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Guidance of Complete Blood Count and Peripheral Smear in Pediatric Infectious Disease Diagnosis

Review Article

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"Do as much as possible for the patient and as little as possible to the patient." – Bernard Lown [1]

Introduction:

Medical literature says clinical decisions and diagnoses are backed up with laboratory tests in up to 70% [2]. Complete blood count (CBC) is one of the most frequently ordered tests: In Mayo Clinic, 1,800 CBCs are ordered every day, in 10-20% of which, abnormalities are detected [3]. This takes us to the point that a good knowledge for interpreting CBC results will be for the benefit of both the patient and the physician herself/himself. In this article, the steering role of complete blood count and peripheral smear (PS) (regarded as its integral part) will be discussed in the context of pediatric infectious disease diagnosis and treatment.

Overview:

Peripheral smear should be first looked over in low magnification in its entirety, and the area which is most suitable for examination should be determined. For instance, the tip of the PS, where blood film is the thickest and red blood cells (RBC) accumulate, is more suitable for malaria parasites to be searched for. The areas where RBCs gather irregularly suggests the presence of cold aglutinins in blood.

Aggregates of substances with amorphic or crytalline structure should be interpreted as precipitations of cryoglobulin particles formed in infections like hepatitis C. These precipitated particles are falsely reported as leukocytosis or thrombocytosis by automated counters.

Organisms like Neisseria, Borrelia, Ehrlichia, Histoplasma, Trypanosoma, and Microfilaria can be spotted in PS on the condition that bacteremia or parasitemia (as well as candidemia) is highly intense [4]. For instance, a concentration of at least 1-5 × 10^5 colony forming units of yeast organisms per mililiter should be present in circulation in order that a diagnosis of candidemia could be made [5].

Red Blood Cells:

In PS, large spaces between RBCs, rouleaux formation, and clumping of RBCs point to a surfactant- or lipid-based substance in circulation. For example, polyoxoethylated castor oil, which is used for enhancing the solubility of hydrophobic antifungals may be the cause of such detections [6].

Changes in RBC mophology is not important for the diagnosis of infectious diseases, but are rather observed during the course of hematologic, hepatic, renal, and metabolic disorders. Parasites targeting RBCs (Plasmodium spp. and Babesia spp.) are discernible to the experienced eye. Platelets or platelet clumps which are on RBCs may be mistaken for these erythrocyte parasites. Although human babesiosis has not been reported to date in some countries including Turkey, indirect evidence of the infection may be present [7].

Erythrocyte ghosts are structures consisting of erythrocyte membrane without any or minor hemoglobin content. The hemoglobin content has leaked into the plasma as a consequence of intravascular hemolysis. Erythrocyte ghosts are encountered in fulminant infections caused by certain bacterial species, especially Clostridium perfringens [6].

White Blood Cells:

Normally two-five white blood cells (WBC) are seen in every high-power field in direct microscopy. Numbers less or more than that are called leukopenia and leukocytosis, respectively. Automated cell counts may give pseudoleukocytosis reports because of nucleated RBCs in circulation. Peripheral smear serves to correct this error [8].

Corrected WBC = Observed WBC × [100 / (100 + NRBC*)]

***NRBC:** The count as the number of nucleated RBCs per 100 WBCs

In PS, the ratio of polymorphonuclear leukocytes to mononuclear cells varies with age, but the most abundant leukocytes in adolescents and adults are neutrophils. In these periods of life; neutrophils, lymphocytes, eosinophils, monocytes, and basophils constitute 45-70%, 20-40%, 1-6%, 2-10%, and less than 1% of leukocytes, respectively. Increase or decrease in these WBC series may be absolute or relative. For example, relative lymphocytosis means that lymphocyte percentage is above normal, total WBC count being in the normal range [2].

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Children less than five years of age have relative lymphocytosis, which is normal [9]. Other causes of relative lymphocytosis include acute viral infections, connective tissue disorders, thyrotoxicosis, and adrenocortical insufficiency. Leukemia, leukemic phase of lymphoma, infectious mononucleosis, hepatits, cytomegalovirus infection, pertussis, and chronic intracellular infections like tuberculosis and brucellosis are among the causes of absolute lymphocytosis [2].

Nuclei of mature neutrophils are made up of two-five segments/lobes, which are interconnected with a thin thread. Their cytoplasm is pale pink or colorless and contains azurophilic or specific granules [10]. Immature (young) neutrophils are called (from the oldest to the youngest) stab (band), metamyelocyte, myelocyte, promyelocyte, and myeloblast.

Myeloblasts are the precursors of granulocytes (neutrophils, eosinophils, and basophils). They have a basophilic cytoplasm. Their nuclei, which are round or oval, have two to five nucleoli, and have a thin and reticular chromatin structure.

Promyelocytes are a bit larger than myeloblasts and have primary granules in their cytoplasm. Nucleoli and chromatin structure are denser.

Myelocytes are smaller than promyelocytes. They have relatively more cytoplasm. Their round or oval nuclei have denser chromatin, and are devoid of nucleoli.

Metamyelocytes are differentiated from myelocytes with their indented nuclei.

In band forms, the nucleus is without segments and in the shape of a straight or curved stab.

One of the immunologic responses of human body to bacterial infections, especially pyogenic ones, is increasing the number of neutrophils (neutrophilia). Neutrophilia is observed not only in infections, but also in every sort of acute inflammation (e.g., myocardial infarction, burns, malignancy). If neutrophil count rises above 40,000/mL, this extent of neutrophilia is called leukemoid reaction. It is present in situations with acute inflammation, including infections. The differences between leukemia and leukemoid reaction are the cells in the latter, which are more mature than myelocytes and increased activity of alkaline phosphatase [11].

In severe infections, microbicide-containing granules inside neutrophil cytoplasm increase both in number and visibility. This is called toxic granulation [2]. Vacuolization should be dealt with similarly.

Döhle bodies are light-colored and peripherally-located structures in neutrophils. When seen, they provide a very sensitive finding for the presence of infectious or other inflammatory processes [6].

Normally, band neutrophils and metamyelocytes are expected not to exceed 8% and 0,5%, respectively, of total number of neutrophils. The term “left shift” is used for an increase of these percentages, which corresponds to a relative increase in neutrophil precursors mentioned above [2].

The opposite of left shift (“right shift”) does exist. However this situation, which is recognizable by hypersegmentation of neutrophils (one neutrophil with an at least six-segmented nucleus or five-segmented nuclei in at least 5% of neutrophils), is an indication of noninfectious processes, such as megaloblastic anemia, iron deficiency anemia, or renal insufficiency [12].

Large lymphocytes with cytoplasmic granules are called large granular lymphocytes, which are essentially cytotoxic T lymphocytes or NK cells. On the other hand, reactive (activated) lymphocytes are cells that have large, indented, or irregular nuclei, and distinctive cytoplasm; they tend to gather around RBCs [2]. Immunophenotyping is a better method to recognize the type of lymphocytes and should be resorted to when necessary.

Epstein-Barr virus (EBV), is the most frequent cause of infectious mononucleosis cases, in which a marked atypical lymphocytosis is generally present. These atypical lymphocytes are often cytotoxic ($CD8^+$) T lymphocytes formed in response to EBV-infected B lymphocytes [13]. Atypical lymphocytes are found in abundance in the second and third week of EBV infection and may persist for up to two months in PS [5]. Human immunodeficiency virus, cytomegalovirus, herpesvirus type 6, adenovirus type 12, and Toxoplasma gondii may also lead to mononucleosis syndromes.

Monocytes are the largest cells in PS. They have a grayish blue cytoplasm with a ground-glass appearance. Their nuclei are large and their shapes are reminiscent of various objects, including horseshoe. Monocytosis is observed in chronic infections like tuberculosis, inflammatory disorders like Crohn’s disease, and leukemia [2].

In severe sepsis caused by various organisms, including SARS-CoV-2, “critical green inclusion” bodies can be seen in neutrophils and monocytes. The patients, in whose blood these inclusions were detected, have passed away in days [14].

Eosinophils are involved in the tissue pathogenesis caused by parasitic helminth infections and atypical pneumonia caused by Chlamydia trachomatis [15]. Thus eosinophilia may be a clue for clinically relevant infections.

Basophils do not carry any significance in the diagnosis of infectious diseases.

Platelets:

While infections, like any other inflammatory process that elevates serum interleukin levels (especially interleukin-6), may increase the circulating platelet count, they can also decrease it both due to effects on platelet production and platelet survival [16,17]. Thrombocytopenia in bacterial infections can occur as a part of sepsis with disseminated intravascular coagulation [17]. Patients with mild symptoms have a slightly increased platelet count, whereas thrombocytopenia is a hallmark of severe COVID-19 infections [18].

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