Hematology **Editor: C.T. Nebe**

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Significance of teardrop cells in peripheral blood smears

Abstract: Teardrop erythrocytes (syn. dakryocytes) play a key role in the evaluation of peripheral blood smears in patients with anemia, especially as part of the "leukoerythroblastic picture". Teardrop-shaped red blood cells can be seen in a wide range of diseases that lead to bone marrow fibrosis, which is often accompanied by extramedullary hematopoesis. The differential diagnoses encompass primary myelofibrosis (PMF), myelodysplastisc syndromes during the late course of the disease, rare forms of acute leucemias and myelophtisis caused by metastatic carcinoma. Rarely, MF associated with post-irradiation, toxins, autoimmune diseases, metabolic conditions, inborn hemolytic anemias, iron-deficient anemia or β-thalassaemia can lead to the formation of teardrops as visualized on peripheral blood smears.

Keywords: blood smear evaluation; bone marrow fibrosis; dacryocytes; extramedullary hematopoesis; myelofibrosis; myeloproliferative disease; red blood cells; teardrop cells.

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Definition

Teardrop erythrocytes are poikilocytes that allow for conclusions to be drawn about changes in the formation of blood. They have a blunt rounded side and a thinning leaking tip, similar to a tear (Figure 1A). They must be distinguished from artificial "teardrops" that occur in technically inferior preparations of blood smears which often point in one direction in a field of view. "Pseudo-teardrops", caused by the deposition of other erythrocytes, are also not included in this category (Figure 1B). There should be more than one teardrop erythrocyte in a blood smear to warrant a comment in the microscopic assessment. For purely diagnostic purposes, it is often not necessary to quantify teardrops, but it does help with determining the progression of the underlying disease.

Significance

The observation of teardrop erythrocytes ranges from individual forms in a blood smear to numerous teardrop shapes in patients with marrow fibrosis and/or extramedullary hematopoiesis, often yielding a leukoerythroblastic blood smear. The more frequently teardrops occur, the greater their significance in terms of the differential diagnosis will be. In healthy subjects, in reactive inflammatory conditions and in anemia of chronic disease (ACD) and other forms of anemia without marrow fibrosis, they do not occur, or only rarely (e.g. iron deficiency anemia, myelodysplastic syndrome-refractory anemia/MDS-RA, refractory anemia with ringed sideroblasts/RARS). On the other hand, teardrop erythrocytes can be an expression of myelofibrosis and extramedullary hematopoiesis (EMH).

While teardrop red blood cells occur with concurrent anemia or pancytopenia, they are also found as part of the so-called "leukoerythroblastic picture" (Figure 1C). In the latter, one observes not only teardrop shapes, but also nucleated erythrocytes and leukocytosis with myeloid precursors in the peripheral blood. Such changes are often found in patients with solid tumors, prompting the treating physician to look for possible bone marrow metastasis. Both, the suspicion of primary myelofibrosis (PMF) and the suspicion of bone marrow infiltration by tumor cells should always be followed up with further bone marrow diagnostics. This is why it is important to communicate teardrop red blood cells in the comment of the microscopic assessment. In addition to bone marrow aspiration, a bone marrow biopsy is essential here, as tumor cells are difficult to aspirate in the case of pronounced myelofibrosis and because the final classification of a myeloproliferative disease may only be possible in the light of histological findings and in

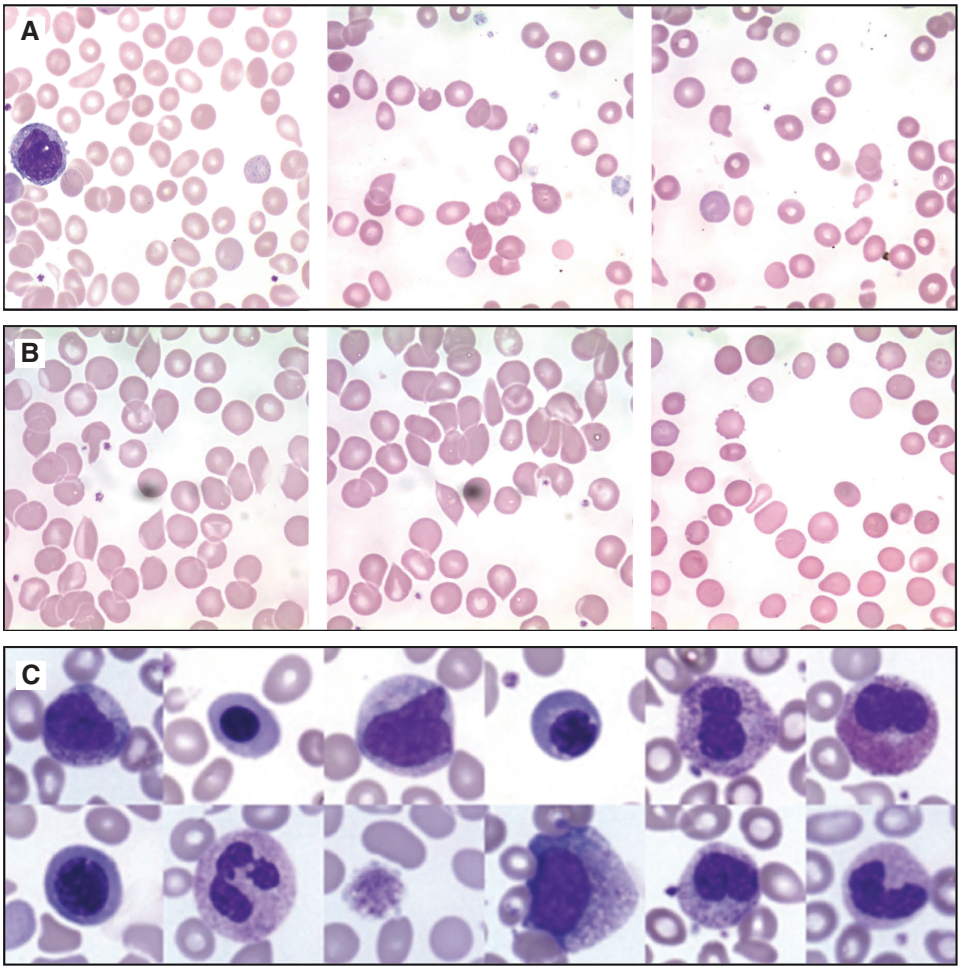

Figure 1 Teardrop red blood cells in the peripheral blood smear.
(A) Genuine teardrop erythrocytes in a case of primary myelofibrosis (PMF) (Pappenheim, 100× magnification). (B) Artifacts: "False teardrops" by juxtaposition of several erythrocytes or teardrops with pointed ends, not typical of real dacryocytes (Pappenheim, 100× magnification). (C) Leukoerythroblastic changes in PMF with transition to AML. Leukocyte morphology in PMF with numerous early myeloid precursors, normoblasts and a giant platelet (Pappenheim, 100× magnification).

many cases only after an extended molecular and immunohistochemical workup.

Below, the cause and differential diagnosis of teardrop red blood shapes in the microscopic examination of blood smears will be discussed, which plays a pivotal role in clarifying the cause of anemia, particularly in elderly patients.

Teardrop shapes due to myelofibrosis

Especially when teardrop shapes are associated with anemia or pancytopenia, the finding is suggestive of the existence of a primary or secondary myelofibrosis. Myelofibrosis is characterized by an accumulation of reticulin and collagen fibers causing fibrotic changes in the bone marrow. Teardrop erythrocytes are especially common with PMF [1] and in connection with other advanced myeloproliferative neoplasms and primary MDS, which may be accompanied by a pronounced fibrosis during the late stage. The fibrosis in the bone marrow leads to mechanical changes in the erythrocyte membrane and cytoskeleton resulting in "teardrop shapes" [2, 3].

The cause of bone marrow fibrosis is a phenomenon that has been extensively studied in the past, in which the composition of the tissue micro environment and production of pro-fibrotic cytokines (such as TGFβ, PDGF) as well as growth factors (such as FGF-R) by megakaryocytes and stromal cells plays an important role [4]. Due to the

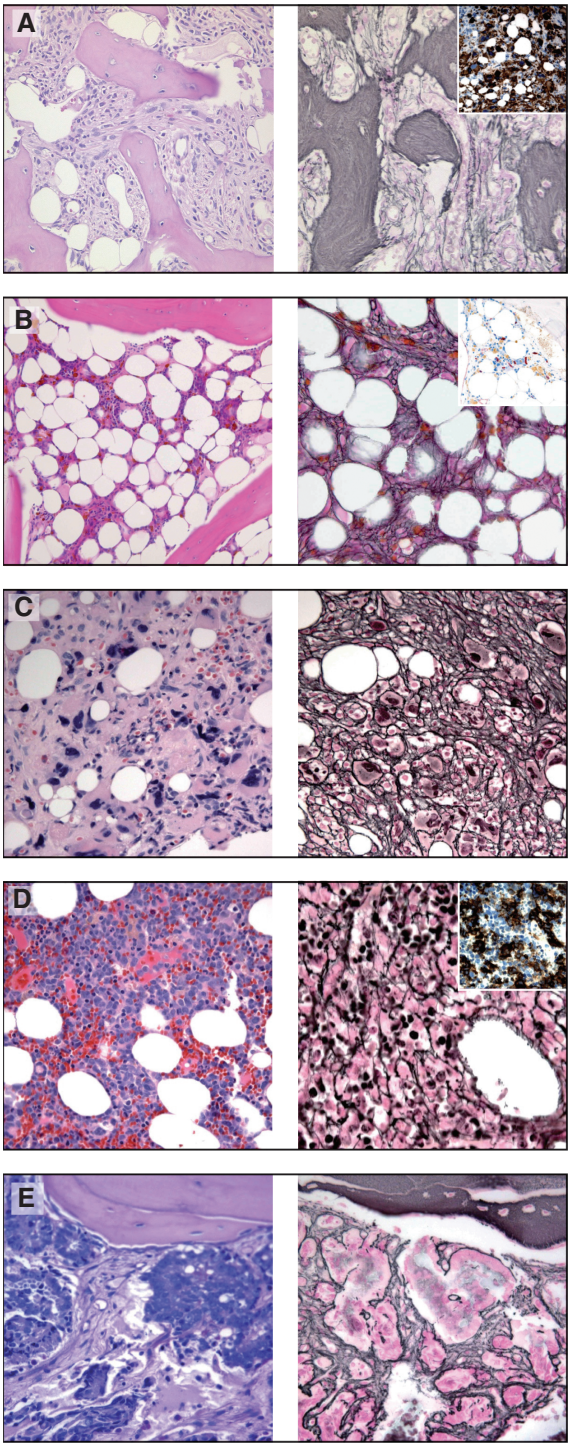

Figure 2 Diseases associated with myelofibrosis: typical changes in the bone marrow biopsy.
(A) PMF: Numerous atypical megakaryocytes in clusters, highlighted by CD61 immunohistochemical staining (insert). End stage (stage III) myelofibrosis with dense, diffuse increase of both reticulin and collagen fibers and prominent osteosclerosis with irregular and deformed, widened trabeculae (H&E and Gordon, 40× lens). (B) Hypoplastic MDS with advanced myelofibrosis. [H&E, Gordon, CD34 (insert) 40× magnification]. (C) Megakaryocyte-rich MDS with associated myelofibrosis [H&E Gordon, CD61 (insert), 40× magnification]. (D) Acute megakaryoblastic leukemia (AML M7). Small, monomorphic blasts with megakaryocytic marker expression [H&E Gordon, CD61 (insert), 40× magnification]. (E) Bone marrow infiltration by prostate cancer cells; tumor cells arranged in glandular and cribriform patterns with displacement of normal hematopoiesis and increase of reticulin fibers as part of the tumor-associated stroma (PAS, Gordon, 40× magnification).

resulting loss of bone marrow space with destruction of the normal bone marrow architecture, cytopenias and an altered erythrocyte morphology occurs resulting in poikilocytosis and teardrop shapes. In the case of PMF, there are typically also dysmorphic platelets at the same time.

The older term of "myelophthisic anemia" includes anemias that are associated with bone marrow fibrosis and have very different causes, such as infiltration by epithelial or lymphoid tumor cells, but also bone marrow fibrosis after irradiation.

Teardrop shapes due to extramedullary hematopoiesis (EMH)

Extramedullary hematopoiesis in the spleen forces erythrocytes through close-meshed spleen sinusoids into the peripheral blood. The fact that the teardrops disappear after splenectomy in connection with autoimmune-related hemolytic anemias without myelofibrosis points to a significant influence of the spleen in the formation of dacryocytes [5].

Interpretation of teardrops in blood smears and integration with other findings

In the peripheral blood, teardrops are particularly often observed in advanced cases of PMF, where a significant increase in the fiber volume has already occurred. They can thus be used in order to assess the progression of PMF. Interestingly, findings in the peripheral blood smear correlate with the amount of collagen but not reticulin fibers in the marrow [6, 7]. In the final stage of PMF, the hematopoietic marrow is replaced by collagenous connective tissue (Figure 2A). Simultaneously, one can observe a thickening of the cortical bone. The blood count at this stage often shows thrombocytopenia, anisocytosis with numerous teardrop shapes and a normochromic to hypochromic anemia.

As myelofibrosis can also be observed in other progressive myeloproliferative diseases (MPN) as well as essential thrombocythemia (ET) and polycythemia vera (PV), teardrop shapes are not pathognomonic of PMF, but may also be observed in other bcr-abl negative MPNs, bcr-abl positive CML and in advanced stages of myelodysplastic syndrome (Figure 2B,C).

Myelofibrosis may also occur with certain forms of ALL [8] and AML [8], particularly in connection with megakaryoblastic leukemia (Figure 2D). Circulating blasts in the peripheral blood in these diseases may explain the reason for point to the possibility of myelofibrosis in these patients.

Other rare causes of myelofibrosis are previous radiation, toxin exposure (e.g., benzene) or certain types of medication (e.g., hydroxyurea), metabolic causes [9] and autoimmune myelofibrosis, such as the extremely rare, idiopathic autoimmune myelofibrosis [10].

A variety of tumors can lead to bone marrow metastasis. Due to the frequency of these tumors in men, the cause is often prostate cancer (Figure 2E) or lung cancer (especially small-cell lung cancer) and, in women, breast cancer. Besides, carcinomas in the gastrointestinal tract [8] and sarcomas (especially Ewing sarcoma and neuroblastoma, rhabdomyosarcoma) can lead to bone marrow infiltration. Next to epithelial and sarcomatous tumors, malignant lymphoid tumors should also be considered. In particular, hairy cell leukemia is typically associated with pancytopenia and bone marrow fibrosis. When the blood count shows pancytopenia, it is helpful to not only focus attention on erythrocyte morphology, but also to screen the smear for atypical lymphoid cells. However, in the case of lymphomatous infiltration of the bone marrow, teardrop shapes are encountered in the blood smear far less often, since infiltration often does not affect the whole bone marrow and is not accompanied by EMH.

Other causes for dacryocytes in a blood smear are severe hemolytic anemia associated with an increased breakdown of red blood cells in the spleen and secondary splenomegaly with extramedullary hematopoiesis. Likewise, β-thalassemia major and intermedia can be a cause for teardrops. Typically, one observes microcytic, hypochromic anemia and poikilocytosis with numerous target cells.

In connection with megaloblastic anemia caused by folic acid or vitamin B-12 deficiency, which is associated, in contrast to the thalassemia syndromes, with a high MCV and MCH, individual teardrop shapes can occur together with macroovalocytes.

In summary, teardrop erythrocytes, in the presence of anemia, often indicate primary or secondary myelofibrosis. In addition, these cells are found in bone marrow infiltration by epithelial tumor cells – or less commonly, lymphoma – cells, or in the context of acute leukemias. They are not specific to a single entity. Most of the time, additional laboratory parameters (MCV, MCH) and the morphology of other cells in the smear (e.g., leukoerythroblastic blood smear or target cells in the case of beta-thalassemia) as well as the clinical context allow for the correct classification. The occurrence of "teardrop erythrocytes" should prompt the treating physician to look for extramedullary hematopoiesis (for example, as an explanation for splenomegaly or hepatomegaly) or to perform a bone marrow biopsy.

Dacryocytes (similar to fragmentocytes) in a blood smear are not a substitute for the detection of extramedullary hematopoiesis or myelofibrosis, but serve as an important indicator during the search for the cause of anemia. Both, dacryocytes and fragmentocytes are not recognized by modern hematology analyzers and computerized microscopes. This underlines the importance of manual assessment of a panoptically stained blood smear. This is why manual assessment cannot be discarded during the work-up of anemias of undetermined cause.

Acknowledgments: The authors wish to thank Dr. H. Diem, Würmtal Laboratory in Gauting, Germany, for constructive discussions. This paper has emerged from a collaboration of the members of the Laboratory working group of the DGHO.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.

Received February 6, 2014; accepted February 6, 2014

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