Spotlight on hematology

Causes for the occurrence of microcytic erythrocytes without changes in shape

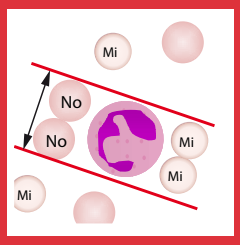
Acquired

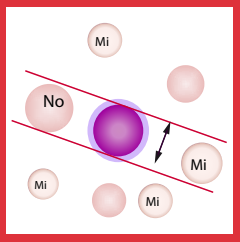
- Iron deficiency
- Anemia with chronic diseases
- Myelodysplastic syndromes with iron incorporation deficiency (sidero-achrestic anemia)
- Acquired sideroblastic anemia
- Hyperthyreosis
- Lead-, cadmium-, aluminum poisoning

Inherited

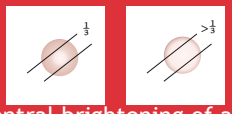
- Thalassaemias
- Other hemoglobinopathies
- Congenital sideroblastic anemia
- Atransferrinemia
- Ferro chelate deficiency

Microcytosis and hypochromasia in microscopy





Comparison with normocytes
Two normozytes correspond to approx. the diameter of one neutrophil or one normocyte approx. to the diameter of a small lymphocyte nucleus.



The central brightening of a normocyte is approximately one-third of the cell diameter.

Microcytic erythrocytes

MQZH 2016-1

Introduction

Microcytic erythrocytes can appear in the peripheral blood with and without shape changes. The morphological appearance is as varied as the different underlying causes. Whether microcytic cells lead to a low MCV (mean corpuscular volume) depends on whether the changes affect the major proportion of the cells or only part of the population.
In our proficiency testing survey specimen 2016-1 H3A, there was microcytosis and hypochromasia. The patient suffers from polycythamia vera (PCV). Regular phlebotomies (therapeutic bloodletting) lead to iron deficiency and thus to microcytosis of the erythrocytes. The erythrocyte count is increased due to polycythemia vera.

Erythrocytes are referred to as microctic
when the MCV < 80 fl or the diameter is < 6 µm.

Mechanism of development of microcytic erythrocytes without changes in shape

If one looks at erythropoiesis, the hemoglobin synthesis begins in the proerythroblast. It continues up to the level of the polychromatic erythroblasts. Then the maximum hemoglobin concentration in the cell leads to condensation in the nucleus and thus makes the nucleus incapable of undergoing mitosis after the fourth mitosis. If the hemoglobin concentration in the erythrocytes, and thus during mitoses also in the cell nucleus, is abnormally low, a further fifth mitosis at the level of the polychromatic erythroblasts results. This leads to the formation of small, round microcytic erythrocytes.
In contrast, disturbances of mitosis (e.g. by vitamin B12 deficiency) lead to an early stop after the third mitosis, premature nucleus loss and thus to the formation of abnormally large erythrocytes.

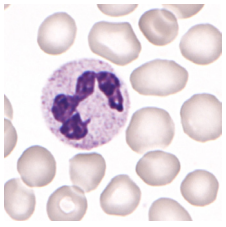
Aspects of automated erythrocyte analysis

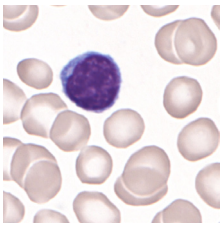
Hypochromasia

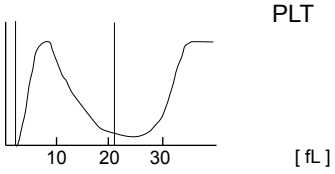
In microcytic erythrocytes without changes in shape, the mean corpuscular hemoglobin (MCH) of the cell is usually reduced. Whether the medium hb concentration of the cell is also reduced, can depend on the device technology used. In devices with hydrodynamic focusing or optical measurement of rolled up ERCs, the MCHC reference range is relatively narrow. This allows to very reliably detect a reduced average hb concentration in cells.

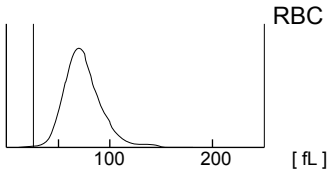
Microcytosis

Microcytic erythrocytes without changes in shape usually do not reach an MCV of < 65 fl in humans; therefore there is no risk of analytical measurement errors in hematology devices.
However, microcytic erythrocytes with form changes often have a very low cell volume and in hematology machines with 3-part differentiation can lead to interferences in the platelet measurement.









MQ 2016-1 H3A Mycrocytosis: morphology and histograms

Spotlight on hematology

Microcytic erythrocytes with changes in shape

Fragmento-, kerato, akanthocytes, „bite cells“ and microspherocytes represent only part of the erythrocyte population.

The reasons for these changes are varied and an accurate morphological assessment can be crucial for making a diagnosis. In the case of fragmento- and keratinocytes, the correct recognition of the same can be indicative of possibly life-threatening situations requiring immediate intervention.

Possible causes for fragmentocytes

- DIG disseminated intravascular coagulation e.g. in the case of acute promyelocyteleukemias or metastasized carcinomas
- MAHA microangiopathic hemolytic anemia , e.g. with
  - Thrombotic thrombocytopenic purpura
  - HUS - hemolytic uremic syndrome
  - drug-induced
  - HELLP syndrome
  - Extensive burns
    Mechanical injuries , artificial heart valves, extracorporeal circulation

Keratocytes and bite cells

In the English-speaking world, fragmentocytes (schistocytes) are distinguished from two other morphologically abnormal erythrocyte variants. The morphological distinction of these forms can be interesting depending on the question since its emergence, as compared to that of fragmentocytes, can be caused by other pathophysiological processes.

About
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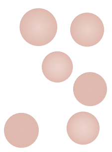
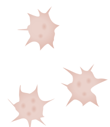
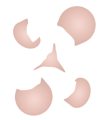
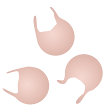
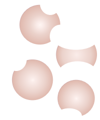
Morphological overview of various forms of microcytic erythrocytes

	Microcytes without changes in shape	Microspherocytes	Acanthocytes	Fragmentocytes (syn. schistocytes)	Keratocytes (syn. „horn cells“)	Bite cells
Appearance Microscopy						
Morphological Description	Regular round shape	• Small, spherical cells • No central brightening	• 3-20 prickly projections of unequal length and distribution • The ends are usually pointy, occasionally also button-like • No central brightening *Important: Demarcation from normocytic echinocytes. Cells with central brightening and equally distributed projections of similar length.*	Erythrocyte fragments: • Egg shell shape • Helmet shape • Triangular shape • Half-moon shape • No central brightening	• Special form with paired spines (usually 2, rarely 4-6) • Pre-keratocyte: ERC with pseudo vacuole at the cell periphery • Central brightening	• Round shape still recognizable to different extents, with a „bite“ on one or two sides. • Central brightening • Classic „bite-cell”, “double-bite-cell“ or „apple-core-bite cell“
Mechanism of development	Reduced Hb synthesis leads to increased mitoses and to formation of microcytic cells	ERC fragments with a relative lack of membrane form microspherocytes	A structural defect of the erythrocyte membrane (often of the lipid distribution) leads to an increase of the cell surface without an increase of the cell volume. The formation of spiny protrusions results.	Constrictions of fibrin strands in the vessel lumen with tearing-off of a cell portion and remaining residual fragment Denaturing of spectrin by heat Damage due to mechanical effects	Fusion of membranes touching another with formation of a pseudo-vacuole. Subsequent membrane rupture.	During the passage through the spleen, Heinz bodies (precipitates of denatured hemoglobin) are removed from the cells. The remaining ERC appears as if „a bite had been taken out“
Causes	Acquired Iron deficiency, anemia with chronic disease, MDS, etc. Inherited Thalassamias and congenital hemoglobinopathies, congenital sideroblastic anemia, etc.	see fragmentocytes/schistocytes hereditary spherocytosis autoimmune hemolytic anemia	Abetalipoproteinemia (hereditary) Severe hepatic impairment Myelodysplastic syndromes Rare neurological disorders (neuroacanthocytosis) after splenectomy	DIG-disseminated intravascular coagulation MAHA-microangiopathic hemolytic anemia HELLP syndrome Extensive burns Mechanical damage	see fragmentocytes/schistocytes also with kidney disorders: glomerulonephritis, uremia and after transplantation	Unstable hemoglobin Chemical damage Heinz bodies are usually detectable only after splenectomy or during hemolytic crisis. Supravital stains e.g. brilliant cresyl blue required.