Spotlight on hematology

Fragmentocytes (Schistocytes) MQZH 2017-04

Introduction

Erythrocytes designated as fragmentocytes (Lat. frangere = to rupture) or schistocytes (Gr. schistos = to split), are a morphological atypia, which are distinguished by extensive tearing off of the cell membrane. The loss of cell volume is smaller relative to the loss of cell membrane, for which fragmentocytes are hyperchromic.
The cause for these form changes is mechanical cell damage, which can have different causes. Particularly significant from a diagnostic perspective is the formation of fragmentocytes through constriction of fibrin strands in the lumen of vessels of microcirculation with thrombotic microangiopathy (TMA). The two most important with a syndrome accompanying TMA are TTP (thrombotic thrombocytopenic purpura) and HUS (hemolytic uremic syndrome), which will cause the death of the patient if not treated. Due to the special formation mechanism and their clinical significance, fragmentocytes should be demarcated from other deformed erythrocytes (poikilocytosis). Our round robin test preparation 2017-4H3B originates from a patient with a known immune thrombocytopenia (ITP) and hypovolemic shock.

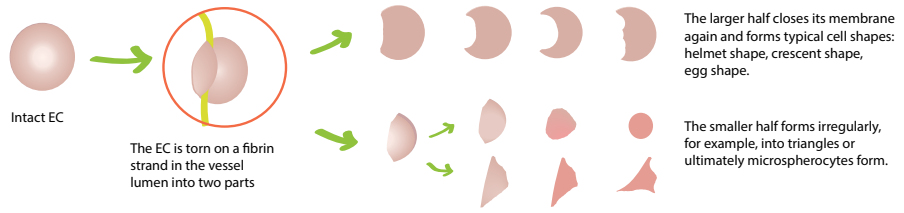
Causes for the formation of fragmentocytes

Thrombotic microangiopathy (TMA)
With TMA, free thrombocytes and fibrin strands deposit on the vascular endothelium of microcirculation due to different reasons. They damage thrombocytes and erythrocytes that flow by, which leads to thrombocytopenia and anemia with fragmentocytes. The resulting microangiopathic hemolytic anemia (MAHA) presents itself with a negative DAT, elevated LDH, and elevated bilirubin as well as low haptoglobin. Thrombocytes accumulate in the vessels in the form of microthrombi consisting of thrombocytes and Von Willibrand factor. TMA is a systematic disease that can affect all organs; affected particularly frequently are the brain, heart, and kidneys.

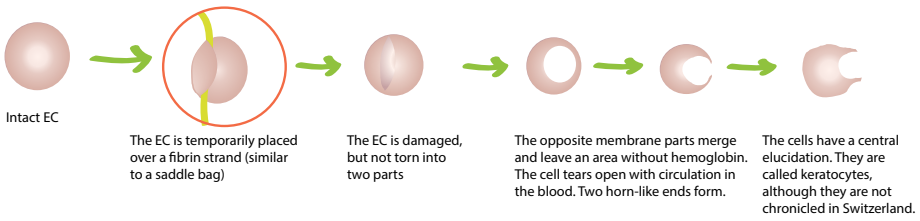
The TTP is primarily found in adults, for which renal insufficiency is less pronounced than with HUS, which more likely appears in children and typically leads to kidney failure.

Disseminated intravascular coagulation (DIC)
The same mechanism can also lead to the formation of fragmentocytes with disseminated intravascular coagulation, e.g. in the course of obstetric complications, sepsis or malignancies, such as acute promyelocytic leukemia (APL).

Schematic depiction of the formation of fragmentocytes



Formation mechanisms from similar shapes, which are not included in the fragmentocytes



Macroangiopathic causes
Mechanical damage to artificial heart valves or through an unusual increase of turbulence in the blood flow (shear forces) with severe heart defects, e.g. aortic stenosis or with malignant hypertension.

Additional causes
- Extensive burns (heat damage of the spectrin in the EC membrane)
- Mechanical damage of the erythrocytes through extracorporeal circuits (extracorporeal membrane oxygenation, ECMO)
- Malignancy with bone marrow carcinosis

Primary thrombotic microangiopathy (TMA)

Thrombotic thrombocytopenic purpura (TTP)
The cause is a congenital or secondary defect of the zinc protease ADAMTS13, which ultimately leads to the intravascular formation of thrombi.

In addition to the currently pronounced thrombocytopenia and microangiopathic hemolytic anemia (MAHA) with fragmentocytes, the exam also reveals renal insufficiency, neurological symptoms, and fever (classical pentad). However, this classical form is often not fully pronounced. Due to the high mortality rate (up to >90% without treatment), plasma exchange therapy should be started with evidence of MAHA with numerous fragmentocytes in conjunction with a high LDH and thrombocytopenia without an alternative explanation.

Hemolytic uremic syndrome (HUS)
STEC HUS
Triggers are bacterial toxins, e.g. Shiga toxin producing Escherichia coli. In the case of HUS, there is a hemolysis (MAHA) with fragmentocytes, a, thrombocytopenia, and renal insufficiency to acute kidney failure. In most cases there is a precursory episode of diarrhea (approx. 90%).

In 2011 a large-scale EHEC epidemic (EHEC=enterohemorrhagic Escherichia coli) occurred in Germany with 732 HUS cases, from which 28 patients died.

aHUS (associated with complement)
This HUS type is based on abnormalities of the complement system.

Secondary thrombotic microangiopathy

- Pregnancy (HELLP syndrome, etc.)
- System. diseases (e.g. vasculitis)
- Infections (e.g. HIV)
- Disseminated tumors
- Medications (e.g. Mitomycin C)
- Glomerulonephritides
- Malignant arterial hypertension
- Transplants of solid organs or bone marrow or stem cell transplants
- Patients under immune suppression

Spotlight on hematology

Automated process for verifying fragmentocytes

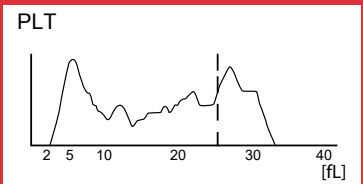
Device flags with indication of fragmentocytes or, with larger devices, partially even the counting of fragmentocytes may be helpful when preparing the findings.

The fragmentocyte count of the devices is readily at hand and demonstrates a high predicative value for negative sample in previous works (samples without fragmentocytes are reliably recognized). In the case of suspicious device findings / flags, the fragmentocytes must be looked for microscopically.

Interferences with the thrombocyte measurement

Hematology analyzers show problems with the correct determination of the thrombocyte count - depending on the method for measuring the thrombocytes. If thrombocytes and erythrocytes are measured in the same measurement channel, interference between the thrombocytes and the small fragmentocytes will occur. This can simulate an inaccurately high (inaccurately normal) thrombocyte value.

Respective device flags and atypically jagged Tc curves, which no longer touch the baseline in the range of the upper discriminator, are an indication of these interferences. If there is doubt as to the correctness of the thrombocyte value due to warning signs or due to the distribution curve, this should be reviewed with the help of the counting chamber.



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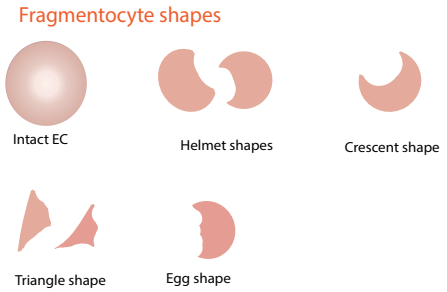
Diagnostics and morphological criteria of fragmentocytes

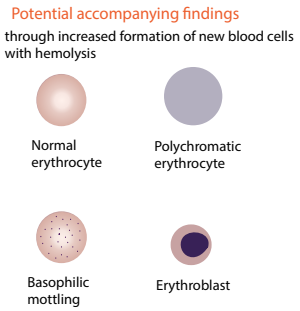
Microscopic examination of the peripheral blood smear is the gold standard even today. The ICSH (International Council for Standardization in Hematology) published the following recommendations in 2011 for the microscopic examination:

Technique
Examination of the proper smear location. (At least) 1000 erythrocytes are assessed. The share of fragmentocytes is specified as a percentage.

Morphology
- Fragmentocytes are always smaller than normal EC and have no central elucidation
- The following typical forms are included for fragmentocytes: helmet shapes (helmet cells), crescent/ egg shape (micro-crescents). If there are other shapes, small fragments are also included in triangular shapes.

As accompanying findings, there are also frequently signs of an increased formation of new blood cells with polychromasia (reticulocyte increase), basophilic mottling, and potential erythroblasts.



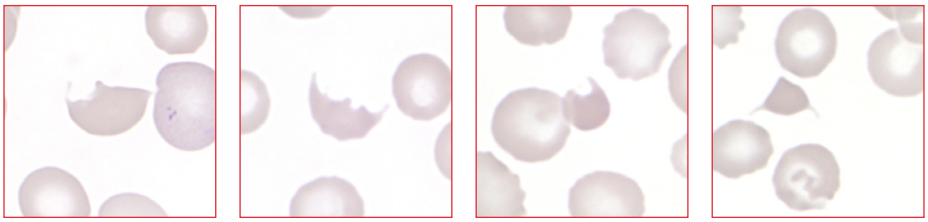


Assessment

The fragmentocyte count as a percentage is only recommended if the fragmentocytes in the examined blood depict the primary morphological abnormality. If fragmentocytes develop in the context of other serious morphological changes (anisopoikilocytosis), the ICSH only recommends a qualitative indication.
A value > 1% of fragmentocytes applies for the suspected diagnosis of thrombotic microangiopathy (TMA). If there are no fragmentocytes in the smear in the case of a clinical suspicion of TMA, the examination should be repeated regularly, as the fragmentocytes can develop with a delay.

Images from MQ 2017-4 H3B

Fragmentocytes



No Fragmentocytes