiology; however it should be considered that clonal disorders such as CMML and MDS have an established association with rheumatic conditions [56, 57]. In other words, both reactive and



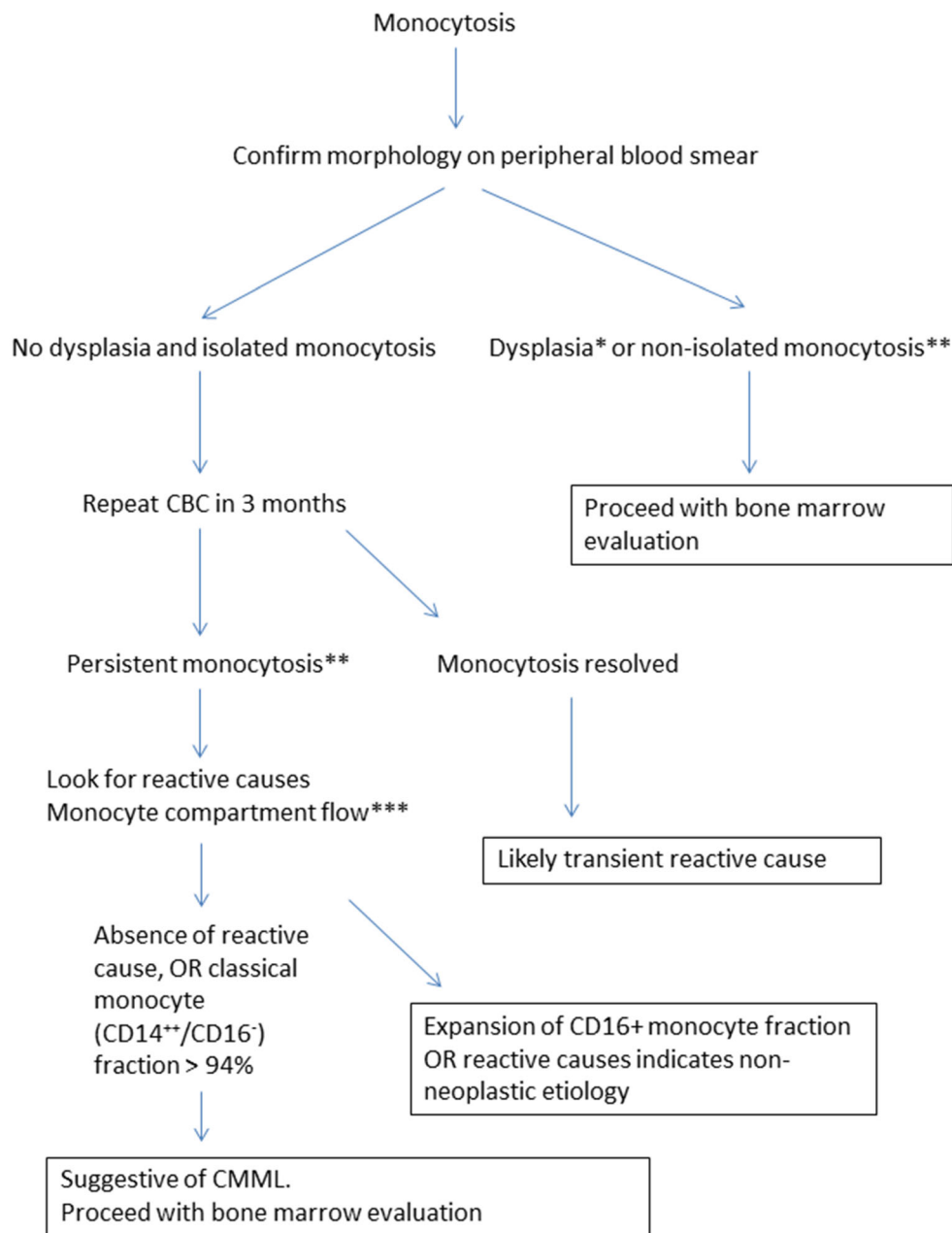
**Fig. 2** Bone marrow aspirate evaluation of a patient with chronic myelomonocytic leukemia. **a** Shows hematoxylin and eosin staining at  $\times 1000$  magnification. Arrow points to monocytes. **b** Shows dual staining of CMML bone marrow aspirate with alpha-naphthyl butyrate-esterase and naphthol AS-D chloroacetate esterase indicating increased monocytic cells (staining only alpha-naphthyl butyrate-esterase) for shown at  $\times 1000$  magnification (Courtesy: Kaaren K Reichard, MD)



**Fig. 3** Figure showing flow cytometry-based monocyte repartitioning patterns in normal individuals, reactive monocytosis and chronic myelomonocytic leukemia (CMML). In CMML, there is a preferential expansion of the classical ( $> 94\%$ , MO1, CD14<sup>+</sup>, CD16<sup>-</sup>) monocyte fraction as opposed to intermediate (MO2, CD14<sup>+</sup>, CD16<sup>+</sup>) and non-classical fraction (MO3, CD14<sup>dim</sup>, CD16<sup>+</sup>) (Courtesy: Michael M. Timm)

clonal causes could exist in the same individual and appropriate judgment should be employed in each clinical situation (Fig. 4).

**Fig. 4** Figure outlining a stepwise approach for a patient presenting with monocytosis. Abbreviations: CBC = complete blood count; CMML = chronic myelomonocytic leukemia



\*Absence of dysplasia does not exclude clonal or neoplastic causes.

\*\*Non-isolated monocytosis means presence of additional abnormalities in complete blood count testing such as basophilia, eosinophilia, anemia or thrombocytopenia OR clinical indicators of malignancy such as splenomegaly, bone pain, weight loss etc. and should prompt a bone marrow evaluation and appropriate malignancy work-up.

\*\*\*In the presence of rheumatic conditions, the sensitivity and specificity of monocyte compartment flow cytometry in the diagnosis of CMML is lower, and bone marrow evaluation should be considered.

## Conclusion

In summary, monocytosis is a common hematologic finding with a broad range of etiologic possibilities. We provide an algorithmic approach for investigating

monocytosis and highlight the recent advances in phenotypic characterization of monocytes. Future areas of research should involve characterization of monocyte compartment heterogeneity, both in normal and disease-states through novel technologies such as

CytoF. This would not only increase the precision of monocyte repartitioning as a diagnostic tool but also offer novel insights into disease biology.

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## Declarations

**Conflict of Interest** The authors declare no competing interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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