Blood Cells

Morphology & Clinical Relevance

2nd edition

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American Society for Clinical Pathology
Press
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Preface to Blood Cells, 2nd Edition

The 1st edition of Blood Cells has been a “best seller” since its release and has gained wide acceptance from the many different users: students, teachers, and practitioners alike, throughout the world. The reviews have been very encouraging and have highlighted the salient features of the book, which offers something for everyone: the experienced, the inexperienced, the trainer, and the trainee.

This 2nd edition of Blood Cells maintains all of the good features of the 1st edition that proved helpful to thousands of users in their everyday professional practice and/or learning process. There are too many changes throughout the new text to list. But larger scale modifications and additions offered in the 2nd edition include:

(a) incorporation of and expanded set of comparative reference values/features tables in chapters throughout the text (while maintaining a gathered set of quick reference tables in a new chapter 27)

(b) expansion of chapter 14 on microorganisms that may be seen in peripheral blood smears, particularly of the malarial & microfilarial parasites

(c) treatment of hereditary Heinz body hemolytic anemia in chapter 16 and reactive plasmacytosis in chapter 18

(d) up-to-date revision to chapters 20 (acute leukemias), 21 (chronic leukemias/chronic myeloproliferative neoplasms), 22 (myelodysplastic syndromes & myelodysplastic/myeloproliferative neoplasms), and 23 (chronic lymphoproliferative disorders) to reflect the latest WHO classification of tumors of hematopoietic & lymphoid tissues

(e) incorporation of over 150 additional images expanding the range of morphologic variation depicted and adding cell types & entities not previously illustrated

(f) addition of a completely new set of self assessment questions

We have also modified both the index and the table of contents to make it even easier to navigate all the content.

This edition will also see the 1st e-book version of Blood Cells, to enhance its appeal to many more than the thousands already in love with the 1st edition. We wish to convey our sincere thanks to all the reviewers and users of the 1st edition for their thoughtful and encouraging comments*, and we hope that readers/users of the 2nd edition will be even more pleased with the work. We are grateful to Joshua Weikersheimer of the ASCP Press for his care in improving the design, quality, and organization of the book and for help in obtaining many new images for this edition.

Gene Gulati, PhD & Jaime Caro, MD

Blood cells come in different sizes and shapes in health and in disease. The degree of such a variation in health is relatively small but it may become significantly larger in certain conditions. To be successful in practice of hematology, be it in a classroom, laboratory, clinician's office, outpatient clinic, or an inpatient unit of a hospital, it is important for every practitioner to be familiar with the characteristics and clinical relevance of individual normal and abnormal cells and with the morphologic findings associated with various clinical conditions. This atlas is designed to provide such information in a concise and clinically relevant manner for students, teachers, and practitioners of hematology at all levels.

Examination of an appropriately prepared and stained blood smear often provides information that is helpful in ruling in or out clinically suspected condition(s). At times, it may even provide a definite diagnosis not suspected from the clinical findings. In order to detect, identify, and relate all blood cell findings to specific clinical condition(s), the examiner should be either familiar with all features of all normal and abnormal cells along with those of artifacts which may mimic blood cell abnormalities and/or at least have available near the microscope a handy source of reference to guide him/her in such an endeavor. This manuscript describes in a concise, yet succinct, manner almost all blood smear findings a practitioner of hematology may encounter in his/her practice. The vast collection of photomicrographs presented in this manuscript represents the lifetime experience of the authors in their practice of hematology, with significant contribution from Bong H Hyun, MD, the mentor of the primary author. The authors have attempted to present the photomicrographs in the form actually encountered in daily practice rather than selecting only the best appearing. The trainees in hematology will find the basics provided in the manuscript invaluable in the learning process while the practitioners will find the entire atlas to be a useful resource for teaching and/or daily practice.

*Blood Cells* is organized into 6 sections. Artifacts, artifactual changes in blood cells, contaminants, and miscellaneous findings, along with an approach to blood smear examination, are covered in the 1st section. The morphology and clinical relevance of red cells, white cells, and platelets, and their respective precursors, both normal and abnormal, are described in the 2nd section. The 3rd section illustrates morphology of various organisms/parasites encountered in blood smears. Peripheral blood findings with emphasis on morphologic changes associated with various disorders/conditions are discussed in the 4th section. The 5th section compares and contrasts blood cells with their mimics, citing helpful distinguishing features throughout. The Quick Comparative Reference Values & Features portion tabulates comparative laboratory findings and features of all blood cells, their precursors and various hematologic disorders and comprises the last section.

A special feature of *Blood Cells* is the presentation of normal and abnormal morphology of individual cell types in proximity, wherever possible. Another exclusive feature of *Blood Cells* is that (in order to be all inclusive to the extent feasible) the authors have, without worrying about redundancy, utilized multiple cases to illustrate morphologic features associated with individual clinical conditions. The chapters are organized in a logical manner thus making it easy for the reader to find and pursue a desired subject matter. All photographs presented in this atlas were taken from Wright or Wright-Giemsa stained blood smears at 1,000× magnification, except wherever indicated otherwise.

*Gene Gulati, PhD, SH(ASCP)*

*Jaime Caro, MD*
List of Quick Comparative Reference Values & Features Tables

<table>
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<th>Description</th>
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<tr>
<td>t27.1</td>
<td>Red cell morphology compared with corresponding automated red cell indices</td>
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<td>t27.17</td>
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<td>t27.18</td>
<td>Chronic myeloproliferative disorders</td>
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<td>t27.19</td>
<td>Myelodysplastic syndromes</td>
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<tr>
<td>t27.20</td>
<td>Immunophenotypes of chronic lymphoproliferative disorders</td>
</tr>
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</table>
Any 1 or more of the following organisms may be seen in the peripheral blood: malaria, Babesia, Anaplasma, Ehrlichia, cocci, bacilli, fungi (Histoplasma, Candida, Cryptococcus), Leishmania, Toxoplasma, Borrelia, Bartonella, trypanosomes, and microfilariae. With the exception of Ehrlichia and Anaplasma, which are almost always seen within cells, and microfilariae, which are extracellular, all organisms may be present intracellularly and/or extracellularly. Morphologic characteristics of these organisms are described here.

### Intracellular organisms

#### Anaplasma

**synonyms:** formerly Ehrlichia

*Anaplasma* appear as clusters of purple dots within intracytoplasmic vacuoles (phagosomes) of neutrophils and the infection has recently been renamed from human granulocytic ehrlichiosis (HGE) to human granulocytic anaplasmosis (HGA). Morphologically, these clusters of purple dots or so-called elementary bodies of *Anaplasma* resemble a mulberry and hence are often referred to as morulae. Nonspecific laboratory features associated with HGA include leukopenia, thrombocytopenia, and elevated levels of serum transaminases. Anemia with normocytic and normochromic red cells may also be noted in some cases. Clinical manifestations of HGA are similar to those of other tick-borne illnesses including lyme disease, borreliosis, and babesiosis, and are more severe in the elderly or immunocompromised. There are also reports of patients co-infected with HGA and one of the other tick-borne diseases. The HGA is generally seen in the northeast and midwest. It is caused by *Anaplasma phagocytophilum*. Serologic and molecular tests are available for confirming the diagnosis.

#### Ehrlichia

**synonyms:** none

Clinical and laboratory findings of ehrlichiosis (human monocytic ehrlichiosis [HME]) are similar to that of anaplasmosis (HGA) except (a) the morulae of *Ehrlichia* are found in monocytes instead of neutrophils, (b) it is caused by *Ehrlichia chaffeensis*, and (c) it is seen in the southeast, south-central and mid-Atlantic regions of the United States.

### Organisms that may be intracellular or extracellular

#### Malaria & Babesia

**Malarial parasites**

*Plasmodium species* are the most widespread worldwide including temperate zones, *P falciparum* occurs primarily in the tropical countries, *P ovale* is prevalent mainly in the west coast of Africa, and *P knowlesi* has been reported in Malaysia and other southeast Asian countries. Travel history is important for the diagnosis, which must, however, be confirmed by laboratory investigation. Microscopic examination of thin and thick blood smears (stained with a Romanowsky stain, such as Wright, Wright-Giemsa, and/or Giemsa) by an experienced person for the presence of parasites is considered the gold standard.
for the diagnosis of malaria and for speciation of the parasite. Microscopic examination of thick blood smears is time-consuming and may not be fruitful or necessary in all cases, especially when the parasite speciation is feasible from the microscopic examination of the thin blood smear. Additional diagnostic tools, available in some but not all clinical laboratories worldwide and at CDC in the United States, include serologic tests, rapid immunologic assays (rapid diagnostic tests, eg, Binax Now Malaria test), and PCR based molecular assays. Serologic tests detect antibodies against malaria parasites and hence measure past exposure rather than current infection. Rapid immunologic test is used in some laboratories as an initial diagnostic step, particularly in off hours, when microscopic examination of the blood smears by an experienced person is not feasible. It is, however, recommended that the rapid diagnostic test be followed by the microscopic examination of the blood smear to confirm at least the negative results. Because of overlap in the morphologic characteristics of various Plasmodium species, one may need to resort to the molecular assay for the definitive diagnosis and speciation in some cases. It has been reported that a definitive diagnosis of Plasmodium knowlesi can only be made, at least at this time, with a molecular assay. The morphologic features that may be helpful in the differential diagnosis of Plasmodium species, at least in some cases, are described below and outlined in 14.1. The degree of parasitemia, as determined by counting 1,000 red cells on the stained thin blood smear and assessing the percentage of infected red cells, is considered helpful in choosing the course of treatment. Nonspecific laboratory findings may include any or all of the following: a variable degree of normocytic normochromic anemia, thrombocytopenia, neutrophilia with left shift, a few reactive lymphocytes, a few plasmacytoid lymphocytes or plasma cells, reticuloctysis, increased bilirubin, increased lactate dehydrogenase (LDH), increased blood urea nitrogen (BUN), increased creatinine, decreased glucose, and acid-base disturbances. Destruction of parasitized red cells in the spleen may lead to splenomegaly in chronic malarial infection.

### 14.1 Differential morphologic characteristics of Plasmodium species & Babesia in the blood smear

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>P vivax</th>
<th>P falciparum</th>
<th>P malariae</th>
<th>P ovale</th>
<th>P knowlesi</th>
<th>Babesia</th>
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**Trophozoites**

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**Schizonts**

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<td>8-36†</td>
<td>6-12</td>
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**Gametocytes**

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<th>may be</th>
<th>may be</th>
<th>na</th>
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<td>round or ovoid</td>
<td>ovid or round</td>
<td>round or ovoid</td>
<td>na</td>
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<td>Tetrad</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>may be</td>
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<td>rare</td>
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†seen with Giemsa stain, ‡usually not seen in the blood; na=not applicable
III: Infectious Agents in Blood

Red cells containing *P. vivax*

*synonyms: none*

*i14.5-i14.7*

These cells are slightly macrocytic but normal in shape, and usually contain Schüffner dots (coarse red granules), particularly when stained with Giemsa. All stages of the organism development, that include trophozoites, schizonts, and gametocytes, may be seen in the blood. Trophozoites are seen in the form of small rings (early trophozoites) or large rings with ameboid cytoplasm (late trophozoites). Individual red cells usually contain 1 ring but rarely 2 rings may be seen in individual red cells. Each trophozoite has a single chromatin dot, which stains red, and a variable amount of cytoplasm, which stains blue. A schizont consists of 12-24 merozoites in random configuration with a dense central yellowish-black pigment. Each merozoite consists of a red chromatin dot and blue cytoplasm. A gametocyte may be large (macrogametocyte) or small (microgametocyte) and consists of a large, eccentrically placed, red chromatin dot, abundant blue cytoplasm, and pink-orange-yellow pigment within its cytoplasm.

*P. falciparum*

*synonyms: none*

*i14.8-i14.10*

This organism is characterized by the presence of only the trophozoite and in some cases also gametocyte stage of organism development in the peripheral blood. Red cells containing the organisms are of normal size and shape but those containing the gametocytes appear a little stretched out giving them the appearance of ovoid cells. Schüffner dots are absent. Trophozoites exist only in the ring form. Individual rings may contain 1 or 2 red chromatin dots with small amount of blue cytoplasm, which is nonameboid. Ring forms of *P. falciparum* are generally smaller than the ring forms of *P. vivax*. Applique forms (ring located near the periphery of the red cell) may also be seen. The presence of multiple rings in individual red cells is not an uncommon finding. Schizonts are rarely seen in the blood smear. Gametocytes are banana shaped or crescent shaped with a large central chromatin dot and abundant blue cytoplasm essentially filling most, if not all, of the red cell. The number of gametocytes seen in the blood smear is usually very small but their presence is diagnostic of *P. falciparum*.

Red cells containing *P. malariae*

*synonyms: none*

*i14.11-i14.13*

These cells are normal in size and shape. Schüffner dots are absent. All stages of organism development may be seen in the peripheral blood. Early trophozoites appear in the form of small rings, each of which consists of 1 red chromatin dot and a small amount of blue cytoplasm. Late trophozoites appear as large rings, each with 1 chromatin dot and abundant, blue, ameboid cytoplasm. Each schizont consists of 8-12 merozoites in a rosette configuration with a dense central yellow-black pigment. Each merozoite consists of a red chromatin dot and a small amount of blue cytoplasm. Gametocytes are small, round structures and fill up ~1/2 of the red cell. Each gametocyte has a large, eccentric, red chromatin block and abundant blue cytoplasm with pink-orange-yellow pigment.

Red cells containing *P. ovale*

*synonyms: none*

*i14.14-i14.16*

These cells are oval/ovoid and slightly macrocytic and contain Schüffner dots (coarse red granules), particularly when stained with Giemsa. All stages of organism development may be seen in the peripheral blood. Early trophozoites appear in the form of small rings, each of which consists of 1 red chromatin dot and a small amount of blue cytoplasm. Late trophozoites appear as large rings, each with 1 chromatin dot and abundant, blue, ameboid cytoplasm. Each schizont consists of 4-16 merozoites in a rosette configuration and each merozoite consists of a red chromatin dot and a small amount of blue cytoplasm. Gametocytes are small, round structures and fill up ~1/2 of the red cell. Each gametocyte has a large, eccentric, red chromatin block and abundant blue cytoplasm with pink-orange-yellow pigment.
Red cells containing *P knowlesi*

synonyms: none

These cells are of normal size and shape. All 3 developmental stages (trophozoites, schizonts, and gametocytes) may be seen in the peripheral blood. Early trophozoites appear in ring form (bluish), usually with a single red chromatid dot. However, ring forms with 2 chromatid dots (often at opposing poles of the ring) or even 3 chromatid dots may be encountered. Generally, each infected red cell contains 1 ring but 2 or more rings per red cell may be present in some red cells in some cases. Applique forms (ring located near the periphery of the red cell) may also be seen. Late or mature trophozoites appear as rings that are slightly larger, amoeboid and irregular in shape with thickened/denser bluish cytoplasm, and usually a prominent red chromatid dot. In some red cells the cytoplasm, instead of forming a ring, may extend across the red cell and form a bandlike structure, as is the case with *P malariae*. Stippling and Schüffner dots are generally absent in trophozoites. A schizont occupies 2/3 to nearly the whole red cell and contains 2-5 divided chromatid masses and 8-16 merozoites. Fine stippling (sometimes referred to as Sinton & Mulligan stippling) and malarial pigment in the form of brownish black masses or small granules may be evident in red cells containing schizonts. The gametocytes are seen, but infrequently and that also in a small number of red cells and when present, they appear round, occupy 2/3 of to nearly the entire red cell, and contain compact red chromatin and dark brown pigment scattered throughout the bluish cytoplasm.

Babesia

synonyms: none

*Babesia* organisms may be seen within or outside the red cells in the peripheral blood of patients with severe babesiosis, which occurs more commonly in splenectomized or immunosuppressed individuals. Babesiosis is generally transmitted by ticks. Cases of transfusion-associated babesiosis have also been reported. It is endemic in parts of Massachusetts and the east coast and has been reported in California, Indiana and Wisconsin. The organisms involved may represent *B microti*, *B bovis*, *B divergens* or as yet unrecognized species of *Babesia*. Only the ring forms (merozoites/trophozoites) are seen in the blood. Individual red cells may contain single or multiple (up to 12 have been reported) rings and each ring may contain 1, 2 or 3 chromatin dots, which stain red-purple with Wright or Wright-Giems. Rings with 3 chromatid dots are considered specific for *Babesia*, as are the 4 rings arranged in a tetrad form, appearing like a “Maltese cross.” Individual rings are small (1-5 μm) and may be round, oval, elongate, ameboid or pyriform. The cytoplasm is agranular and stains blue with Wright or Wright-Giemsa. Patients with subacute or chronic babesiosis may have very low level of parasitemia and consequently the organism may not be detectable in the blood smear. Nonspecific laboratory features that may be associated with babesiosis include bicytopenia (anemia & thrombocytopenia) or pancytopenia and elevated hepatic enzymes in serum. Serologic tests and the clinical history are especially helpful in the diagnosis of such cases. Molecular tests are also available for confirming the diagnosis.
Bacteria

Cocci

Cocci are typically round organisms of uniform size (usually ~1 μm in diameter) seen extracellularly or within certain white cells, primarily neutrophils, bands and monocytes. They may occur singly, in pairs, in clusters and/or in chains and generally stain dark blue, purple or black with Wright or Wright-Giemsa. Gram stain is necessary to classify them into Gram+ or Gram−. Their presence in the peripheral blood may be referred to as coccemia, bacteremia or septicemia. Blood culture is the method of choice for definite identification and speciation. Nonspecific hematologic findings that may be associated with septicemia generally include a variable degree of usually normocytic normochromic anemia, neutrophilia with left shift or leukemoid reaction, and a variable platelet count, which may be increased, normal or decreased. Neutropenia with left shift of neutrophils has also been associated with septicemia in some cases. Cocci in the peripheral blood smear, though seen rarely, may be associated with a variety of conditions including severe burns, immunosuppressive states, meningitis, pneumonia, peritonitis, cholangitis, traumatic or surgical wounds, empyema, intestinal obstruction, biliary obstruction, postpartum endometritis, and septic abortion.

Bacilli

Bacilli are rod shaped organisms that may also appear extracellularly or within phagocytic cells (eg, monocytes, neutrophils and bands). They may also occur singly, in pairs, and/or in chains. Rarely, they may occur in clusters. Staining characteristics are variable between pale blue to purplish black with Wright or Wright-Giemsa. Gram stain is necessary to classify them into Gram+ or Gram−. Some of the bacilli, such as Mycobacterium tuberculosis and Mycobacterium avium intracellulare, are acid-fast stain positive. The presence of bacilli in the peripheral blood may be referred to as bacillemia, bacteremia or septicemia. Nonspecific hematologic findings that may be associated with septicemia generally include a variable degree of usually normocytic normochromic anemia, neutrophilia with left shift or leukemoid reaction, and a variable platelet count, which may be increased, normal or decreased. Neutropenia with left shift of neutrophils has also been associated with septicemia in some cases. Bacilli in the peripheral blood smear, though seen rarely, may be associated with a variety of conditions including severe burns, immunosuppressive states, tuberculosis, infection with Mycobacterium avium intracellulare, pneumonia, peritonitis, cholangitis, traumatic or surgical wounds, empyema, intestinal obstruction, biliary obstruction, postpartum endometritis, and septic abortion.

Bartonella

Bartonella bacilliformis is the causative agent for bartonellosis that occurs primarily in Columbia, Ecuador and Peru. The disease is also known as Oroya fever or Carrion disease. It is transmitted by sandflies. The organism appears as round or rod shaped coccobacilli either adhered to or within red cells. Hemolytic anemia of variable severity (mild to marked) is a common complication of this febrile disorder. Severe anemia may be associated with reticulocytosis and normoblastemia. Leukocytosis with left shift of neutrophils and/or lymphocytosis may also be noted.
Various species of the genus *Borrelia*, a spirochete, cause relapsing fever. *Borrelia recurrentis* is the causative agent of louse-borne relapsing fever, whereas several different species are known to cause tick-borne relapsing fever. *Borrelia recurrentis* organisms, in the shape of pale staining curved coils, may be seen in the blood smear during the febrile period. With the production of antibodies, the organisms disappear and the fever subsides. Relapse(s) occur after a week or so, due to production of new antigenic variants of the organism. *Borrelia burgdorferi* organisms, causative agent of Lyme disease, are usually not seen in the blood smear. *Borrelia recurrentis* infection has been noted primarily in South America and African countries. Nonspecific hematologic findings that may be associated with borreliosis generally include a variable degree of usually normocytic normochromic anemia, neutrophilia with left shift, and a variable platelet count, which may be increased, normal or decreased. Neutropenia with left shift of neutrophils has also been associated with borreliosis in some cases.

**Borrelia**

*synonyms: spirochete*

*Borrelia* organisms, in the shape of pale staining curved coils, may be seen in the blood smear during the febrile period. With the production of antibodies, the organisms disappear and the fever subsides. Relapse(s) occur after a week or so, due to production of new antigenic variants of the organism. *Borrelia burgdorferi* organisms, causative agent of Lyme disease, are usually not seen in the blood smear. *Borrelia recurrentis* infection has been noted primarily in South America and African countries. Nonspecific hematologic findings that may be associated with borreliosis generally include a variable degree of usually normocytic normochromic anemia, neutrophilia with left shift, and a variable platelet count, which may be increased, normal or decreased. Neutropenia with left shift of neutrophils has also been associated with borreliosis in some cases.

**Fungal organisms**

*synonyms: yeast*

Fungal organisms in the peripheral blood smear, though seen rarely, include various species of *Candida*, *Cryptococcus*, *Histoplasma*, and rarely others. Among these, *Histoplasma* and *Candida* are seen relatively more often than others in the peripheral blood and bone marrow. Special stains and culture are the methods of choice for definite identification and speciation. The presence of fungal organisms in the peripheral blood may be referred to as fungemia, septicemia, or named after the individual fungal species, eg, candidiasis, histoplasmosis, and cryptococcosis. Nonspecific hematologic findings that may be associated with fungemia generally include a variable degree of usually normocytic normochromic anemia, neutrophilia with left shift or leukemoid reaction, and a variable platelet count, which may be increased, normal or decreased. Neutropenia with left shift of neutrophils has also been associated with fungemia in some cases.

*Histoplasma* may be seen extracellularly and/or within some of the phagocytic cells (primarily the monocytes/macrophages) in the blood, bone marrow, and/or various other tissues and body fluids. It is a budding yeast but the organisms generally appear in the shape of a crescent or ring surrounded by a clear area called halo. The organisms stain purplish red with Wright or Wright-Giemsa. Their presence in the peripheral blood and/or other tissues including bone marrow is referred to as histoplasmosis. Disseminated histoplasmosis typically occurs in immunosuppressed patients.

Among its various species, *Candida albicans* is the one most commonly encountered in the peripheral blood. It may appear either as a round or oval, dark blue-red structure surrounded by a clear zone or as a budding yeast in the shape of a pair of round or oval dark blue-red structures surrounded by a clear zone. These organisms may also be seen extracellularly or within phagocytic cells such as monocytes and neutrophils. Their presence in the peripheral blood, generally referred to as candidemia or fungemia, is typically associated with impaired immune system or immunosuppression.
Protozoa

**Leishmania**
*synonyms: Kala-azar organisms*

*Leishmania* organisms appear similar to *Histoplasma* in size, shape and color but are distinguished by the presence of a dark staining dotlike kinetoplast. They also appear, within the phagocytic cells (primarily monocytes/macrophages) and/or extracellularly in bone marrow and/or other tissues and rarely in the peripheral blood. Nonspecific laboratory features may include bicytopenia (anemia & leukopenia) or pancytopenia, hypoalbuminemia, hypergammaglobulinemia, elevation of hepatic enzymes in serum, and myelodysplasia. Infection with *Leishmania* is referred to as leishmaniasis and it manifests clinically in 2 forms, cutaneous or mucocutaneous and visceral (spleen, liver and bone marrow). Clinically severe leishmaniasis is seen primarily in immunosuppressed patients. Leishmaniasis is seen across much of Asia, Middle East, Africa, and in some parts of South America and southern Europe. It is rarely seen in the US and that also primarily in troops returning from areas where leishmaniasis is prevalent. It may be transmitted congenitally from an infected mother to the newborn, parenterally via blood transfusion, or by the bite of an infected sandfly. Serologic and molecular tests are available for confirming the diagnosis.

**Toxoplasma gondii**
*synonyms: none*

*Toxoplasma gondii* is the causative agent for toxoplasmosis, which may be congenital or acquired. The latter form is usually acquired from infected cats. Rarely, if ever, the trophozoite forms of the organism (a protozoan) may be seen in the thin and/or thick blood smears. Diagnosis is usually confirmed by serology. Nonspecific hematologic findings that may be associated with toxoplasmosis include a variable degree of usually normocytic normochromic anemia, lymphocytosis, and/or mild thrombocytopenia.

**Trypanosomes**
*synonyms: none*

*Trypanosoma cruzi* is the organism that causes American trypanosomiasis or Chagas disease that is prevalent in Central America, South America and Mexico. Transmission is by blood sucking reduviid bugs (also known as kissing bugs). It can also be transmitted through blood transfusion, organ transplant, transplacentally (mother to baby), and by laboratory accident. *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense* cause the so-called African trypanosomiasis or sleeping sickness seen in East Africa and West Africa (including central Africa) respectively. The transmission is by a triatomid bug, also known as tsetse fly (*Glossina* species). Transmission through other routes occurs rarely, if ever. The organisms are seen in the blood only during the acute febrile stage of the disease. The diagnosis is generally made by demonstrating the parasites (organisms) in the blood, body fluids and/or tissue sections. Morphologically, a trypanosome (seen in the so called trypomastigote stage in the patient’s blood) has a small kinetoplast located at the posterior end, a centrally located nucleus, an undulating membrane, and a flagellum running along the undulating membrane. Their length ranges from 14-33 μm in the blood smear stained with a Romanowsky stain. The subspecies of *Trypanosoma brucei* (*rhodesiense & gambiense*) are indistinguishable from each other morphologically. The only difference between *Trypanosoma cruzi* and *Trypanosoma brucei* is that the former has a relatively larger kinetoplast. Serological tests are available but useful either as screening tests or in the chronic phase of the disease. Molecular tests have also been developed for the diagnosis of trypanosomiasis but they are neither readily available nor widely used. Nonspecific hematologic findings that may be associated with trypanosomiasis generally include a variable degree of usually normocytic normochromic anemia, neutrophilia with left shift, and a variable platelet count, which may be increased, normal or decreased. Neutropenia with left shift of neutrophils has also been associated with trypanosomiasis in some cases.
Extracellular organisms

Microfilariae

**synonyms:** filarial

Microfilariae are the larval forms of the threadlike round worms (nematodes) that cause the disease known as filariasis. 8 different species of the parasite belonging to the family “filariae” are known to infect humans. *Wuchereria bancrofti, Brugia malayi,* and *Brugia timori* inhabit the lymphatic system and are responsible for causing what is known as lymphatic filariasis. *Loa loa* (the eye worm), *Mansonella streptocerca,* and *Onchocerca volvulus* (causative agent for river blindness) have a niche for subcutaneous fat layer and cause subcutaneous filariasis. *Mansonella perstans* and *Mansonella ozzardi* like to occupy the serous cavity of the abdomen and are the etiologic agents of the so called serous cavity filariasis. In the US, filariasis is rarely seen and found also primarily in the migrants from the endemic areas. Many mosquito bites over several months to years are needed to get lymphatic filariasis. Clinical manifestations may become apparent several years after the infection. Consequently, many infected persons may remain asymptomatic for years. There is some variation in clinical manifestation of the disease caused by different species. The common manifestations of chronic lymphatic filariasis include lymphedema, hydrocele, and elephantiasis, leading to debilitating, painful, and disfiguring swelling of many organs including extremities (legs in particular), scrotum, and breasts. 6 different species of microfilariae that may be seen in the peripheral blood are *Wuchereria bancrofti,* *Brugia malayi,* *Brugia timori,* *Loa loa,* *Mansonella perstans,* and *Mansonella ozzardi.* Among these, only *W bancrofti,* *B malayi,* *B timori,* and *Loa loa* are pathogenic. The microfilariae of pathogenic species are sheathed, whereas those of nonpathogenic species lack the sheath. The vector for *W bancrofti* and *B malayi,* which are prevalent in the Caribbean, Latin America, Africa and Asia, is the mosquito. The vector for *Loa loa,* which occurs primarily in Central and West Africa, is the tabanid fly. All of these microfilariae appear as ribbonlike structures measuring 200-300 μm in length and 5-8 μm in width. The long bodies of these organisms are generally filled with nuclei. The only morphologic feature that is helpful in distinguishing among these 3 species is the distribution of nuclei in the tail portion. Characteristics of individual species of microfilariae are described below and outlined in t14.2. Travel history is important for the diagnosis, which must, however, be confirmed by demonstrating microfilariae in the blood smear stained with Wright, Wright-Giemsa, or Giemsa. Nonspecific hematologic findings that may be associated with filariasis generally include a variable degree of usually normocytic normochromic anemia, neutrophilia with left shift, eosinophilia, and a variable platelet count, which may be increased, normal or decreased. Neutropenia with left shift of neutrophils has also been associated with filariasis in some cases.

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**Loa loa**

**synonyms:** African eyeworm

It is found primarily in central and west Africa and it causes loiasis, the cause of the so called “eyeworm.” Adult worms inhabit the subcutaneous tissue, where they move about freely. Male worms measure 30-34 mm in length and 0.35-0.43 mm in width, whereas females measure 40-70 mm in length and 0.5 mm in width. The microfilariae circulate in the blood with diurnal periodicity. Peak parasitemia is seen in the early afternoon. They are sheathed and measure 250-300 μm in length and 6-8 μm in width in stained blood smears. The tail is tapered and the nuclei extend to the tip of the tail.
### Differential features of various species of microfilariae

<table>
<thead>
<tr>
<th>Species</th>
<th>Geographic distribution</th>
<th>Vector</th>
<th>Length (μm)</th>
<th>Sheathed</th>
<th>Tail shape</th>
<th>Nuclei in the tail</th>
<th>Seen in the blood</th>
<th>Type of filariasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Wuchereria bancrofti</em></td>
<td>Africa, Asia, Caribbean, Latin America</td>
<td>mosquitoes</td>
<td>240-300</td>
<td>yes</td>
<td>gently curved</td>
<td>no</td>
<td>yes, usually at night</td>
<td>lymphatic</td>
</tr>
<tr>
<td><em>Brugia malayi</em></td>
<td>Africa, Asia, Caribbean, Latin America</td>
<td>mosquitoes</td>
<td>240-300</td>
<td>yes</td>
<td>tapered</td>
<td>gap between terminal and subterminal nuclei</td>
<td>yes, usually at night</td>
<td>lymphatic</td>
</tr>
<tr>
<td><em>Brugia timori</em></td>
<td>Indonesia</td>
<td>mosquitoes</td>
<td>310</td>
<td>yes</td>
<td>curved and tapered</td>
<td>yes, single file</td>
<td>yes, usually at night</td>
<td>lymphatic</td>
</tr>
<tr>
<td><em>Loa loa</em></td>
<td>Central &amp; West Africa</td>
<td>deerflies</td>
<td>230-250</td>
<td>yes</td>
<td>tapered</td>
<td>yes</td>
<td>yes, usually in the day time</td>
<td>subcutaneous</td>
</tr>
<tr>
<td><em>Mansonella ozzardi</em></td>
<td>Americas, Caribbean</td>
<td>black flies, midges</td>
<td>160-205</td>
<td>no</td>
<td>tapered hooklike</td>
<td>no</td>
<td>yes, any time</td>
<td>serous cavity</td>
</tr>
<tr>
<td><em>Mansonella perstans</em></td>
<td>Africa, South America</td>
<td>midges</td>
<td>190-200</td>
<td>no</td>
<td>blunt</td>
<td>yes</td>
<td>yes, any time</td>
<td>serous cavity</td>
</tr>
<tr>
<td><em>Mansonella streptocerca</em></td>
<td>Central &amp; West Africa</td>
<td>midges</td>
<td>180-240</td>
<td>no</td>
<td>curved</td>
<td>no (seen only in tissues)</td>
<td>yes</td>
<td>subcutaneous</td>
</tr>
<tr>
<td><em>Onchocerca volvulus</em></td>
<td>Africa, Latin America, Middle East</td>
<td>black flies</td>
<td>220-360</td>
<td>no</td>
<td>tapered pointed sharply bent</td>
<td>no (seen only in tissues)</td>
<td>no</td>
<td>subcutaneous onchocerciasis (river blindness)</td>
</tr>
</tbody>
</table>
**Wuchereria bancrofti**

*synonyms: none*

It is found worldwide and it is the most prevalent cause of lymphatic filariasis. Male worms measure ~40 mm in length and 0.1 mm in width, whereas females measure 80-100 mm in length and 0.24-0.30 mm in width. Larvae of the worm, generally referred to as microfilariae, circulate in the blood with nocturnal periodicity. Peak parasitemia is therefore noted at night. The microfilariae are sheathed and measure 244-296 μm in length and 7.5-10 μm in width in stained blood smears. The body is gently curved and the tail is often tapered to a point. The nuclear column that constitutes the body of the microfilaria is loosely packed. The nuclei can be visualized individually throughout the column except the tip of the tail, which is empty.

**Brugia malayi**

*synonyms: none*

It is confined mainly to tropical Asia and is the second most prevalent cause of lymphatic filariasis. Adult worms reside in the lymphatics, primarily in the limbs, the pelvis, and the scrotum in males. Male worms measure 13-23 mm in length and 70-80 μm in width, whereas females measure 43-55 mm in length and 130-170 μm in width. The microfilariae circulate in the blood with nocturnal periodicity. Peak parasitemia is therefore noted at night. The microfilariae are sheathed and measure 177-230 μm in length and 5-7 μm in width in stained blood smears. The sheath stains pink with Giemsa. The tail is tapered, with a significant gap between the terminal and subterminal nuclei.

**Brugia timori**

*synonyms: none*

It is found primarily in some islands of Indonesia and it is the least prevalent cause of lymphatic filariasis. Adult worms reside in the lymphatics, primarily in the limbs, the pelvis, and the scrotum in males. The microfilariae circulate in the blood with nocturnal periodicity. Peak parasitemia is therefore noted at night. They are sheathed and measure on average 310 μm in length in stained blood smears. The sheath does not stain pink with Giemsa. Compared to *Brugia malayi*, these have (a) longer cephalic space and (b) a larger number of single file nuclei towards the tail.

**Mansonella ozzardi**

*synonyms: none*

It is endemic in Latin America and it causes a form of serous cavity filariasis. Adult worms reside in serosal cavities (pleural, pericardial, and peritoneal) and retroperitoneal spaces. Adult worms are rarely, if ever found in humans. The microfilariae are unsheathed and circulate in the blood without periodicity. They measure 160-205 μm in length in stained blood smears. The tail tapers to a point and is bent in a small hooklike shape. The nuclei end well before the end of the tail.

**Mansonella perstans**

*synonyms: none*

It is found in central Africa and Latin America and it causes a form of serous cavity filariasis. Adult worms reside in serosal cavities (pleural, pericardial, and peritoneal) and retroperitoneal spaces. Male worms measure ~45 mm in length and 60 μm in width, whereas females measure 70-80 mm in length and 120 μm in width. Clinical manifestations of filariasis caused by *Mansonella perstans* are poorly defined. The microfilariae are unsheathed and circulate in the blood without periodicity. They measure 190-200 μm in length and 4.5 μm in width in stained blood smears. The tail is blunt and the nuclei extend to the tip of the tail. The microfilariae may be found in cerebrospinal fluid.
14: Infectious Agents

**Plasmodium malariae i14.11-i14.13**

- **i14.11** Trophozoite (ring)
- **i14.12** Schizont
- **i14.13** Gametocyte

**Plasmodium ovale i14.14-i14.16**

- **i14.14** Trophozoite (ring)
- **i14.15** Schizont
- **i14.16** Gametocyte

**Plasmodium knowlesi i14.17-i14.19**

- **i14.17** Trophozoite (ring)
- **i14.18** Schizont
- **i14.19** Gametocyte

**Babesia i14.20-i14.22**

- **i14.20** Intracellular Babesia rings
- **i14.21** Intracellular and extracellular (1) Babesia rings with 1 possible tetradlike structure
- **i14.22** Intracellular Babesia: rings & 2 tetrad forms
Bacteria i14.23-i14.29

14.23 Intracellular cocci in neutrophils
14.24 Intracellular cocci in a monocyte
14.25 Intracellular cocci in red cells

Fungal organisms i14.30-i14.33

14.30 Intracellular fungi in neutrophils
14.31 Intracellular fungi in a monocyte
14.32 Extracellular fungi with hyphae
Leishmania

Trypanosomes

Trypanosoma brucei gambiense

Trypanosoma cruzi

Toxoplasma gondii
### Microfilariae 14.44-14.51

#### Loa loa 14.44-14.45

14.44  Thin smear, 500× (Wright-Giemsa)

14.45  Thin smear, 1000× (Wright-Giemsa)

#### Wuchereria bancrofti 14.46-14.47

14.46  Thick smear, 500× (Wright-Giemsa)

14.47  Thick smear, 500× (Giemsa)

#### Brugia malayi

14.48  Thin smear, 500× (Wright-Giemsa)

#### Brugia timori

14.49  Thick smear, 500× (Wright-Giemsa)

#### Mansonella ozzardi

14.50  Thin smear, 500× (Giemsa)

#### Mansonella perstans

14.51  Thin smear, 500× (Wright-Giemsa)
Chapter 21

Chronic Leukemias/
Chronic Myeloproliferative Neoplasms

Chronic leukemias

synonyms: none

These are characterized by predominance of mature or maturing cells in the blood and bone marrow. The white cell count is generally increased and the platelet count is usually either normal or increased. Based on the lineage of the predominant cell type, chronic leukemias are also divided initially into myeloid and lymphoid forms, and then each is further classified into several subtypes, based on the morphologic features of leukemic cells and accompanying pertinent hematologic findings described below.

Chronic myeloproliferative neoplasms or CMN

synonyms: chronic myeloproliferative disorders or CMPD

This group of chronic diseases involving bone marrow and blood, includes chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The recent WHO classification of hematopoietic tumors has expanded the group by including also chronic neutrophilic leukemia, chronic eosinophilic leukemia/hypereosinophilic syndrome, and another category called CMN, unclassifiable, all of which are relatively rare disorders. A related disorder also included in this group of CMN is mastocytosis. Peripheral blood findings of individual disorders are described here.

Chronic myelogenous leukemia or CML

synonyms: chronic myeloid leukemia, chronic granulocytic leukemia or CGL

Chronic myelogenous leukemia usually has 3 phases, a chronic phase, an accelerated phase, and a blast crisis phase.

Chronic phase of CML

The chronic phase is generally characterized by an increased white cell count (20–400 × 10⁹/L, generally 20–200 × 10⁹/L) due to an increase in granulocytes in different stages of maturation. Among the various stages of granulocyte maturation, myelocytes and segmented neutrophils make up the 2 largest components. Absolute basophilia with or without absolute eosinophilia is invariably present. Blasts account for <2% of the white cells. Mild absolute monocytosis may be seen. The platelet count is usually either normal or increased but rarely may be decreased. Mild normocytic and normochromic anemia is a common finding. The morphology of blood cells, particularly of white cells and red cells, including their precursors, is usually normal. An occasional megakaryocyte, normal or abnormal, may be found in the blood smear of some cases. The granulocyte maturation pattern in the bone marrow is almost identical to that in the blood. Bone marrow examination, though not considered essential for initial diagnosis of chronic phase, is often necessary for confirming the diagnosis by cytogenetics and/or molecular studies and for differentiating between different phases of CML. The finding of Philadelphia chromosome [t(9;22)(q34;q11)] or BCR/ABL fusion gene or RNA transcript confirms the diagnosis of CML.
**Accelerated phase of CML**

This phase is characterized by 1 or more of the following findings in the blood and/or the bone marrow:

(a) blasts accounting for 10-19% of white cells in the blood and/or of all nucleated cells in the bone marrow

(b) basophils representing ≥20% of the white cells in the blood

(c) persistent thrombocytopenia (<100 × 10^9/L) unrelated to therapy

(d) persistent thrombocytosis (>1,000 × 10^9/L) despite appropriate therapy

(e) increasing spleen size and increasing white cell count unresponsive to appropriate therapy

(f) cytogenetic evidence of clonal evolution [ie, development of additional genetic abnormalities: eg, extra Philadelphia chromosome, trisomy 8, trisomy 19, isochromosome 17q, and t(3;21)(q26;q22)]

The finding of clusters or sheets of megakaryocytes, significant fibrosis, and/or marked granulocytic dysplasia in the bone marrow may also be considered suggestive of accelerated phase of CML.

**Blast crisis phase of CML**

This phase often resembles acute leukemia and is characterized by 1 or more of the following findings in the blood and/or bone marrow:

(a) blasts accounting for ≥20% of the white cells in the blood and/or of all nucleated cells in the bone marrow

(b) large aggregates/clusters/sheets of blasts in the bone marrow biopsy section

(c) extramedullary proliferation of blasts

The lineage of blasts is myeloid (including all subtypes, eg, myeloblasts, monoblasts, and megakaryoblasts) in ~70% of cases and lymphoid (including both subtypes, B & T) in ~30% of cases. Additional means, such as special cytochemical stains, immunophenotyping, and/or molecular technics are utilized in determining or confirming the lineage of blasts.

**Polycythemia vera or PV**

*synonyms: primary polycythemia, essential polycythemia*

Polycythemia vera is characterized by increased red cell mass as a result of increased red cell production independent of the mechanisms that normally regulate erythropoiesis. Serum erythropoietin level is below the reference range in many cases. Over 95% of cases harbor the somatic gain of function mutation of the Janus 2 kinase gene in exon 14 (V617F) or exon 12. The diagnosis requires exclusion of secondary erythrocytosis, familial polycythemia, and all other chronic myeloproliferative neoplasms. Clinically, 3 phases of PV have been recognized, an early or so called prodromal phase, an overt proliferative phase commonly known as polycythemic phase or polycythemia vera, and a spent phase that is also known as postpolycythemic phase.

*The early/prodromal/prepolycythemic phase:* It is characterized by a borderline or mild erythrocytosis. The red cells are normocytic and normochromic. None of the other features of the polycythemic phase, described below, are present and patients are asymptomatic. These patients may be followed with periodic measurements of serum erythropoietin level and assessment of JAK2 mutation status. True polycythemia vera may manifest over time.

*Polycythemic phase or polycythemia vera:* The typical peripheral blood findings include increased hemoglobin (over 18.5 g/dL in men and 16.5 g/dL in women) in the absence of any cause of secondary erythrocytosis, +/- thrombocytosis (over 400 × 10^9/L), +/- leukocytosis (over 12 × 10^9/L), often with neutrophilia and basophilia, and +/- low serum erythropoietin level. The red cells are generally normocytic and normochromic unless concurrent iron deficiency complicates the disease course resulting in the production of microcytic and hypochromic red cells. The WHO has proposed a set of 2 major criteria and a set of 3 minor criteria to facilitate the diagnosis of PV.
The diagnosis requires the presence of either
(a) both major criteria and 1 minor criterion
(b) first major criterion and any 2 of the 3 minor criteria; both sets of criteria are outlined below

**Major criteria:**
1. hemoglobin $>18.5$ g/dL in men and $>16.5$ g/dL in women or other evidence of increased red cell mass*
2. presence of JAK2 mutation

*Hgb or Hct $>99$th percentile of method-specific reference range for age, sex, and altitude of residence
or Hgb $>17$ g/dL in men, $>15$ g/dL in women if associated with a documented and sustained increase of at least $2$ g/dL from an individual's baseline value that cannot be attributed to correction of iron deficiency
or elevated red cell mass ($>25\%$ above mean normal predicted value)

**Minor criteria:**
1. bone marrow showing hypercellularity with increased proliferation of all 3 cell lineages
2. serum erythropoietin level below the reference range
3. endogenous erythroid colony formation in vitro

**Spent or postpolycythemic phase** (synonyms: postpolycythemic myelofibrosis or post-PV-MF): It is generally characterized by cytopenias including anemia, myelofibrosis, and extramedullary hematopoiesis. Typical peripheral blood findings associated with this phase include leukoerythroblastosis, red cell poikilocytosis including variable number of teardrop cells, and variable degrees of cytopenias (anemia, +/- thrombocytopenia, +/- leukocytopenia). The red cells may be normocytic and normochromic or microcytic and hypochromic. The PV may transform into myelodysplastic syndrome or acute leukemia in some cases. The WHO has developed the following sets of criteria for the diagnosis of post-PV-MF:

**Required criteria:**
1. documentation of a previous diagnosis of WHO-defined PV
2. bone marrow fibrosis grade 2-3 (on 0-3 scale) or grade 3-4 (on 0-4 scale)

**Additional criteria** (any 2 of the following are required):
1. anemia (Hgb below the reference range for appropriate age, sex, and altitude considerations) or sustained loss of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment requirement for erythrocytosis
2. leukoerythroblastosis in the blood smear
3. increasing splenomegaly defined as either an increase in palpable splenomegaly of $>5$ cm from baseline (distance from left costal margin) or the appearance of newly palpable splenomegaly
4. development of $>1$ of 3 constitutional symptoms: $>10\%$ weight loss in 6 months, night sweats, unexplained fever ($>37.5^\circ C$)

**Essential thrombocythemia or ET**

*synonyms: primary thrombocythemia, hemorrhagic thrombocythemia, primary thrombocytosis, essential thrombocytosis, idiopathic thrombocytosis* i21.9-i21.12

It is usually characterized by marked thrombocytosis often with variable size platelets (small to giant forms). Platelet clumps and abnormally shaped platelets may be seen. A variable degree of anemia is common. The red cells may be normocytic and normochromic or microcytic and hypochromic due to iron deficiency associated with chronic hemorrhage. The white cell count is usually normal but may be slightly elevated. The differential leukocyte count is generally normal. An occasional megakaryocyte (denuded or intact) and/or normoblast may be seen in the blood smear in some cases. The diagnostic criteria for ET include
(a) persistent increase in platelet count to $\geq 450 \times 10^9/L$
(b) lack of evidence for the diagnosis of any other myeloproliferative disorder, myelodysplastic syndrome associated with thrombocytosis, and secondary thrombocytosis
prominent megakaryocytic proliferation marked by an increase in the number of large
to giant megakaryocytes, loosely dispersed or in clusters, in the bone marrow
There is no known specific cytogenetic abnormality associated with ET. By molecular
studies, JAK2 mutation is associated with ET in ~50% of patients. Transformation of ET into
myelodysplastic syndrome or acute myeloid leukemia may occur but is uncommon.

**Primary myelofibrosis or PMF**

_synonyms: chronic idiopathic myelofibrosis or CIBM, agnogenic myeloid metaplasia,
myelofibrosis with myeloid metaplasia, chronic granulocytic-megakaryocytic myelosis,
myelofibrosis and osteosclerosis i21.13-i21.20

There are usually 2 phases of PMF, a cellular or prefibrotic phase and a fibrotic phase. Bone
marrow examination along with the peripheral blood findings and clinical features are
necessary for the specific diagnosis. The peripheral blood findings in the cellular phase i21.13-i21.15
are variable and nonspecific, and include mild normocytic and normochromic anemia, mild
to moderate leukocytosis, mild to marked thrombocytosis, no or mild leukoerythroblastosis,
and no or minimal red cell poikilocytosis including teardrop cells. Large and/or giant
platelets and a variable number of circulating cells of megakaryocytic lineage (normal and/
or abnormal) may be seen in some cases. The bone marrow is hypercellular with increased
granulocytic and megakaryocytic proliferation (often abnormal) and minimal, if any, fibrosis.
The classic blood smear of PMF in fibrotic phase reveals leukoerythroblastosis, often
including a few blasts (<10%), and red cell poikilocytosis with prominent teardrop cells
i21.16-i21.20. Additional peripheral blood findings include moderate to marked anemia with
normocytic and normochromic red cells; low, normal or elevated white cell count; and low,
normal or elevated platelet count with or without giant and/or abnormally shaped platelets.
A variable number of circulating cells of megakaryocytic lineage (normal and/or abnormal)
may be seen in some cases. The bone marrow typically shows significant fibrosis with or
without osteosclerosis, decreased cellularity, and prominent megakaryocytic proliferation.
Morphologically, the megakaryocytes appear abnormal.

JAK2 mutation has also been noted in associated with PMF in ~1/2 of patients.

**Chronic neutrophilic leukemia or CNL**

_synonyms: none i21.21

It is an extremely rare disorder, which is characterized by persistent unexplained neutrophilia
(≥25 × 10^9/L) in the blood, hypercellular bone marrow due to neutrophilic proliferation, and
hepatosplenomegaly. The white cell count is increased and the peripheral blood smear
reveals primarily segmented neutrophils and bands (80%-100%) with immature neutrophilic
granulocytes (metamyelocytes, myelocytes, and promyelocytes) accounting for none to 10%.
An occasional blast may also be found in the blood smear. A variable degree of normocytic
and normochromic anemia is evident. The platelet count and morphology are usually
normal. The diagnosis requires exclusion of
(a) all possible causes of reactive neutrophilia
(b) all other myeloproliferative disorders
(c) myelodysplastic syndrome
Bone marrow examination reveals increased cellularity due primarily to neutrophilic
proliferation with blasts usually accounting for up to 5% of all nucleated cells. There is no
specific cytogenetic or molecular abnormality associated with this disorder.

**Chronic eosinophilic leukemia or CEL**

_synonyms: chronic eosinophilic syndrome

It is also an extremely rare disorder, which is generally characterized by persistent peripheral
blood eosinophilia (≥1.5 × 10^9/L), prominent eosinophilic proliferation in the bone marrow,
and tissue infiltration by eosinophils. Mature as well as immature forms of eosinophils,
including blasts (<20%), are frequently seen in the blood and bone marrow. The morphology
of eosinophilic cells may be normal or abnormal. There is no specific cytogenetic or molecular
abnormality associated with this disorder.
**Chronic myeloproliferative neoplasm, unclassifiable or CMN, U**  
*synonyms: undifferentiated myeloproliferative neoplasm*  
*21.22-21.27*  
The term CMN, U is reserved for cases which reveal clinical, laboratory and morphologic features that overlap 2 or more of the specific chronic myeloproliferative disorders described above.

**Mastocytosis**  
*synonyms: none*  
Mastocytosis is characterized by a clonal, neoplastic proliferation and accumulation of mast cells in 1 or more tissues. Its subtypes include cutaneous mastocytosis or CM, extracutaneous mastocytoma, mast cell sarcoma, systemic mastocytosis or SM (which may be indolent, aggressive or associated with another clonal hematologic nonmast cell lineage disease), and mast cell leukemia or MCL. In CM, the mast cell infiltration is confined to the skin but in SM, the bone marrow is almost always involved with or without involvement of other tissues including skin, spleen, liver, lymph nodes, and gastrointestinal tract. Presence of mast cells in the peripheral blood (usually >10%) and in the bone marrow (usually >20%) characterizes the mast cell leukemia. The mast cells often appear abnormal, stain positive with antibodies against tryptase and express CD45, CD2, CD9, CD25, CD33, CD68, and CD117. Peripheral cytopenias reflective of bone marrow dysfunction may also be noted.

### 21.1 Chronic myeloproliferative disorders

<table>
<thead>
<tr>
<th>Features</th>
<th>Chronic myelogenous leukemia</th>
<th>Polycythemia vera</th>
<th>Essential thrombocytopenia</th>
<th>Primary myelofibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>↓</td>
<td>↑</td>
<td>↓ or N</td>
<td>↓</td>
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<tr>
<td>Hematocrit</td>
<td>↓</td>
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<td>↓ or N</td>
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<tr>
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<td>N</td>
<td>N or ↓</td>
<td>N or ↓</td>
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<td>↑</td>
<td>N or ↑</td>
<td>variable</td>
</tr>
<tr>
<td>Platelets</td>
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<td>N or ↑</td>
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</tr>
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<td>Eosinophilia</td>
<td>+ to ++</td>
<td>+/−</td>
<td>−/+</td>
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<td>Blasts (%)</td>
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<td>0–10</td>
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<td>−/+</td>
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</tr>
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<td>+/−</td>
<td>−/−</td>
<td>−/−</td>
<td>+/− to +</td>
</tr>
<tr>
<td>Megakaryocytes</td>
<td>+/−</td>
<td>−/−</td>
<td>+/− to +</td>
<td>+/− to +++</td>
</tr>
</tbody>
</table>

+/− = usually present but may be absent in some cases; −/− = usually absent but may be present in some cases; + to +++ = increasing degree of positivity; ↓ = decreased; ↑ = increased; N = normal; variable = increased, normal, or decreased
Chronic myelogenous leukemias i21.1-i21.14

21.1-21.3 3 different cases showing variable degree of leukocytosis, neutrophils at various stages of maturation & basophils

21.4 In accelerated phase: a blast & two basophils

Blast crisis in chronic myelogenous leukemias i21.5-i21.6

21.5 3 blasts, a myelocyte & a monocyte

21.6 Several blasts, mature & immature neutrophils & a basophil

21.7 Erythrocytosis & a neutrophil

21.8 Erythrocytosis & basophilia

Essential thrombocythemia i21.9-i21.12

21.9 Marked thrombocytosis, a giant platelet, clumping of platelets, poikilocytosis & anisocytosis

21.10 Thrombocytosis, clumping of platelets & poikilocytosis

21.11 Thrombocytosis, clumping of platelets, a megakaryocyte nucleus & poikilocytosis

21.12 Thrombocytosis & a blast cell
Primary myelofibrosis (PMF): cellular phase

21.13 Increased number of platelets, giant platelets & 2 neutrophils

21.14 2 megakaryoblasts, 3 mononuclear megakaryocytes & 2 giant platelets

21.15 Increased number of platelets with many giant forms

21.16 Many teardrop cells & decreased number of platelets

21.17 Many teardrop cells, a blast cell, a dysplastic normoblast & decreased number of platelets

21.18 A blast cell, giant platelets & decreased number of platelets

21.19 A blast cell, a normoblast, large platelets & Howell-Jolly bodies

21.20 A blast cell, a mononuclear megakaryocyte & a lack of platelets

PMF: fibrotic phase

Chronic neutrophilic leukemia

21.21 Neutrophils & a blast
Myeloproliferative neoplasms, unclassifiable 21.22-21.27

21.22 A blast, a myelocyte & hypersegmentation of neutrophils

21.23 Increased number of platelets, a blast cell & a mononuclear megakaryocyte

21.24 2 mononuclear micromegakaryocytes & 1 giant platelet

21.25 Leukocytosis, neutrophils at various stages of maturation & monocytosis

21.26 Leukocytosis with many myelocytes

21.27 Leukocytosis, a blast, four myelocytes, a metamyelocyte, a hypogranular neutrophil & a mononuclear megakaryocyte
1. Examination of a Romanowsky stained blood smear viewed under 10× objective lens (ie, 100× magnification) is helpful in visualizing all of the following EXCEPT:
   A. clumps of blood cells
   B. large cells, such as megakaryocytes
   C. contaminants such as endothelial cells & epithelial cells
   D. eosinophilic granules

2. A properly made wedge shaped blood smear always has all of the following EXCEPT:
   A. a small feather edge
   B. a readable area of reasonable length
   C. accumulation of white cells at the feather edge
   D. a thick area

3. Which one of the following types of white cells has the tendency to be drawn towards the edges of the blood smear?
   A. monocytes
   B. eosinophils
   C. basophils
   D. neutrophils

4. A rough estimate of total white cell count per microliter of blood can be obtained by multiplying the average number of white cells per field viewed under 50× oil objective lens (ie, 500× magnification) by a factor of:
   A. 1,000
   B. 3,000
   C. 5,000
   D. 7,000

5. A fairly reliable estimate of the platelet count per microliter of blood is generally obtained by multiplying the average number of platelets per field viewed under 100× oil objective lens (ie, 1,000× magnification) by a factor of:
   A. 5,000
   B. 10,000
   C. 15,000
   D. 25,000

6. Artifactual changes associated with red cells do NOT include:
   A. crenated red cells (echinocytes)
   B. teardroplike cells
   C. nucleated red cells
   D. sicklelike cells

7. Artifactual changes associated with white blood cells do NOT include:
   A. pyknosis/karyorrhexis/necrobiosis
   B. stain precipitate
   C. toxic vacuolation
   D. toxic granulation
8. Abnormally shaped red cells in this image of a blood smear from a 19-year-old male are:
   A. sickle cells
   B. teardrop cells
   C. hemoglobin SC poikilocytes
   D. artifactual changes in red cells

9. The pale-staining amorphous precipitates seen in this image of a blood smear from a 44-year-old male represent:
   A. artifact
   B. fibrin
   C. cryoprotein
   D. platelet clumps

10. What does this image of a blood smear from a 40-year-old male reveal?
    A. platelet satellitosis
    B. neutrophil satellitosis
    C. platelet clumping
    D. platelet emperipolysis

11. What does this image of a blood smear from a 50-year-old male reveal?
    A. hypersegmented neutrophil
    B. karyorrhexis
    C. LE cell
    D. Howell-Jolly bodies

12. What does this image of a blood smear from a 22-year-old female reveal?
    A. platelet clumps
    B. protein globules
    C. stain precipitate
    D. cocci in clusters

13. What does this image of a blood smear from a 33-year-old male reveal?
    A. echinocytes
    B. acanthocytes
    C. schistocytes
    D. spherocytes
14. The red cell located in the center of this image of a blood smear from a 16-year-old female represents:
   A. sickle cell  
   B. ovalocyte  
   C. elliptocyte  
   D. red cell with hemoglobin C crystal

15. The red cell inclusion seen in this image of a blood smear from a 52-year-old male represents:
   A. platelet  
   B. Howell-Jolly body  
   C. Pappenheimer body  
   D. basophilic stippling

16. The nucleated cell located in the center of this image of a blood smear from a 70-year-old male with a diagnosis of myelodysplastic syndrome is:
   A. normoblast  
   B. megaloblast  
   C. macronormoblast  
   D. plasmacytoid lymphocyte

17. What does the red cell located in the center of this image of a blood smear from a 60-year-old female contain?
   A. yeast  
   B. artifact  
   C. Cabot ring  
   D. *Plasmodium* trophozoite (ring form)

18. Red cell inclusions seen in this image of a blood smear stained with Prussian blue stain represent:
   A. artifacts  
   B. iron particles  
   C. Howell-Jolly bodies  
   D. basophilic stippling

19. Red cell rouleaux is associated with all of the following EXCEPT:
   A. multiple myeloma  
   B. hyperproteineinemia  
   C. Waldenström macroglobulinemia  
   D. Sézary syndrome