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COMPLETE BLOOD COUNT: INDICATIONS AND INTERPRETATION

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A CORRECT INTERPRETATION OF THE COMPLETE BLOOD COUNT MAKES IT POSSIBLE TO POINT TOWARDS DIAGNOSTIC LEADS AND TOWARDS THE RATIONAL ORDERING OF FURTHER INVESTIGATIONS

Abstract

The complete blood count is the most frequently ordered laboratory test, all conditions taken together. In general terms, it is indicated to confirm a clinical finding, to look for a possible abnormality in an unrevealing clinical picture, or to quantify a known abnormality. Interpretation of the complete blood count involves the analysis of all the quantitative data (numerical values) and of the qualitative data (comments), and the determination of the degree of the quantitative abnormalities. When correct, this interpretation makes it possible to point towards diagnostic leads and towards the rational ordering of further investigations. These data must be integrated with the data of the history, of the clinical examination and with the other laboratory results.

Introduction

The complete blood count is the most frequently ordered laboratory test, all conditions taken together. It provides information on the blood cells that contribute to maintaining the integrity of the organism: oxygenation of the tissues, defence of the organism against pathogens, prevention of the risk of bleeding. The complete blood count expresses the result of:

- the count of the cellular elements of circulating blood (red cells, white cells and platelets), together with parameters that make it possible to characterise the erythrocyte population (red cell indices).

- the differential white cell count: determination of the proportion of the different types of leucocytes (neutrophils, eosinophils, basophils, lymphocytes, monocytes) and the detection of any other cells (abnormally encountered in the blood).

The values of the normal complete blood count vary with age (newborn, child, adult) and with sex. In the adult, in the absence of disease, there is no physiological change of the complete blood count with ageing.

1. Causes of error when performing the complete blood count

These errors are normally detected, taken into account and "corrected" by the laboratory. However, they must be known to the clinician so that, on the one hand, he has a notion of the limits of validity of the results reported and so that, on the other hand, he understands why in certain cases only part of the complete blood count can be reported.

• Analysis of the red cells

Erroneous readings of measured values (RBC, Hb, MCV) lead to alterations of the calculated values (Hct, MCHC, MCH). The errors may be due to: - agglutination of the red cells or haemolysis: only the Hb is accurate - a lactescent plasma or turbidity of the medium (hyperleucocytosis); only the RBC, the Hct and the MCV are accurate.

> **Hyperchromia does not exist:** an MCHC > 36 % is observed exclusively in spherocytosis; in all other cases it is a laboratory error.

• White cell count

After lysis of the red cells, the analyser counts the number of nucleated cells and not directly the number of leucocytes. Yet there may be erythroblasts in the blood (nucleated precursors of the red cell line) which will be counted among the leucocytes, so the count is falsified. In this case, the erythroblasts will be identified by establishing the differential white cell count (in which they are not included) under the microscope, which makes it possible to subtract them from the number of nucleated elements and to correct the differential.

- **Platelet count**

The analyser counts the platelets within defined size limits. Platelet aggregates may cause spurious thrombocytopenias. These aggregates may be the consequence of a difficult venepuncture, of too long a delay between collection and measurement (in that case, re-collect directly at the laboratory, if possible), or may be induced by the anticoagulant (EDTA); in this last case, the patient must be re-sampled on other anticoagulants (citrate or heparin).

As a general rule, in the event of an unusual thrombocytopenia, of an abnormality of the number of leucocytes, or of a distribution not corresponding to the clinical context, a verification must be carried out (differential under the microscope, checking of the platelet count, etc.) on the blood smear.

2. Indications for the complete blood count

In general terms, the complete blood count is indicated in the following cases:

- to confirm a clinical finding or impression; for example, a fall in haemoglobin in the face of a suspicion of anaemia, or a rise in the neutrophils in the face of a possibly bacterial sore throat.

- to look for a possible abnormality in the face of an unrevealing clinical picture, or without clinical signs and without orientation; for example, unexplained asthenia with weight loss, or isolated splenomegaly,

- to quantify a known abnormality; for example, to follow the course of the blast count of an acute leukaemia in the initial phase of treatment

- to monitor a patient in remission; for example of a CML.

The complete blood count must be ordered urgently in the face of symptoms that may raise the fear of:

- a very low Hb level (acute anaemia): major asthenia with pallor, polypnoea, tachycardia, or even a systolic murmur, headaches, "floaters" and intense thirst,

- a major granulocytopenia: fever, infectious syndrome, especially accompanied by sore throat and/or oral ulcerations,

- a thrombocytopenia: haemorrhagic syndrome with purpura.

The finding of a severe anaemia (<7 g/dl), of a major neutropenia (<200/µl) or of a thrombocytopenia at risk (<20 000/µl) must prompt discussion of urgent management in a specialised setting.

3. Interpretation of the complete blood count

A correct interpretation of the complete blood count makes it possible to point towards diagnostic leads and towards the rational ordering of further investigations. These data must of course be integrated with the data of the history, of the clinical examination and with the other laboratory results. The abnormalities detected on the complete blood count may involve the different cell lines:

a. Red cell abnormalities

◆ Anaemia

An anaemia is defined by the fall of the Hb below the normal values. The classification of the anaemia, indispensable to the diagnostic approach, is deduced from the erythrocyte parameters:

The MCV indicates whether the anaemia is normocytic (normal value), microcytic (value below normal) or macrocytic (value above normal).

The MCH and the MCHC indicate whether the anaemia is normochromic (normal values) or hypochromic (values below normal).

The marrow response to the anaemia is judged at the level of the peripheral blood by the **reticulocyte count**. This test is not part of the standard complete blood count, but must be requested for normocytic or macrocytic anaemias when the aetiology is not obvious. A priori, it is pointless to request it in the presence of a microcytic anaemia.

• **the regenerative anaemias** (normocytic or macrocytic) related to a peripheral over-destruction of the red cells (excessive haemolysis), to an acute haemorrhage, or to a defect of erythropoiesis in the course of repair (iron treatment of an iron deficiency, or vitamin treatment of a megaloblastic anaemia).

• **the aregenerative anaemias**

- microcytic (hypochromic or normochromic): related to a defect of Hb synthesis, they lead one to look first for an iron deficiency or an inflammatory syndrome,

- macrocytic, they prompt a search, according to the circumstances, for alcoholism, a vitamin deficiency (vitamin B12 or folate) or a myelodysplasia

- normocytic, they correspond to a production disorder and justify performing a marrow study, which may lead to the diagnoses of aplasia, or even of pure red cell aplasia.

❖ Polycythaemia

Polycythaemia is characterised by a rise in the Hct and in the Hb due to an increase in the total erythrocyte volume (TEV). Spurious polycythaemias must be ruled out from the outset, those in which the rise in the Hct, the Hb and the RBC is not accompanied by an increase in the TEV: tall and plethoric subjects, haemoconcentration (dehydration) through a fall in the plasma volume, spurious microcytic polycythaemia with a rise in the RBC but not in the Hb or the Hct. Spurious polycythaemias are frequent in young adult males.

Polycythaemias may be secondary to hypoxia (chronic respiratory failure, heart disease, prolonged stay at altitude, smoking) or to an inappropriate secretion of EPO (renal disease), or primary (polycythaemia vera).

b. White cell abnormalities

These abnormalities are of two types:

- the quantitative abnormalities, by excess or by default, of the circulating cells normally present in the blood,

- the presence of cells that are normally absent from the circulation ("physiological" cells of the bone marrow, or pathological cells arising from a malignant clone).

❖ Hyperleucocytosis

Hyperleucocytosis may be more or less marked and must, of course, be interpreted with the data of the differential count. It may be reactive and benign (e.g. hyperleucocytosis with neutrophilia in reaction to a bacterial infection) or, on the contrary, malignant (hyperleucocytosis with circulating blasts in the setting of an acute leukaemia).

✓ Neutrophilia (without myelaemia)

It corresponds to a neutrophil count above 7 000/µl. It is most often, but not always, accompanied by a hyperleucocytosis. It may arise from 2 situations:

- reactive, benign, transient and spontaneously resolving: this is the most frequent

- the expression of a myeloproliferative disorder. The situation in which only the neutrophils are increased is exceptional. Neutrophilia is often physiological. In the other cases, it is the expression of a more or less obvious pathological process:

- **The context is suggestive:** bacterial infections (abscess, sore throat, appendicitis, whitlow, genital and urinary infections), progressive inflammatory disease (rheumatoid arthritis, etc.), acute allergic reaction, tissue necrosis (myocardial infarction, acute pancreatitis, etc.), major haemorrhage or haemolysis, advanced and known cancer or Hodgkin's disease, treatment with lithium or corticosteroids, exposure to benzol and to irradiation (at-risk occupations), smoking (> 15 cigarettes/day).

- **The context is not suggestive:** an inflammatory syndrome must be looked for (the rise in the ESR, in the CRP, in fibrin prompts a search for a tumour or a deep-seated infection), but a latent infection may very well not be accompanied by an acceleration of the ESR.

✓ Eosinophilia

Allergies and parasitic infections are the most frequent aetiologies.

✓ Lymphocytosis

The morphology of the cells (normal or not, with or without the presence of hyperbasophilic mononuclear cells) is fundamental for the orientation of the diagnosis. It may be:

- a lymphocytosis reactive to infectious diseases (infectious mononucleosis, CMV and HIV infections, or even whooping cough, an almost exclusive cause in the child),

- malignant haemopathies (CLL, lymphomas, etc.), the dominant aetiologies in the adult. In this case, **immunophenotyping** completes the morphological study and plays a decisive role in the diagnosis.

✓ Monocytosis

It may be reactive (bacterial, viral or parasitic infections, onset of recovery from marrow aplasia or from agranulocytosis) or proliferative (acute leukaemias, myelodysplasias).

❖ Leucopenia

Leucopenia is essentially the result of a neutropenia, sometimes of a lymphopenia associated or not with other cytopenias. Leucopenias may have multiple aetiologies.

✓ Neutropenia

The risk of infection becomes significant below 500/µl. When there are fewer than 200/µl, one speaks of agranulocytosis. Neutropenia may be isolated or associated with other cytopenias.

The neutropenia is moderate (between 800 and 1700/µl):

• if it is stable and isolated, think of a distribution disorder or of the ethnic neutropenia of black subjects

• rule out bacterial (typhoid, brucellosis), parasitic (malaria, etc.), viral (viral hepatitis, measles, influenza, HIV infection) and drug-induced causes

• think of an immune disorder, of Felty's syndrome (polyarthritis + thrombocytopenia)

• if splenomegaly and/or thrombocytopenia, think of a hypersplenism.

The neutropenia is profound (<800/µl), perform a bone marrow aspirate:

• if several lines are involved (frequent association with an anaemia, a thrombocytopenia, the presence of abnormal cells on the complete blood count) it may be an acute leukaemia, a myelodysplasia or another haemopathy.

• if there is pure granulocytic involvement, look for an immuno-allergic or toxic cause, or an LGL leukaemia (large granular lymphocytes). In the absence of a diagnostic argument, one will speak of "chronic idiopathic neutropenia".

✓ Lymphopenia

In the majority of cases, it is an acquired lymphopenia: chemotherapy, radiotherapy, immunosuppression for organ transplantation, HIV infection).

c. Platelet abnormalities

❖ Thrombocytosis (or hyperplatelet count)

It entails a risk of thrombosis.

- the secondary, reactive, transient thrombocytoses, frequent, most often moderate (<800 000/µl),

- the "essential" thrombocythaemias, primary, chronic, rarer and usually higher (up to 2000000/µl) with an increased thrombotic risk.

The discovery of a thrombocytosis makes it imperative to carry out a work-up in order to recognise its aetiology and to decide on a therapeutic course of action. This orientation work-up must, in the first instance, look for the cause of a secondary thrombocytosis. Besides the clinical data (history and physical examination), it rests on the analysis of the complete blood count with examination of the blood smear, on the inflammatory work-up and on the iron work-up. The causes of secondary thrombocytosis are varied, of a more or less clear mechanism, and sometimes associated in the same patient:

- absence of the spleen (splenectomy above all, asplenia far more rarely); the presence of Howell-Jolly bodies constitutes a strong argument in favour of this hypothesis.

- iron depletion, whatever its aetiology, - inflammatory disease (connective tissue disease, RA, etc.),

- cancer, known or not; one must think first of the broncho-pulmonary and digestive sites,

- major haemolysis and acute haemorrhage, in which the thrombocytosis is directly related to marrow regeneration,

- myelodysplastic syndromes (sideroblastic anaemias, 5q- syndrome).

In the absence of one of these aetiologies, a myeloproliferative disorder must be considered; here again several conditions may be accompanied by a thrombocytosis.

❖ Thrombocytopenia

The aetiologies are numerous:

- a fall in production owing to a reduced number of megakaryocytes [aplasia, malignant proliferation of another cell line (leukaemias), invasion by cancer metastases]

- a peripheral destruction

- a sequestration in an enlarged spleen (hypersplenism).

d. Other abnormalities

❖ Myelaemia

Myelaemia is defined as the presence in the peripheral blood of immature cells of the granulocytic line (metamyelocytes, myelocytes, promyelocytes and sometimes even blasts)

A very moderate myelaemia (2% of myelocytes or metamyelocytes, for example) cannot be considered worrying if it is transient. Present on several occasions, it must be considered pathological. The circumstances are numerous and of very different meanings: in the case of recovery from agranulocytosis, a moderate, transient myelaemia is frequent. During severe bacterial infections, notably broncho-pulmonary or intra-peritoneal, a marked myelaemia (up to 10-15%) may be associated with a strong neutrophilia (or even a neutropenia) in an infectious context. Certain malignant conditions are accompanied by a persistent myelaemia:

- A marked hyperleucocytosis with splenomegaly must make one think of a CML and prompt a cytogenetic study; the association of a splenomegaly with tear-drop red cells (dacryocytes) suggests a primary myelofibrosis (chronic myeloid splenomegaly) and makes it imperative to perform a BMB (bone marrow biopsy); when the hyperleucocytosis is moderate, without morphological abnormality of the red cells but with a cytopenia of the other lines (anaemia and/or thrombocytopenia), one must think of various malignant conditions (acute leukaemia, marrow metastases of a cancer, marrow invasion by a lymphoma, primary myelofibrosis, chronic myelomonocytic leukaemia) and perform a marrow study comprising a bone marrow aspirate and possibly a BMB, according to the diagnostic orientation.

❖ Presence of other immature cells in the blood

Other cells normally absent from the blood may be observed there. Thus, one may find:

- **erythroblasts** (precursors of the erythroblastic line) may be associated with myelaemia (one then speaks of erythromyelaemia). One must think first of an acute haemolysis (haemolysis work-up) or of a marrow invasion (in this case, there may be an isolated leucopenia, or one associated with the fall of another line). In this last situation, a marrow study (aspiration with BMB) is imperative.

- **blasts (or leucoblasts)**; these are immature cells that develop in the bone marrow. They are incapable of differentiating. Their presence indicates a monoclonal proliferation of stem cells. Blasts may have cytological, cytochemical or immunophenotypic features that link them to the lymphoid or myeloid lines. Thus a distinction is made between the acute myeloblastic leukaemias and the acute lymphoblastic leukaemias.

❖ Presence of abnormal lymphoid cells

The development of various lymphoproliferative disorders may be accompanied by the passage into the blood of cells of abnormal morphology. Their recognition and their identification may lead to a diagnosis (malignant lymphomas of different types, different varieties of lymphoid leukaemias).

❖ Pancytopenia

It is defined as the simultaneous fall of the 3 myeloid lines (RBC, neutrophils, platelets) below the normal values. The severity depends on the depth of each cytopenia. A neutropenia below 500/µl may be responsible for a serious bacterial infection, and a thrombocytopenia below 20000/µl for a haemorrhagic syndrome. The anaemia is generally of progressive onset and, for that reason, better tolerated. Pancytopenia may be of central origin through a marrow production disorder (quantitative or qualitative marrow failure, or invasion) or, more rarely, of peripheral origin (destruction or extra-medullary sequestration of the blood elements).

Pancytopenia with regeneration (rise in the reticulocytes): think first of a hypersplenism (in general the pancytopenia is moderate),

Pancytopenia without regeneration (reticulocytes low or not increased). Other elements of the complete blood count may suggest an orientation of the investigations:

◆ **MCV:** - markedly increased (120-140 fl): consider a megaloblastic anaemia first - moderately increased (<110 fl): look for a myelodysplasia. A bone marrow aspirate should be performed in the 2 cases.

◆ **Reticulocytes markedly decreased (<25000/µl):** think of a marrow aplasia; a marrow study must be performed (bone marrow aspirate with BMB),

◆ **Erythromyelaemia:** think of a primary myelofibrosis or of the metastatic invasion of a known or unknown cancer; the BMB is indispensable.

◆ **Presence of abnormal cells on the blood film:** orientation towards different diagnoses according to the nature of the abnormality (e.g. acute leukaemia in the presence of blasts, myelodysplasia in the presence of morphological abnormalities characteristic of the neutrophils); in both cases, the bone marrow aspirate is indispensable.

In the absence of laboratory signs of orientation, the marrow study with bone marrow aspirate and BMB must be carried out. The BMB must be done insofar as aspiration alone cannot bring certainty about abnormalities such as the depletion of the myeloid tissue, the presence of metastatic cells or the existence of a myelofibrosis. This analysis may therefore open the way to the diagnoses of marrow aplasia, fibrosis or tumour invasion.

4. Complete blood count abnormalities associated with certain physiological or pathological situations

In the absence of information on these situations, the discovery of these complete blood count abnormalities must lead one to consider them. In the contrary case, knowledge of these situations should make it possible to interpret the abnormality immediately. These notions must be perfectly well known in order to avoid missing a progressive disease, or carrying out useless investigations that are a source of worry for the patient and of unjustified expense.

a. During pregnancy

◆ Anaemia is frequent during pregnancy. It is important to distinguish the spurious anaemia due to physiological haemodilution (a rise in the plasma volume greater than that of the Hb) during the 2nd trimester of pregnancy from the true anaemias related to pregnancy: microcytic through iron depletion or macrocytic through folate deficiency, above all in multiparous women. The two deficiencies may be associated.

◆ There is often a neutrophilia during the 3rd trimester, always moderate, to be affirmed only after making sure of the absence of infection, especially urinary infection in this context.

◆ Moderate thrombocytopenias (above 100 000/µl) may be observed, readily recurring with each pregnancy and disappearing after delivery. They do not lead to haemorrhagic manifestations. More marked thrombocytopenias must prompt a search for another cause. In all cases, the child will have to be monitored at delivery.

b. In cirrhosis

The generally macrocytic and aregenerative anaemia is multifactorial; it may combine: haemodilution (rise in the plasma volume), vitamin deficiency (folate), toxicity of alcohol on the bone marrow, occult gastrointestinal bleeding (ulcer, oesophagitis, gastritis, etc.), excessive haemolysis

In acute alcoholism, cytopenias may be found which regress on stopping the intoxication. The mechanism is essentially central (sideroblastic anaemia, with neutropenia and thrombocytopenia), sometimes peripheral (haemolytic anaemias with acanthocytosis).

c. In chronic renal failure

A normochromic, normocytic or slightly macrocytic, non-regenerative anaemia, relatively well tolerated even at values of the order of 6 g/dl, is inevitably observed in the course of chronic renal failure. Within the overall management of renal failure, it is now treated and controlled with recombinant erythropoietin (rHuEPO). Indeed, this anaemia is essentially due to erythropoietin deficiency. But there is also a reduction in the lifespan of the red cells.

d. In endocrine disorders

• Hypothyroidism is the main endocrine cause of a normochromic anaemia, often normocytic, sometimes macrocytic (without vitamin deficiency), always non-regenerative. It remains moderate and disappears on correction of the hormone deficiency.

• In hyperthyroidism, a slightly microcytic anaemia without iron deficiency may be observed, and fairly frequently a moderate neutropenia.

• Adrenal insufficiency (Addison's disease) is accompanied by a mild, normochromic, normocytic, non-regenerative anaemia.

• Pituitary insufficiency is accompanied by a central, normochromic, normocytic, non-regenerative anaemia.

e. In inflammatory syndromes

During chronic inflammatory syndromes (polyarthritis, collagen diseases, angiitis, deep abscesses, cutaneous necrosis, cancers, chronic viral infections, etc.) or more acute but intense ones (acute bacterial infection), various changes of the complete blood count may be observed: a frequent, non-regenerative, normochromic, normocytic anaemia, then more and more hypochromic and microcytic after several weeks, hyposideraemic, with a fall in the binding capacity of transferrin, a tendency to a rise in serum ferritin, a hyperleucocytosis related to the neutrophilia with sometimes a myelaemia, and a sometimes marked thrombocytosis (up to 1000000/µl).

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