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The paradox of the serrated sickle erythrocyte: The importance of the red blood cell membrane topography

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Abstract

Red blood cell rheology and adhesiveness play a key role in the occurrence of vaso-occlusive like events in sickle cell anemia. The present paper reviews counter-intuitive findings supporting that rigid and serrated sickle red blood cells do not initiate vaso-occlusion. Instead, the less rigid red blood cells could initiate vaso-occlusion because of their increased adhesiveness to the vascular wall. We suspect that stiffness of sickle erythrocytes and the topography of RBC membrane are factors affecting adhesion to the endothelium.

Literally, “sickle” refers to an agricultural instrument with a short handle and a crescent-shaped wooden structure that is used for reaping or cutting down tall grass and weeds. In stone-age times a variant of the sickle had serrated blades made of naturally occurring volcanic glass (obsidian) or flint to increase its efficiency in cutting (Fig. 1 and 2). Ironically, some sickle erythrocytes do have serrated surface that could be one sided or circumferential (Fig. 3). Other investigators referred to such cells as “Holly Leaf” sickle cells [1, 2]. The shape of sickled cells depends on the rate of deoxygenation. The serrated shape is the result of intermediate rate of deoxygenation causing the formation of smaller domains of short aligned fibers [3]. Slow deoxygenation generates the classic sickle cell morphology due to the formation of single domain of well-aligned fibers [3]. Serrated sickled cells are rigid with decreased deformability and are found in the ISC dense fraction of red blood cells separated on Stractan II [4].

The peripheral smear shown in Fig. 3 is from a 31 year-old African American man with sickle cell anemia. Past medical history was significant for infrequent vaso-occlusive crises (VOC) at a rate of ≤ 1 per year. Other complications included history of leg ulcers and cholelithiasis. His Hb was 6.4 g/dL, Hct 18.5%, MCV 90 fl, MCHC 34 g/dL, reticulocyte count 16% and Hb F 2%. The number of irreversibly dense cells (ISC) was 27% which included both crescent-shaped and serrated erythrocytes.

Previous studies have indicated a paradoxical effect of the rheological properties of RBC on the clinical picture of SS. Traditionally, it has been thought that a low percentage of ISC, a low percentage of dense cells, and a high degree of deformability are beneficial factors and should ameliorate the severity of SS. It turns out that these factors have the opposite effect. Patients (both adults and children) who have decreased cell deformability and increased number of ISC and dense cells have mild disease with respect to the VOC [5-7]. A subsequent study showed patients whose RBC deformability averaged 37% or less of control values and whose dense cells averaged 22% of total circulating cells had fewer VOCs, less mortality, higher incidence of leg ulcers, and lower incidence of urinary tract infection although their Hb F was relatively low [8]. These findings are supported by another recent study [9]. In addition, it has been reported that sickle cell anemia with the highest reduction of RBC deformability were at lower risk to have osteonecrosis [10], another complication for the vaso-occlusive phenotype [11]. This suggests that the stiff ISC does not deform to establish contact with endothelial cells to initiate adhesion and consequent vascular occlusion. The serrated cell, likewise, does not initiate adhesion because the corrugated membrane topography prevents or minimizes the establishment of contact between the ligand and its receptor between the endothelium and the serrated RBC. Thus stiffness of sickle erythrocytes and the topography of RBC membrane seem to be factors that affect adhesion to the endothelium.

Legends to Figures

Figure 1. A stone age serrated sickle tool. Adapted from an image at the European Virtual Museum (<http://www.europeanvirtualmuseum.it/>).

Figure 2. Sickle tool from the Neolithic Age. Photo from Wolfgang Sauber. Museum Quintana Neolithische Sichel. (http://en.wikipedia.org/wiki/Sickle#mediaviewer/File:Museum_Quintana_-_Neolithische_Sichel.jpg)

Figure 3. Peripheral smear from a patient with sickle cell anemia showing numerous ISCs and serrated sickle cells (Arrows).

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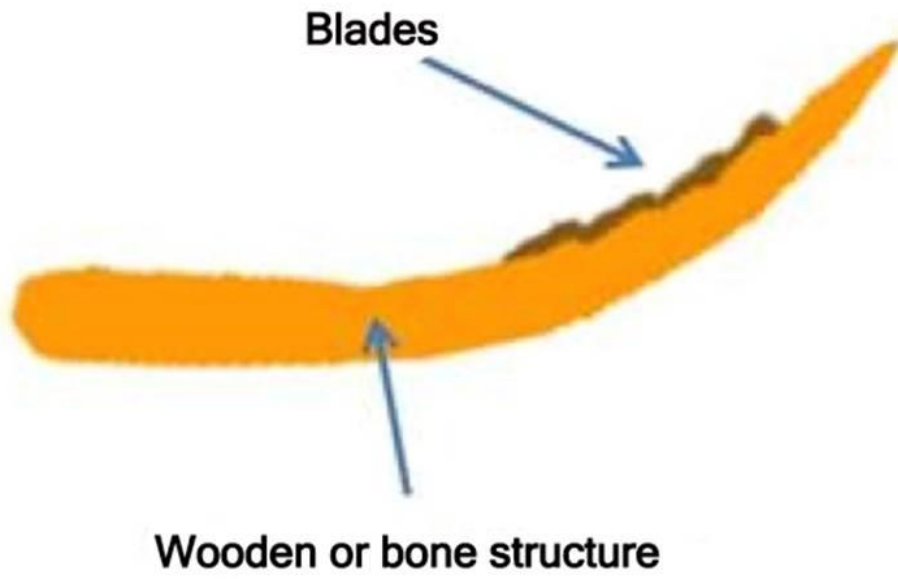


Figure 1



Figure 2

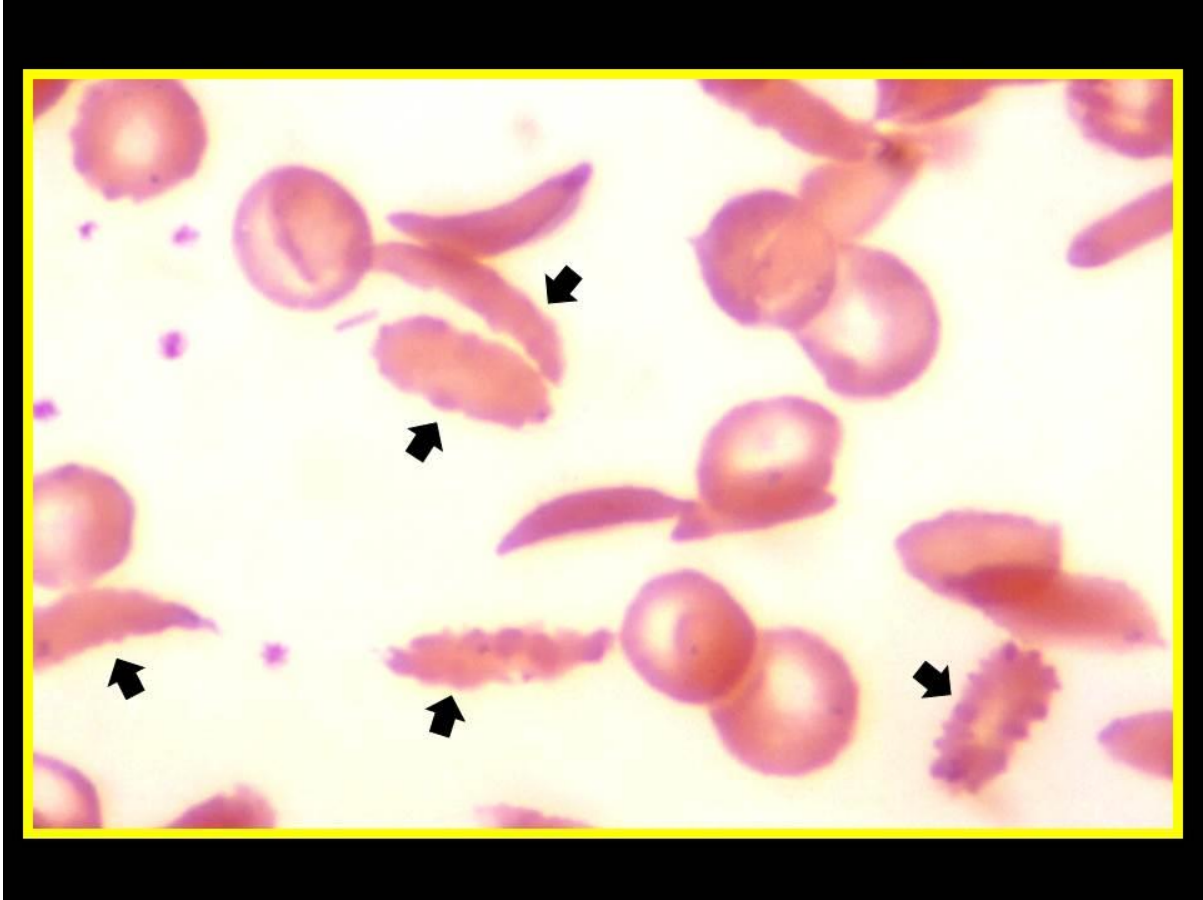


Figure 3