

Peripheral Blood Picture; The Science Beyond the Technique

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Abstract

The peripheral blood picture (PBP) is a diagnostic procedure that involves smearing peripheral blood cells on a slide for cytology. No matter how elementary, PBP is incredibly useful in characterizing a variety of clinical disorders. This article emphasizes the essential scientific and aesthetic foundation of the PBP. However, this work goes into detail on its clinical traits, laboratory uses, and interpretations of various clinical pathologies. The PBP remained a valuable diagnostic test in hematology despite the developments of digital PBP and genetic methods. The hematologist should ensure a high-quality smear, a comprehensive examination, and proper interpretation in respect of the patient's clinical condition. The examiner's expertise and training level have a significant impact on the reliability of the results.

Keywords: Peripheral blood picture, Blood cell morphology, Digital PBP, Peripheral smear evaluation

Introduction

Peripheral blood picture (PBP) technique, as a component of complete blood count (CBC), is an effective diagnostic tool. CBC is the most utilized laboratory test on the planet, with over 4 billion tests performed annually. If aberrant CBC findings are obtained, more research is demanded. The PBP is increasingly becoming a necessary skill since it frequently offers quick, dependable access to knowledge about a spectrum of hematologic illnesses [1].

The peripheral blood picture provides a window into the bone marrow's functioning condition, the place where all the components of blood are made. It is especially crucial when evaluating cytopenic conditions (e.g., anemia, leukopenia, and thrombocytopenia). Reviewing the blood smear is a crucial supplement for additional clinical evidence; in some circumstances, the peripheral blood picture by itself is enough to make a diagnosis [2]. This article focuses on the fundamental scientific and aesthetic basis of the PBP.

Indications of PBP

There are several clinical reasons to conduct a PBP examination, including to aid in the diagnosis of numerous ailments, your healthcare professional could conduct this test as part of a general health examination. Once a diagnosis has been determined and therapy has begun, this test is also used to monitor or assess the efficacy of the treatment. After a full blood count with an automated test has been completed and a blood abnormality or deficit is suspected, the PBP is frequently requested as a more conclusive screening tool [1]. Unexplained cytopenias, such as anemia, leukopenia, or thrombocytopenia; unexplained leukocytosis, lymphocytosis, or monocytosis; unexplained jaundice or hemolysis; signs of congenital hemolytic

anemias, such as splenomegaly, jaundice, or bone pains; and presumed acute or chronic myeloproliferative or lymphoproliferative diseases are frequently encountered indications [2–5]. These indications are just an example and not a limitation.

Evaluations on the PBP: When, Why, and How?

A PBP ought to be made as soon as possible to view the specimen's morphology under a light microscope. A microscopic PBP inspection provides clear visual images of the cells, whereas CBC analyzers use sensors to quantify and distinguish the cells in the sample using electrical impedance and light scattering. White blood cells (WBC), red blood cells (RBC), and platelets may all be seen clearly under a 100X lens. In reality, 10% to 30% of CBC tests call for a PBP follow-up [5]. A thorough morphological study of the PBP could support or refute the findings of the CBC and reveal new data that can only be obtained by examining the morphology of the blood cell under a microscope [2].

Furthermore, only a reviewer with experience can evaluate the relative relevance of reported findings and interpret their significance concerning other clinical evidence. A skilled eye will also recognize other morphological nuances that an automated reviewer could miss [1].

Patients with a hematological illness may not need to have the peripheral smear reviewed. Simple diagnoses, such as iron deficiency anemia (IDA), can be made based solely on clinical information and routine laboratory results (such as mean corpuscular volume [MCV], and serum ferritin) [6]. However, the perception of the PBP is particularly crucial in several situations. Let's take the example of a high monocyte count reported by a CBC test. The PBP will typically be generated and

examined in the lab to ensure that the CBC test did not mistake blasts for monocytes. According to much research, samples containing blast cells can experience this mistake in more than 70% of cases [7]. Another common instance is when a CBC test indicates a diminished platelet count. There may be many clinical causes for this, but unexpectedly, poor sample preparation is frequently one of them. Even after being collected in a tube with an anticoagulant, usually, EDTA is used to inhibit its natural clotting, platelet clumps can still happen because platelets tend to clot. These aggregates are incorrectly analyzed by the CBC machine as they pass through, leading to an erroneously low platelet count being reported (a clinical condition called thrombocytopenia) [8]. Laboratory technicians can characterize this as a false alert and a pseudothrombocytopenia if these clumps are found using a PBP analysis. More than 20% of requested PBP were proven to be necessary to verify low CBC platelet counts in various preformulation testing [9].

PBP approach

The reviewer must establish a methodical procedure for evaluating the peripheral smear. One system that can be modified to accommodate unique preferences and maximize efficiency is shown below.

The majority of the time, wedge procedures are used to manually or automatically prepare peripheral blood smears (**Figure 1**). Making smears from an anticoagulated blood sample that may have been left to settle for some time, just a tiny drop of blood that has not been allowed to clot or has not been thoroughly mixed ought to be utilized. It is impossible to exaggerate the value of a clean slide free of dust, grime, grease, and fingerprints. When a significant number of target cells or stomatocytes are only seen in discrete regions of the smear, the presence of such contaminants can frequently be inferred [2]. This issue can be resolved by doing the technique again with alcohol-cleaned slides. The best-qualified and stained slide for inspection is the initial action in determining the best location for reviewing the peripheral blood smear. Selecting an ideal spot requires scanning the entire slide at low power. Every slide has flaws that could prevent a precise morphological assessment [10]. An excessively thick end of the smear makes the erythrocytes there seem small and dark due to stacks or clusters of red cells in this region. If you want to check for the existence of malarial parasites, this part of the slide can be helpful. Red cells acquire a "brick-like" or "cobblestone" design in this region because the other end of the slide (the feather edge) will be too thin. Red blood cells in this region are not biconcave discs. However, this region may be helpful when looking for microscopic cytoplasmic inclusions, cellular fragments, cells that contain Auer rods, and big circulating tumor cells. Red cells will be more or less equally spaced in the ideal region, and the central pallor will be noticeable. Two or more cells should rarely be touched in healthy people [11].

The PBP reveals an aberrant distribution of red cells; this could be caused by a variety of illnesses, including:

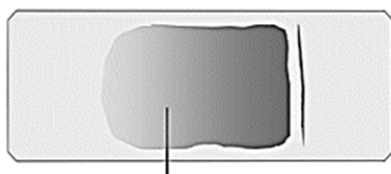


Figure 1: Peripheral blood smear (wedge technique).

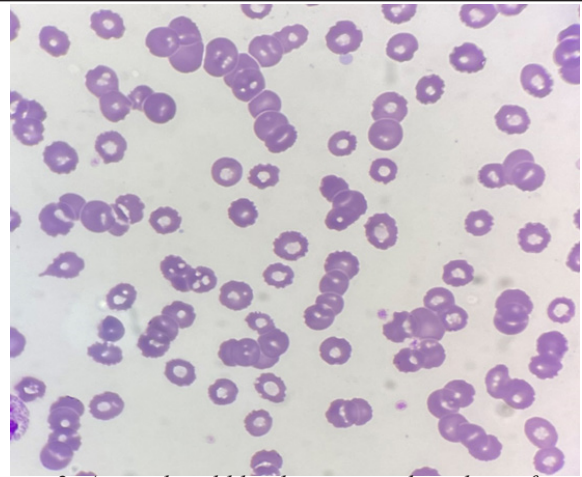


Figure 2: A peripheral blood picture with rouleaux forms in Multiple myeloma (100X).

- Rouleaux development due to raised plasma protein levels. The rouleaux formation phenomenon, which occurs in this situation, causes the red cells to resemble a stack of coins. Multiple Myeloma is where this is most frequently observed (**Figure 2**).
- Unusual red cell assemblages may indicate the existence of cold agglutinins.
- Collections of amorphous or crystalline matter could indicate the existence of cryoglobulin precipitates, which could happen in hepatitis C patients [12].
- The presence of wide, clear patches, circular gaps between red cells, rouleaux development, and red cell aggregates on an otherwise well-prepared smear have all been correlated with the presence of circulating surfactants or oil-based materials [13, 14].
- Fat droplets surrounding red cells or (ghost cells) can be found in hypertriglyceridemia or hypercholesterolemia patients, together with lipemic plasma and small lipid droplets covering and encircling the periphery of erythrocytes [15].

Alterations in Leukocyte Morphology

Multi-lobulation

Hypersegmentation of neutrophils is defined as having more than five lobes and denotes either a megaloblastic process or, rarely in iron deficiency anemia. Patients with heat stroke may also exhibit grape-like (botryoid) numerous lobulations [16,17].

Diminished lobulation

In the pseudo-Pelger-Huet variant of the Pelger-Huet anomaly, mature neutrophil lobulation is reduced. This variant can be inherited or acquired in patients with myelodysplastic syndromes. These cells frequently have a "pince-nez" look due to their bilobed nucleus joined by a thin strand. They also frequently have minimal or no granulation [18].

Granulation

Toxic systemic disorders are characterized by non-specific findings of dark blue, gritty granules. They are azurophilic grains with unusual staining characteristics [19]. When a child has recurrent pyogenic infections, giant cytoplasmic granules within neutrophils may be a sign of the Chediak-Higashi syndrome [20].

Dohle bodies

Patients with infection are most likely to have these light blue,

peripheral Döhle bodies in their neutrophils. This observation is extremely sensitive to infectious or inflammatory disease when combined with other neutrophil alterations (such as left shift, toxic granulation, and cytoplasmic vacuoles). Furthermore, Döhle bodies were also documented in pregnant women, myelodysplastic patients, and burn patients. They are blue because they are regions of rough endoplasmic reticulum containing attached ribosomes [21]. Patients with the May-Hegglin abnormality exhibit large platelets and similar-appearing inclusions [22].

Alterations in Erythrocyte Morphology

Red cell abnormalities are conditions that are frequently seen that require immediate attention.

Size variability

Sideroblastic anemias, thalassemia, chronic disease-related anemias, and iron deficiency anemias are among the few differential diagnostic events for adult microcytosis. Based on the PBP alone, it can be challenging to differentiate between iron deficiency and thalassemia traits. In addition, prolonged lead exposure in children might result in microcytosis [23,24].

There is a wider divergence for macrocytosis. Reticulocytes have a bluish tint and are larger than regular red blood cells (polychromatic cells). Large, oval-shaped erythrocytes called oval-macrocytes are indicative of megaloblastic processes such as folate and cobalamin insufficiency. In addition, round-macrocytosis can also be present in liver disease and primary bone marrow failure conditions including aplastic anemia and myelodysplastic syndromes [25, 26].

Shape variability

The most crucial red cell abnormality to notice is probably fragmentation (also known as schistocytes or helmet cells), which can signify serious illnesses like disseminated intravascular coagulation (DIC), hemolytic uremic syndrome (HUS), or thrombotic thrombocytopenic purpura (TTP). In moderate cases or early in the course of many disorders, morphological changes can be imperceptible and simple to miss. In a typical PBP, schistocytes may typically make up less than 0.5% of the erythrocytes [27].

Due to their spiculated form, sickle cells are distinctive. The cells in people with SC illness or SA condition are only partially sickled, which tempers their morphologic appearance and makes them appear more "boat-like" or "oat-like" [28,29]. Target cells have an additional drop of hemoglobin (Hb) in the middle that resembles a "bell-like." They are a hallmark of hemoglobinopathies such as thalassemia and Hb C, Hb D, and Hb E as well as liver illness (especially obstructive liver disease), post-splenectomy situations, and obstructive liver disease [30]. Bite cells (degmacytes) or blister cells are produced by phagocytes that have retrieved stiff precipitates of hemoglobin that have been denatured (Heinz bodies); these damaged cells may be the first sign of hemolytic anemia induced by oxidant sensitivity, such as a shortage of glucose-6-phosphate dehydrogenase (G6PD) [31].

Erythrocytes with spicules have an erratic shape. Echinocytes, burr cells or crenated cells are those with similarly sized, regularly spaced projections; they are most frequently observed in uremia or as a preparation artifact [32]. Acanthocytes, also known as spur cells, are those with unevenly sized and spaced

projections and are most frequently encountered in liver illness. Separate presentations are made of the underlying illnesses connected to these alterations as well as the mechanisms through which they happen [33].

In a group of 50 hospitalized with COVID-19 patients, two-thirds displayed pincer or mushroom-shaped cells on the PBP. This may imply that oxidative stress, in addition to the virus, may have a substantial role in the pathophysiology of erythrocytes [34].

Red cell membranes without hemoglobin, sometimes known as red cell ghosts, are never typically observed in peripheral blood. They are red blood cells that have experienced intravascular lysis and have had hemoglobin leak into the plasma. In some fulminant bacterial infections, red cell ghosts may be observed; *Clostridium perfringens* is the most frequently found pathogen linked to this finding [35].

Troubling Findings

A few inconsistencies should never emerge on a peripheral smear taken under normal circumstances and always denote a pathologic workflow:

Blasts and tumor cells

Various early white cells can be seen during pregnancy or a leukemoid reaction, which is normal [36]. However, it is never typical to find blast forms on the peripheral smear (such as lymphoblasts or myeloblasts). There ought to be extra testing done on these patients (such as a review of the peripheral smear, a hematologic consultation, and a bone marrow examination). Blasts are juvenile cells with big nuclei, nucleoli, and a sparse border of dark blue cytoplasm that are indicative of an underlying neoplastic hematologic trouble [37].

Myelogenous leukemia can be identified by the presence of inclusions inside a blast cell that include Auer rods, which are rod-like clusters of granules in the cytoplasm [37]. Patients with follicular lymphoma may show tiny lymphoid cells with cleft nuclei (small cleaved B-cells or centrocytes) in the bloodstream [38]. Patients with splenic marginal zone lymphoma may have lymphoid cells with bipolar villous projections (**Figure 3**) [39, 40]. Hairy cell neoplasm can cause lymphoid cells to have irregular or "hairy" cytoplasm [41]. In patients with adult T-cell leukemia/lymphoma, lymphoid cells with hyper-

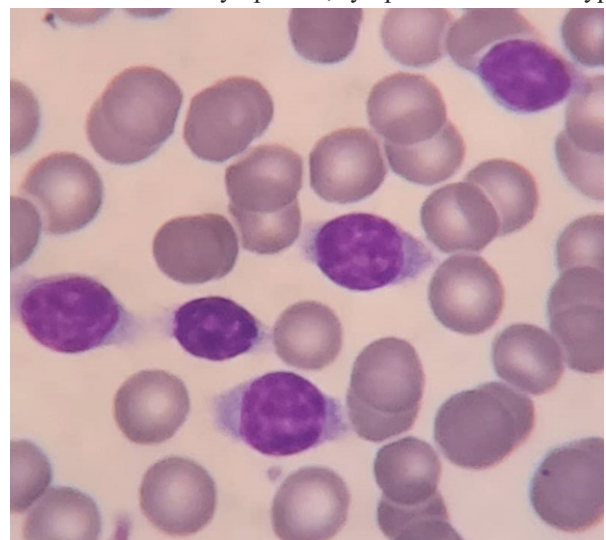


Figure 3: A PBP with splenic lymphoma with villous lymphocyte projections (100X).

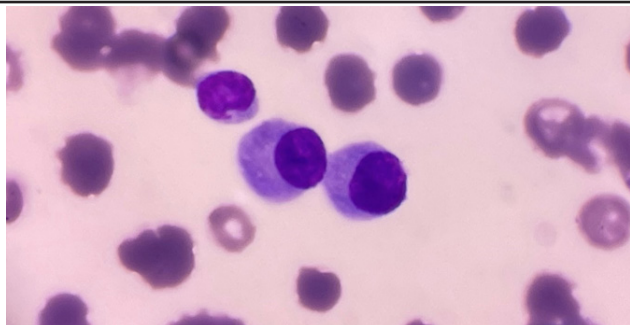


Figure 4: Multiple myeloma patient peripheral blood image with Plasma cells (100X).

lobulated nuclei (clover leaf or reider cells) may be present [42]. Patients with cutaneous T-cell lymphoma may have unusual lymphoid cells (Sézary cells) in their bloodstream that have "cerebriform" nuclei [43].

Typically, plasma cells are absent from the PBP. They are counted as lymphocytes because of how they look, which includes having a definite, obvious perinuclear area with lots of Golgi structures. Multiple myeloma and primary systemic amyloidosis can both exhibit circulating plasma cells in peripheral blood (**Figure 4**) [44, 45]. An extreme plasma cell count in the peripheral blood of $>2000/\mu\text{l}$ ($>2 \times 10^9/\text{L}$), or >20 percent of WBCs, characterizes plasma cell leukemia, a seldom occurrence [46]. Inflammatory (reactive) plasma cells are a frequent feature of many infectious and inflammatory ailments and can resemble plasma cell leukemia [47].

Smudge cells are lymphocytes that appear to have flattened out or gotten smudged while being spread out on the glass slide. These "smudge" cells, which demonstrate B-CLL cells' fragility or susceptibility to deformation when mechanically manipulated, are thought to be typical of CLL [48].

Osteoclasts are giant cells (multi-nucleated cells) that possessed the propensity to replenish calcified bone matrix. During leukemia or dysplastic hemopoietic illness, this cell is incredibly unlikely to be lost in circulation (**Figure 5**) [49].

Organisms

On rare occasions, and particularly in patients with serious sepsis, it may be discovered that the invader is contained in the blood's neutrophils or monocytes. You might see the following

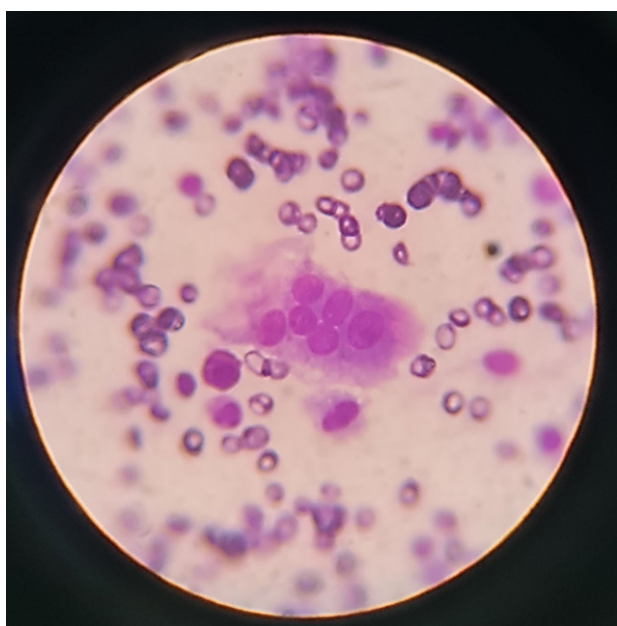


Figure 5: An Osteoclast cell shed in the peripheral blood film.

kinds of organisms:

1. Bacteria, such as Anaplasma, Ehrlichia, or other types [50-53].
2. Fungi, including Histoplasma [54,55].
3. Parasites, including both intracellular (such as malaria, babesia) and extracellular (trypanosomes, microfilaria) types [56-58].

Occasionally, organisms outside of cells can be observed on the peripheral smear in cases of enormous bacteremia or parasitemia. The peripheral smear has a low sensitivity for identifying these pathogens [50-58].

When a patient has a serious condition of malaria (such as cerebral malaria or severe anemia), the circulating neutrophils and monocytes may include pigmented inclusions made of hemoglobin that has been partially degraded by plasmodial organisms (hemozoin, malarial pigment) [59]. Neutrophils or monocytes with bright green cytoplasmic inclusions have occasionally been observed in patients with severe ailments (sepsis, liver failure) [60,61]. Those who contracted SARS-CoV-2 during the coronavirus 2019 (COVID-19) outbreak have been documented to have these inclusions [62]. Rarely, PBP from systemic lupus erythematosus (SLE) patients contains neutrophils that have consumed nuclear material (known as "LE cells") [63].

Digital PBP

If certain anomalies on the CBC are present, some hematology analyzers are connected to tools that can utilize predetermined criteria to generate a blood smear. The analyzers can also be linked to automated image processing software, which can take digital pictures of the blood film at high magnification and save them. The results can then be examined by image analysis software that uses deep learning techniques and pattern matching to identify specific aberrant findings, which can then be given to a hematologist for additional examination [64].

Unfortunately, the majority of PBP reviews are carried out manually. Less than 20% of big hematology laboratories use a "digital PBP" workflow. Although a PBP digital method is practical and makes the review process simpler, it has several drawbacks. The broad context of the blood smear, which is essential for making accurate clinical decisions, is obscured from the medical technician with only a small number of fields of view and roughly 100 WBC snapshots. There are no available smear regions of interest, such as the feathered edge, which is necessary to confirm the presence of platelet aggregates and big cells at the edge of the smear. Additionally, identifying the best analysis area to collect WBC images presents a problem for PBP digital methods due to variations in smear durations and sample preparation quality. WBC morphology is hampered if the device chooses a less-than-ideal region. As a result, a lab technician must typically use a manual microscope as a fallback [65].

The PBP Examination Results: What Does It Mean?

A sickness or condition is not automatically confirmed by the PBP Examination results. The medical provider assesses the PBP values along with the other clinical symptoms and indications. Other investigations frequently use PBP findings to develop a diagnosis [5].

The pattern of the blood cell morphology, together with other

findings seen under a microscope, will point the medical provider in the proper path for determining the cause of the issue, its seriousness, and whether more investigation/examination is required. All these elements would help give the patient an appropriate course of treatment. The outcomes of the laboratory tests shouldn't be viewed as the results of a single test. After comparing the test results with pertinent clinical findings and any supporting tests or evidence, they must be interpreted. The significance of your findings will be explained by your medical providers based on the entire clinical scenario [1, 5].

Relevant Useful Information

The results of the PBP may be impacted by some medications you are taking. Therefore, it is crucial to let your medical provider know the full list of drugs you are currently taking, including any herbal remedies. This will reduce the likelihood of misdiagnosis and help the medical professional read your PBP test findings more accurately [66].

Conclusion

As a crucial part of the first assessment of all patients with hematologic diseases, examination of the PBP should be taken into consideration together with a review of the results of peripheral blood counts and erythrocytes indices. Romanowsky stain of blood films usually offers crucial hints in the identification of anemias and different leukocyte and platelet abnormalities. The amount of expertise and experience of the examiner substantially impact the validity of the results.

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