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by Arne M. de Kreuk

Received: April 29, 2024.

Accepted: May 10, 2024.

Citation: Arne M. de Kreuk. Sickle cell and autoimmune disease: a double whammy.

Haematologica. 2024 May 16. doi: 10.3324/haematol.2024.285445 [Epub ahead of print]

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Sickle cell and autoimmune disease: a double whammy.

Arne M. de Kreuk

Department of Haematological Medicine, King's College Hospital NHS Foundation Trust, London, United Kingdom

arne.dekreuk@nhs.net

In this issue of *Haematologica*, Dr Tang and colleagues report in detail on the prevalence of autoimmune disease in 338 adults with sickle cell disorder (SCD) in the Netherlands.¹ They found a high proportion (10.7%) to have a concomitant autoimmune condition, approximately twice as high in comparison with other reports. Mausoléo et al recently reported a prevalence of 5.6% of autoimmune disorders in a 266-patient cohort of similar age.² Mausoléo et al did not include diabetes type 1, thyroid disorders, sudden deafness syndrome and alopecia areata in their analysis, which accounted for approximately half of the cases in Dr Tang's cohort. When excluding these conditions, the prevalence of autoimmune disease in these two comparable cohorts is similar, confirming both authors' observation that autoimmune disorders are more prevalent among patients with sickle cell disorder than in the general population.

What is remarkable about the Amsterdam cohort, is the apparent absence of rheumatoid arthritis and autoimmune hepatitis, which were the most frequently noted conditions in other cohorts.²

Apart from the possibility of confirmation bias during clinical assessment in these retrospective cohorts, perhaps genetic and environmental factors could clarify the variability in autoimmune diagnoses.

Development of autoimmunity

People coming from the same geographical regions as patients with SCD are more likely to develop autoimmune conditions such as systemic lupus erythematosus in comparison with Caucasian people. However, the co-existence of sickle cell and autoimmune disease is very likely more than just due to geographical overlap. Sickle cell disorder has the ability to create a favorable micro-environment for autoimmunity to develop. Chronic inflammation and endothelial cell activation results in cytokine release such as TNF- α , IL-6 and IL-1, with subsequent activation of cells of the immune system. Increased susceptibility to infections in SCD probably has a similar effect, contributing to long-term exposure of the immune system to a variety of antigens (Figure 1).

In addition, SCD is characterized by high levels of circulating microparticles derived from red cells, platelets, monocytes and endothelial cells both in steady state and in acute crisis. Microparticles are cellular components released from cells damaged through inflammation or apoptosis. One of their hallmark features includes reduced cell membrane integrity, characterized by flipflopping of phosphatidylserines to the outer layer of the cell membrane, which attracts predominantly phagocytic cells. Red cell-derived microparticles have been shown to be prothrombotic with the ability to activate complement.³ Microparticles of other cells also provide a source of pro-inflammatory substances, including auto-antigenic material due to the presence of cellular components such as DNA, RNA and histones. Microparticles may circulate before being cleared and may have affinity for binding specific tissues. A multitude of effects can take place, including recruitment of cells of the immune system with exposure of these cells to auto-antigenic material within the microparticles, and binding of antibodies and formation of immune complexes.⁴

The tendency towards developing autoimmunity in sickle cell disorder is confirmed by the high prevalence of a variety of autoantibodies.^{2,5} Prospective long-term follow up of sickle cell

patients without autoimmune symptoms but with a high autoantibody titer (in particular ANA) suggests a high risk of developing auto-immune disease.⁶

Development of autoimmune disease

For autoimmunity to become pathological and lead to autoimmune disease requires more than just increased exposure to (auto)antigens. To achieve T-cell hyperactivity and/or B-cell overstimulation, downregulation of immune tolerance is needed. There is an abundance of evidence on regulation and dysregulation of innate and adaptive immunity, which goes well beyond the scope of this Editorial. However, it is worth noting that sickle cell disorder appears to have a few downstream effects that may push autoimmunity towards the development of autoimmune disease. For example, free heme (resulting from intravascular hemolysis) was found to stimulate the innate immune system and downregulate tolerance via activation of e.g. toll-like receptor 4 (TLR4).⁷ Activated toll-like receptors in turn play a pivotal role in the pathogenesis of autoimmune disease.⁸

Again, levels of elevated proinflammatory cytokines and growth factors are elevated in SCD in comparison with the healthy population due to chronic inflammation and endothelial cell activation. Of interest for the development of autoimmune disease is B-cell activating factor (BAFF), which promotes survival of autoantigen binding B-cells. During inflammation, BAFF appears to downregulate anti-inflammatory (IL-10 positive) regulatory B-cells. Indeed, sickle cell patients with clear autoimmune phenomena seem to have a reduced functionality of regulatory B-cells, resulting in another mechanism of downregulation of tolerance.⁹

Relevance for clinical practice

The findings of Dr Tang et al have implications for daily practice. The high prevalence of autoimmune conditions raises the question of whether screening for these conditions should become part of the standard annual review in sickle cell disorder. Autoimmune disease requires a different therapeutic approach from sickle cell, and it is important that clinicians looking after these patients try to unpick the intertwined symptoms of the two conditions. In particular in the case of SLE and rheumatoid arthritis, an autoimmune genesis may very well be overlooked and symptoms dismissed as part of vaso-occlusive disease. Similarly, the often-elevated liver function tests in SCD may mask an underlying autoimmune hepatitis.

At the same time, one could hypothesize that uncontrolled SCD may drive towards further autoimmunity and autoimmune disease, although this theory is at present not supported by data showing a lower prevalence of autoimmune disease in patients on disease-modifying treatment in the study by Dr Tang or the other papers. It is a fact though that certain treatments for autoimmune disorders, in particular corticosteroids, have the ability to worsen vaso-occlusion which in turn may require a different management strategy for the affected patient's SCD. Piccin et al have published a useful algorithm for trying to discriminate between sickle cell and autoimmune conditions, and summarized possible implications for treatment.¹⁰

Future directions may include research into disease modifiers that interact at the crossroads between vaso-occlusion, hemolysis and progression of autoimmune disease; from this perspective hemopexin would be an interesting target. From a clinical perspective, the data presented calls for building up more joint expertise between hematologist and rheumatologist.

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Figure 1. A simplified perspective of mechanisms contributing to autoimmune disease in sickle cell disorder.

Key processes involved in sickle cell disorder (hemolysis, vaso-occlusion and infection) are responsible for endothelial dysfunction and ischemia, resulting in tissue damage and pain. Pro-inflammatory cytokines, free heme and microparticles generated during sickling can promote development of autoimmunity as well as downregulate immune tolerance, ultimately advancing to clinical autoimmune disease. The grey zone of overlapping end organ damage between sickle cell and autoimmune disease results in further generation of pro-inflammatory cytokines and microparticles, promoting the environment for autoimmunity and autoimmune disease to develop.

Autoimmune disease

Sickle cell disease

