Article Review

The role of acute and chronic splenic dysfunctions in aetiopathogenesis of anaemia in sickle cell disease: narrative review of hyperhaemolytic implications of autosplenectomy, autoimmunity, infections, and splenomegaly

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Abstract

Background: Splenic dysfunction (SD) in SCD occurs due to one of two 'diametrically opposed' anatomical manifestations: splenomegaly or autosplenectomy. Literature on SD-associated hyperhaemolysis is predominated by splenomegaly, acute splenic sequestration crisis (ASSC) and chronic hypersplenism (CH). However, autosplenectomy predisposes to haemolytic erythrocytopathic infections (HECI) and autoimmune haemolysis (AIH). This narrative review highlighted the aetiopathogenesis, management, and prevention of hyperhaemolysis due to both splenomegaly and autosplenectomy in SCD.

Method: Online literature search using terms relevant to splenomegaly, autosplenectomy, and hyperhaemolysis in SCD. Only articles that examined aetiopathogenesis, management, and/or prevention of hyperhaemolysis due to SD vis-à-vis sequestration, hypersplenism, immune-suppression, infections, and autoimmunity in SCD were selected.

Findings: Literature search revealed three major categories of SD-associated hyperhaemolysis in SCD: 1) Autosplenectomy-associated impaired immune-response, leading to HECI; 2) Autosplenectomy-associated impaired immune-tolerance, leading to AIH; 3) Splenomegaly-associated sequestration, leading to ASSC/CH.

Conclusion: Autosplenectomy and splenomegaly are anatomically mutually exclusive but concordant in hyperhaemolysis in SCD. While autosplenectomy is an 'indirect' cause of hyperhaemolysis (HECI/AIH), splenomegaly is a 'direct' cause of hyperhaemolysis (ASSC/CH). Transfusion, chemotherapy, and/or immune modulation can treat HECI, AIH, ASSC or CH. Prevention against HECI is achievable through, chemoprophylaxis and immunization. The role of hydroxyurea in 'preventing and reversing' autosplenectomy must be considered cautiously by physicians, because hydroxyurea may 'inadvertently' cause splenomegaly (ASSC/CH). Surgical splenectomy should only be considered in recurrent ASSC or severe CH, and such patients should be offered peri-operative vaccinations and post-operative chemoprophylaxis.

Keywords: Sickle cell disease, splenomegaly, sequestration crisis, hypersplenism, autosplenectomy, infection induced haemolysis, autoimmune haemolysis.

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Introduction

Haemoglobin-S (HbS) is a beta chain genetic variant of the normal haemoglobin-A (HbA).[1,2] HbS evolved from HbA as a result of a point mutation that caused GAG>GTG base transition at codon-6 of the β-globin gene on chromosome-11, which corresponds to a substitution of glutamic acid (a polar amino acid) by valine (a neutral amino acid) in the sixth position of the β-globin chain (βGlu6Val).[1,2] Because of this substitution, HbS has less anionic potential, slower electrophoretic mobility, and reduced deoxygenated solubility that leads to polymerization and red cell sickling.[1,2] The prevalence of sickle β-gene in tropical African countries is as high as 25-30%.[3] The prevalence is high because sickle cell trait (SCT) protects against severe malaria[3] and confers survival advantage through natural selection,[4] balanced polymorphism,[5] as well as immunological and biochemical protective mechanisms against the infection.[6] There are at least five different sickle β-gene mutation haplotypes that vary in HbF levels and disease severity. The Arab-Asian and Senegal haplotypes are associated with relatively higher HbF levels and milder sickle cell disease (SCD), while the Benin, Bantu, and Cameroon haplotypes are associated with relatively lower HbF levels and severer SCD.[7]

The red cells of individuals with SCT have the HbAS phenotype containing both HbS (20-40%) and HbA (60-80%).[8] The relative preponderance of HbA in SCT red cells prevents sickling and undue haemolysis under physiological conditions.[8] Consequently, SCT red cells have normal life span, and SCT carriers have normal life expectancy.[9] HbS gene is thus genetically recessive, and SCT is essentially asymptomatic, and is not associated with significant organ damage, except for the occasional occurrence of renal papillary necrosis,[8] splenic infarction at high altitude,[10] or marrow necrosis and bone pain upon exposure to certain haematopoietic growth factors.[11] However, SCD, which arises from the homozygous inheritance of HbS gene or double heterozygosity of HbS gene with another haemoglobinopathy gene (e.g., HbSC, HbSD, HbSE, HbSO, and HbSβthal)[1] is associated with significant morbidity, mortality, and reduced life expectancy.[12,13] The pathophysiology of SCD is dominated by red cell sickling, which is a pathognomonic feature of SCD.[12] Thus, red cells of patients with SCD go through repeated cycles of deoxygenation (in the tissues) and re-oxygenation (in the lungs). This sequence of events creates a dynamic scenario of sickling and un-sickling until the red cell membrane sustains a significant degree of damage, which eventually leads to the formation of irreversibly sickled cells that are invariably and prematurely haemolysed.[14] Consequently, the red cell life span in SCD is shortened to less than 20 days,[15] which cannot be adequately compensated even by maximum erythroid hyperplasia of the bone marrow.[16] Thus, every patient with SCD maintains a certain degree of clinically tolerable steady state haemolysis and anaemia, which can be aggravated by chronic or acute hyperhaemolytic states due to various inherited and acquired haemolytic comorbidities or triggers.[17] In addition to chronic haemolysis and anaemia,[17] the clinical course of SCD is also characterized by pain-free periods of relative well-being referred to as 'steady-state', which is intermittently interrupted by painful periods of vaso-occlusive tissue infarctions and necrosis referred to as 'vaso-occlusive crisis' (VOC).[12] The clinical transition from steady state to VOC is caused by tissue necrosis resulting from polymerization of deoxygenation of HbS and red cell sickling, and is usually triggered by several factors that vary from physiological factors (e.g., menstruation) to pathological factors (e.g., infections) on the one hand, and from psychological factors (e.g., emotional stress) to physical factors (e.g., extreme weather conditions) on the other hand.[12] The pathophysiology of SCD is characterized by red cell sickling that leads to haemolysis and infarction, both of which are aetiologically associated with multi-organ damage and dysfunction (MODD) via vasculopathy, tissue necrosis, reperfusion, infection, and inflammation.[18-23] Consequently, both acute and chronic MODD are common morbidities in patients with SCD.[18-23] The diversity and progressive nature of MODD in SCD suggests that no organ is spared, but the frequency of chronic MODD is generally higher in long-term survivors of the disease.[24,25] Moreover, the risk of MODD that leads to early death is especially higher among SCD patients living in low resource settings where the disease virtually runs its natural course unabated by inadequate prophylactic and therapeutic interventions.[24,25] Conversely, life expectancy is higher among patients living in high resource settings where available prophylactic and therapeutic interventions retard the natural course of the disease and mitigate the risk of MODD.[24,25]

Splenic damage and dysfunctions (SDD) are pathognomonic features of SCD.[26-28] Moreover, SDD in SCD is fascinating in the sense that it can present as one of two 'diametrically opposed' anatomical manifestations, viz: splenomegaly or autosplenectomy. The first and earliest manifestation of SDD (usually seen in infants, young children and occasionally in older

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children and adults) is mediated by reactive splenic hyperplasia, leading to splenomegaly, and hypersplenism.[26-28] The second and later manifestation of SDD (commonly seen in older children and adults) is mediated by repetitive splenic infarctions, which initially causes functional hyposplenism,[29] followed by sidero-fibrosis, shrinkage, and autosplenectomy.[26-28] Both hypersplenism and autosplenectomy are potential causes of hyperhaemolysis, which can aggravate steady state haemolysis, and undesirably increase the transfusion requirements of patients with SCD. There is therefore the need to understand the clinico-pathological roles of SDD in the causation of hyperhaemolysis in patients with SCD.

Majority of the literature regarding SDD-associated hyperhaemolysis in SCD is focused on splenomegaly, sequestration, and hypersplenism, with relatively little reference to the potential hyperhaemolytic role of autosplenectomy. However, autosplenectomy is a 'dual' negative immune modulator that can cause hyperhaemolysis via two mechanisms. First, autosplenectomy diminishes adaptive immune response and virtually abolishes the 'pitting and culling' functions against infected red cells, thereby increasing the susceptibility of SCD patients to malaria and other haemolytic intra-erythrocytic infections.[30] Second, autosplenectomy perturbs immune regulation,[31] diminishes peripheral self-tolerance,[31] and raises the propensity of SCD patient to produce high titre multiple solid tissue auto-antibodies[32,33] as well as haemolytic red cell auto-antibodies.[34] We therefore reckon that autosplenectomy and splenomegaly are directly or indirectly associated with hyperhaemolysis in SCD. Hence, the aim of this overview is to present a concise narrative review of the aetiopathogenesis, management, and prevention of SDD-associated hyperhaemolysis due to autosplenectomy and splenomegaly in patients with SCD.

Methodology

Literature Search and Selection: Literature search was conducted using search terms: 'sickle cell disease, sickle cell anaemia, splenic damage and dysfunction, splenic hyperplasia, splenomegaly, acute splenic sequestration, chronic hypersplenism, hyperhaemolysis, red cell sickling, splenic infarctions, functional hyposplenism, autosplenectomy, immune-suppression, infection, inflammation, drugs, autoimmunity, and autoimmune haemolysis' in various combinations in PubMed, Medline, Bing, Google Scholar, and other online search engines. Only articles that examined aetiology, pathogenesis, and/or management of haemolysis due to acute and chronic splenic damage and dysfunctions vis-à-vis the pathophysiologic inter-relationship between sequestration and hypersplenism; immune-suppression, infections, and haemolysis; inflammation, drugs, and autoimmunity; red cell antibodies and autoimmune haemolysis in patients with SCD were selected for this review. Articles that concentrated on other aspects of SCD were excluded from this review. Overall, 133 relevant publications were selected, which included 132 peer reviewed journal articles and 1 World Health Organization technical report as listed in the reference section.

Results

The literature revealed that SCD is associated with a myriad of SDDs that directly or indirectly predispose the patients to hyperhaemolysis via three inter-related aetiologic categories, as follows. (1): autosplenectomy and impaired immune response, leading to recurrent erythrocytopathic infections; (2): autosplenectomy and impaired immune tolerance, leading to autoimmune haemolysis, the risk of which is increased by transfusion, infections, inflammation, and drugs; (3): splenomegaly with acute sequestration or chronic hypersplenism, leading to intra-splenic red cell destruction. The individual components of these aetiologic categories are outlined in Table 1 and expatiated in the discussion section.

Discussion

There are two types of SDD in SCD, viz: autosplenectomy and splenomegaly. Both aforementioned sickle cell associated SDDs have been directly or indirectly associated with acute or chronic haemolytic aggravation of steady state anaemia in patients with SCD as described below.

1. Autosplenectomy in SCD

The spleen in SCD is usually normal in size and functionally competent at birth but undergoes a sequence of changes with age. The progressive replacement of HbF with HbS heralds the onset of haemolysis with resultant increase in splenic size and activity.[28] Consequently, the spleen becomes palpably enlarged by the fifth month of life or earlier.[28] The development of splenomegaly is due to the complex structure of the splenic circulation, which encourages stasis, hypoxia, and entrapment of sickled red cells

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within the splenic pulp and sinuses.[28] The resultant erythro-stasis leads to marked congestion of the red pulp

Table1: Aetiopathogenesis, management, and prevention of hyperhaemolysis associated with splenic dysfunctions in SCD

Aetiology of hyperhaemolysis	Pathogenesis of hyperhaemolysis	Management of hyperhaemolysis	Prevention of hyperhaemolysis
Autosplenectomy and increased risk of infections.	Loss of immune 'pitting' and 'culling' functions; increased incidence of severe erythrocytopathic infections: malaria, babesia, bartonella.	Antimicrobial therapy; red blood cell (RBC) transfusion if severe anaemia.	Chemoprophylaxis; environmental sanitation; vector barrier protection; vaccination; long term hydroxyurea (HU) may prevent or even reverse autosplenectomy and reduce risk of infections.
Autosplenectomy and increased risk of autoimmunity.	Diminished self-tolerance; increased incidence of autoimmune diseases (AIDs) and autoimmune haemolysis (AIH): spontaneous or triggered by infections, inflammations, transfusions, or drugs.	Immunosuppression; treat any infective triggers; withdraw any trigger drugs; if severe anaemia, identify culprit antibody, transfuse antigen-negative RBCs.	Coombs test for cases of hyperhaemolysis; long term HU may prevent or even reverse autosplenectomy and reduce risk of AIDs and AIH.
Splenomegaly and blood pooling.	(A). Acute splenic sequestration crisis (ASSC) in young children. (B). Chronic hypersplenism (CH) in older children and adults.	(A). Transfuse whole blood to correct both anaemia & shock in ASSC. (B). RBC transfusion for CH	(A). Chronic transfusion may prevent recurrence of ASSC, splenectomy as last option in recurrent cases. (B). Chronic transfusion may shrink splenomegaly in CH; splenectomy as last option in recalcitrant cases.

and sequestration of blood. This leads to recurrent vaso-occlusive infarctions, which has dual adverse impact on the physiology and anatomy of the spleen. First, recurrent infarctions distort the histological and anatomical architecture of the spleen, which leads to functional impairment even though the spleen is manifestly enlarged; this scenario where splenic dysfunction coexists with splenomegaly is referred to as functional hyposplenism.[29] Functional hyposplenism in SCD was first described by Pearson et al in 1969 when he identified some children with SCD who presented with the same susceptibility to infection as in splenectomized patients, even though their spleens were still enlarged because they had not yet completed the process of autosplenectomy.[35] Nonetheless, the spleen of patients with SCD undergoes progressive fibrosis and shrinkage, and the organ is eventually reduced to a small impalpable siderofibrotic mass.[26-28] This process of auto-splenectomy is usually completed between the ages of 6-8 years.[26-28] Consequently, most SCD patients do not have palpable spleen beyond the 8th year of life.[26-28] Autosplenectomy has serious adverse effects with respect to the risks of hyperhaemolysis due to infections and autoimmune diseases as described below.

1a. Autosplenectomy Increases Risk of Hyperhaemolytic Intra-erythrocytic Infections: Erythrocytotropism and Erythrocytopathy

Autosplenectomy imposes dual impact on immune response in SCD. First, autosplenectomy diminishes adaptive immune response to encapsulated and gram-negative bacteria, thus predisposing to overwhelming infections and sepsis.[36] Second, autosplenectomy down regulates the 'pitting and culling' defensive actions against intra-erythrocytic infections, thus increasing the risk of frequent and severe hyperhaemolytic infections such as Malaria, Babesiosis, and Bartonellosis.[30] These red cell invading infections are particularly notorious for causing hyperhaemolysis in SCD.[37] This is because the causative pathogens have special predilections for red

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cells (i.e., erythrocytotropism) within which they proliferate and disrupt cellular architecture (i.e., erythrocytopathy), leading to direct lysis and/or excessive erythro-phagocytosis of the infected red cells,[37] which ultimately triggers acute hyperhaemolytic crisis in SCD. The literature describes three prototype erythrocytotropic infections (Malaria, Babesiosis, and Bartonellosis) that have been associated with classical erythrocytopathic acute hyperhaemolytic crisis in SCD as described below.

1ai. Malaria-Induced Hyperhaemolysis in SCD

Malaria is endemic in many tropical countries within which SCD is very prevalent.[38,39] Five mosquito transmissible Plasmodium species: *P. falciparum, P. vivax, P. malariae, P. ovale* and *P. knowlesi*, have been associated with human infections, with the first two being the most important species.[38] Hence, SCD patients in tropical countries are at double risk of acquiring malaria via mosquito bites and via blood transfusions because a significant proportion of tropical blood donors have asymptomatic malaria infections.[40,41] Interestingly, a recent study had demonstrated that in comparison with blood donors with SCT (i.e. HbAS), donors with HbAA phenotype were associated with higher risk of asymptomatic malarial parasitemia, which implied that HbAA blood carries higher risk of transfusion transmitted malaria (TTM).[42,43] Therefore, patients who are selectively transfused with HbAA blood, such as SCD patients, could be at greater risks of acquiring TTM.[42,43] In addition to having special tropism for hepatocytes during the hepatic phase of their lifecycles, the malaria parasites are also both erythrocytotropic and erythrocytopathic, hence the parasites invade and replicate within the patients red cells during the erythrocytic phase of their life cycles.[44] Consequently, malaria is strongly associated with anaemia even in immune competent non-SCD patients.[45] It is, therefore, conceivable that malaria is an important aetiological factor in the pathogenesis of acute hyperhaemolytic crisis and severe anaemia in immuno-suppressed patients including those with SCD.[46,47] It is thus essential to mitigate the risk of malaria-associated hyperhaemolysis by providing prompt treatment for acute malaria and continuous lifelong anti-malarial chemoprophylaxis in the standard of care for managing SCD in malaria endemic countries.[48] Long-term protection can also be achieved by barrier protection against mosquito vectors at home, and serological screening and deferral of malaria infected prospective blood donors at donation centres.[49] However, malaria vaccine remains the ultimate strategy for sustainable and cost-effective control measure against malaria in tropical countries. Unfortunately, the RTS,S/AS01 vaccine had shown only modest efficacy in preventing symptomatic *P. falciparum* malaria.[50] Despite its modest efficacy, the RTS,S/AS01 vaccine can be adopted as an addition to the existing list of malaria control strategies, but it should not be considered as an independent malaria prevention tool.[50] Accordingly, in 2021, the RTS,S/AS01 vaccine was endorsed by the WHO for use in children in conjunction with other malaria control strategies such as the use of insecticide-treated nets and environmental vector control.[51] Therefore, SCD patients living in *P. falciparum* endemic countries should be encouraged to receive the RTS,S/AS01 vaccine. The vaccine is a non-live recombinant protein-based vaccine,[51] hence it can be given to all SCD patients including those with HIV infections.

1aii. Babesiosis-Induced Hyperhaemolysis in SCD

Babesiosis is a zoonotic tick-borne malaria-like febrile illness caused species of the intra-erythrocytic protozoan parasite called Babesia, which is requires a biological stage in rodents or deers.[52] Babesiosis is particularly common in mid-western and north-eastern USA but is also seen sporadically throughout the world in parts of Europe, Asia and Africa.[52] The four identified Babesia species that cause infection in humans are *B. microti, B. divergens, B. duncani* and *B. venatorum.*[52] However, the life cycle of all four species within humans remain essentially the same.[52] Babesia parasites are intracellular obligate parasites that target the red blood cells.[52] Besides their natural route of transmission via the infected tick vector bites, the parasites are also transmissible by transfusion via the red blood cells of infected donors.[53] Immuno-compromised persons, especially those with splenectomy or hyposplenism, such as SCD patients, are at increased risk of babesiosis.[53] Like malaria parasites, Babesia parasites are both erythrocytotropic and erythrocytopathic; hence, the parasites invade and replicate within the patients red cells.[52] Consequently, babesiosis is an important cause of morbidity and haemolytic anaemia even in non-SCD patients.[52] Thus, patients with SCD living in areas that are endemic for babesiosis are at high risk of infection and hyperhaemolysis due to the combined effects of autosplenectomy, immune suppression, and recurrent transfusion.[53-56] Nonetheless, it is possible to minimize the risk of babesiosis-associated hyperhaemolysis by providing prompt diagnosis and standard anti-babesia chemotherapy for patients with SCD.[52] Long-term prevention strategy is achievable through personal barrier protection against tick vectors coupled with

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environmental vector control programs,[52] while molecular donor screening methods for babesiosis is currently being evaluated for detection and deferral of infected donors within endemic areas.[57] Unlike malaria, an effective vaccine has not yet been developed against babesiosis, but there are potential candidate vaccines in pre-clinical stages of development that will hopefully be available for clinical use in the near future.[58]

1aiii. Bartonellosis-Induced Hyperhaemolysis in SCD

Three zoonotic species of Bartonella (*B. henselae, B. quintana* and *B. bacilliformis*) are known to be responsible for the vast majority of human infections.[59] While the infection caused by *B. henselae* has a worldwide distribution, *B. quintana* and *B. bacilliformis* cases are more geographically restricted infection: *B. quintana* in Europe and USA, and *B. bacilliformis* in Peru, Ecuador and Colombia.[59] Bartonella species are intracellular fastidious Gram-negative bacteria that cause a wide range of febrile illnesses in both immuno-competent and immuno-suppressed persons, with the latter being more severely affected.[59] Bartonella species are spread from animals to humans by fleas, lice, sand flies or contact with flea-infested animals such as cats.[59] In addition to having special tropism for endothelial cells, Bartonella species are also erythrocytotropic and erythrocytopathic.[59] The biological ability of Bartonella species to invade and destroy human red cells is of double clinical significance. First, Bartonella species can be transmitted from an asymptomatic blood donors to blood recipients.[60] Second, Bartonella species can cause significant haemolysis in persons with symptomatic infections.[61,62] Consequently, bartonellosis is an important cause of haemolytic anaemia even in non-SCD patients.[61,62] Thus, patients with SCD living in areas that are endemic for bartonellosis are at high risk of infection due to the effects of auto-splenectomy, immunosuppression and recurrent transfusion.[55,62] Several cases of bartonellosis had been reported in SCD patients in whom the infection often run severe course, cause hyperhaemolytic crisis, aggravate anaemia, and eventually increase the risk of blood transfusion.[63-65] It is therefore important for clinicians to raise their clinic indices of suspicion and investigate all cases of fever and musculoskeletal pains in SCD patients living in bartonellosis endemic areas in order to proffer early diagnosis[66] and initiate appropriate antibiotic therapy[67] so as to avert the risk of hyperhaemolytic crisis. Long-term prevention strategy is achievable through personal barrier protection against vectors coupled with environmental vector control programs,[59] while serological screening and deferral of asymptomatic infected blood donors should be enshrined in the national transfusion services of bartonellosis endemic countries.[60,66] An effective vaccine has not yet been developed against bartonellosis, but there are promising candidate vaccines that are in early stages of development.[68]

1b. Autosplenectomy Increases Risk of Autoimmune Diseases: Anti-Red Cell Antibodies and Autoimmune-Mediated Hyperhaemolysis

Experimental evidence suggests that alterations in the ability of phagocytes to capture or clear apoptotic cells result in autoimmunity.[69] Marginal zone macrophages (MZMs) of the spleen are a small subset of specialized macrophages that are known to interact with apoptotic cellular materials entering the spleen from circulation.[69] MZMs play a central role in the clearance of apoptotic cells thereby minimizing auto-antigen exposure and mitigating immune response to the auto-antigens expressed on apoptotic cellular debris.[69] Moreover, MZMs are important in regulating inflammation and self-tolerance by releasing soluble factors that suppress innate and adaptive immune response against auto-antigens.[69] Immunological research in animals had shown that depletion of MZM led to increased production of pro-inflammatory cytokines, enhanced lymphocyte responsiveness to apoptotic cell derived auto-antigens, and accelerated the progression of autoimmune disease in mice that were genetically prone to systemic lupus erythematosis (SLE).[69] These findings confirmed the central role of MZMs in down regulating the immunogenicity of auto-antigens.[31,69] It has also been reported that in addition to MZMs, human spleen is rich in other autoimmune regulatory cells collectively referred to as splenocytes.[70] Splenocytes include a myriad of 'spleen-resident' immune cells consisting of T and B cells, dendritic, and other macrophages, as well as cells that express extra-thymic autoimmune regulator gene, which specifically regulates tissue-specific antigens expression in order to confer and maintain peripheral immune self-tolerance and avert the development of autoimmune diseases.[31,70,71]

It is thus conceivable that splenectomy (whether surgical or due to autosplenectomy) constitutes a significant risk factor for not only overwhelming sepsis,[36] but also for triggering autoimmune diseases (AIDs) as depicted in both humans and experimental animals.[69,70,72-74] As earlier noted, the natural clinical course of SCD is characterized by autosplenectomy due to repeated attacks of vaso-occlusive infarctions that shrink the spleen into a small functionless siderofibrotic nodule.[26-

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[28] Therefore, asplenia due to autosplenectomy constitutes a risk factor for AIDs in patients with SCD.[75] This is consistent with previous studies that had shown that patients with SCD often produce high titre autoantibodies against a wide range of auto-antigens expressed in solid organs,[32,33] and more recent studies have reported significantly higher prevalence of AIDs in adults with SCD than in the general population.[76,77] In fact, it is believed that AIDs are grossly under-diagnosed, under-reported, and under-estimated in SCD. This is because both conditions (AID and SCD) share many clinical and biological features such as inflammation, pain, and multi-organ damage and dysfunction.[75,78,79] Thus, comorbid AIDs in SCD patients are often 'clinically disguised' since they usually increase inflammation, raise blood viscosity, and aggravate vaso-occlusive morbidities, which often blend with the pre-existing symptoms of SCD.[80] This scenario often leads to delayed diagnosis and increased risk of severe AID-associated organ damage in patients with SCD with comorbid AIDs. For examples, delayed diagnosis of rheumatoid arthritis (RA) would result in severe arthropathy in SCD patients with comorbid juvenile RA;[81] and delayed diagnosis of SLE in SCD patients would lead to immune complex nephropathy,[82-84] which aggravate any pre-existing sickle cell nephropathy.

Although autosplenectomy is a strong risk factor for AIDs, we believe that the risk associated with autosplenectomy in SCD patients is synergistically aggravated by additional risk factors for autoimmunity that are consistently associated with pathogenesis and/and management of SCD. For example, on the one hand autosplenectomy is associated with recurrent infections and chronic inflammation;[36] and on the other hand, infections and inflammation play significant roles in the perturbation of self-tolerance within the concept of the so-called 'second hit hypothesis' in the cascade of events leading towards the development of AIDs.[85] Hence, the high incidence of recurrent infections and chronic inflammation may be partly responsible for higher prevalence of AIDs in adult patients with SCD as compared with the general population.[76,77] We thus reckon that the high prevalence of AIDs in SCD is multi-factorial, and is attributable to the combined, synergistic and inter-related autoimmunity-inducing effects of tissue injury,[86] recurrent infections and chronic inflammation,[76,85] decreased self-tolerance due to autosplenectomy and defective splenic function,[69,70,76] transfusion-associated chronic immune stimulation,[75] release of hidden neo-antigenic epitopes during haemolytic episodes,[87] haptenic effects of drugs,[88,89] and infection-induced molecular mimicry[90,91] as appraised by different authors from different clinical perspectives. It is therefore not surprising that SCD is associated with the production of a wide range of autoantibodies that cause a myriad of AIDs in various solid organs and tissues, e.g., skeletal muscle (myasthenia gravis), smooth muscle (autoimmune hepatitis and cholangitis), nuclear proteins (SLE), joints (rheumatoid arthritis), salivary and lacrimal glands (Sjogren's syndrome), thyroid gland (autoimmune hypothyroidism), kidneys (autoimmune nephritis), and the skin (systemic sclerosis), as well as haemostatic tissue components (anti-phospholipid syndrome) and several other components of the human tissues.[32,33,75,76,92-94] In similarity with solid tissues, the blood is not spared by AIDs in SCD as several cases of autoimmune haemolytic anaemia (AIHA) mediated by warm IgG autoantibodies and cold IgM autoantibodies have been frequently reported among SCD patients.[34,87-91,95-103]

While the majority of reported cases of AIHA in SCD patients apparently arose solely within the autoimmune background of autosplenectomy,[34,87,95] other cases circumstantially arose within a composite autoimmune background of autosplenectomy and other autoimmune cofactors such as transfusions,[101-103] drugs,[88,89] or infections due to certain microbial agents such mycoplasma,[90,91] malaria parasites,[99] and more recently the SARS-CoV-2 virus.[100] It is thus imperative for caregivers to appreciate that SCD patients are prone to AIDs including AIHA, hence all cases of hyperhaemolysis in SCD should be serologically screened for early diagnosis of AIHA in order to initiate early immune modulation therapy, withdraw any offending medication if autoimmune haemolysis is drug-induced, and/or administer appropriate antimicrobial agents if autoimmune haemolysis is infection-induced. Delay in the diagnosis and management of AIHA in SCD can lead to unnecessary transfusion with very high risk of transfusion reactions if the culprit autoantibodies are 'missed or miss-identified' during pre-transfusion crossmatch. Nonetheless, steroidal immune suppressors (such as prednisolone) must be used judiciously in cases of AIHA in patients with SCD as they may trigger VOC, which may dictate the use of non-steroidal immunosuppressants.[104]

It is plausible to predict that the risk and incidence of AIDs, including AIHA, in patients with SCD can be mitigated by the 'spleen-preserving' effect of hydroxyurea, if the drug is started in early childhood

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before the onset of autosplenectomy.[105] Interestingly, hydroxyurea may also 'reverse' splenic fibrosis and 'restore' splenic function in SCD patients with autosplenectomy.[106] These dual 'spleen preservation and restoration'[105,106] effects of hydroxyurea would predictably prevent the development of autosplenectomy-induced morbidities such as sepsis and AIDs in patients with SCD. However, hydroxyurea must be used with caution because it is a 'double edge' sword in the management of SCD splenic dysfunction. This is because although it may 'desirably' preserve spleen or reverse autosplenectomy,[105,106] it can also 'undesirably' lead to massive splenomegaly with hypersplenism that may require surgical splenectomy.[107,108] Moreover, current trends are pointing towards the possibility of preventing AIDs in patients with SCD by using novel anti-inflammatory agents that target and down regulate chronic hyper-inflammation, which is thought to be causally related to the high prevalence of AIDs in SCD.[76,77] There is no doubt that hyper-inflammation in SCD is causally related to both septic (triggered by infections) and aseptic inflammation (triggered by haemolysis and tissue necrosis).[109] Moreover, current evidence suggests that the SCD hyper-inflammatory state is sustained by haem-induced over-activation of neutrophils, which contribute to the production of neutrophil extracellular traps (NETs).[110] NETs are essentially a meshwork of extracellular DNA enriched with histones and neutrophil granule proteins that participate in host defenses against pathogens,[111] but unfortunately, NETs also contribute to vascular injury and crisis in SCD.[112] The balance between NETs generation and NETs clearance is impaired in SCD.[111,113,114] This is because resolution of NET-induced inflammation requires endogenous synthesis of lipid-derived natural anti-inflammatory mediators, namely Resolvins, Lipoxins, and Maresins , which are inadequate in patients with SCD.[111,113,114] Inadequate elimination of NETs has been linked to increased risk of forming anti-DNA auto-antibodies and SLE in SCD.[111,113] Hence, it has been suggested that exogenous administration of Resolvins would potentially have multiple advantages of mitigating crisis, infarctions, and tissue damage,[114] as well as preventing the production of anti-DNA autoantibodies, and reducing the risk of developing SLE in particular, and possibly any inflammation-induced AIDs, in patients with SCD.[111,113]

2. Splenomegaly: Acute Sequestration and Chronic Hypersplenism

Because the natural course of SCD is accompanied by incessant and repetitive splenic infarctions that ultimately lead to autosplenectomy, most SCD patients do not have palpable spleen beyond the 8th year of life.[26-28] Hence, splenomegaly and its complications (hypersplenism, sequestration, and haemolysis) are more likely to occur in younger SCD children within the pre-autosplenectomy age group. Nonetheless, persistent splenomegaly (and its acute and chronic haemolytic complications) may occasionally be encountered in older children and adults with SCD. This is likely to occur in four categories of SCD patients. First, SCD patients with symptomatically mild genotypes such as HbSC, HbSβ-thalassemia, HbSS with high HbF, HbSS with α-thalassemia trait.[115,116] Second, as earlier noted, SCD patients on hydroxyurea therapy have reduced rate of splenic infarction and high prevalence of splenomegaly.[107,108,117] Third, SCD patients who co-inherit splenomegaly-conferring membranopathies such as hereditary spherocytosis or elliptocytosis.[118-120] And fourth, SCD patients living in infection-prone tropical environment. Chronic immune stimulation due to recurrent infections is an important factor in the persistence of splenomegaly among SCD patients living in the tropics where high prevalence of persistent splenomegaly is observed among adolescent and adult patients. A Nigerian study reported that splenomegaly persisted in more than one third of SCD patients between the ages of 10 to 16 years.[121] The high prevalence of persistent splenomegaly among SCD patients in Nigeria and other West Africa countries has been causally linked to malaria endemicity.[121,122] Chronic immune stimulation due to recurrent malaria infections causes splenomegaly by inducing splenic reticuloendothelial hyperplasia.[121,122] This is consistent with the finding of significantly high levels of malaria-specific IgG antibodies in SCD patients with persistent splenomegaly who reside in malaria endemic zones.[123] Splenomegaly in SCD clinically manifests as 'acute splenic enlargement with acute sequestration crisis' or 'chronic splenomegaly with hypersplenism, chronic sequestration, and hyperhaemolysis'. Because the intra-splenic environment is relatively vaso-static and hypoxic,[28] acutely or chronically sequestered red cells invariably sickle, and are thus ultimately haemolysed (i.e., phagocytosed by macrophages) within the spleen as explained below.

2a. Acute Splenic Sequestration Crisis and Haemolysis

Acute splenic sequestration crisis (ASSC) is one of the earliest life-threatening complications seen in SCD patients, with the first occurrence described as early as 5 weeks of age[124] and a median age at first episode of 1-4 years,[125] while 75% of first cases occur before the age of

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2 years.[125] ASSC is rarely observed after 6 years, except in patients with high HbF levels or in those on regular blood transfusion.[126] ASSC is defined as an acute splenic enlargement with a concomitant fall in the Hb concentration of at least 20 g/l from baseline level and a normal or increased basal reticulocyte count.[127] It occurs when red cells are acutely trapped in the splenic vasculature resulting in abdominal pain and distension, pallor, and haemodynamic symptoms of tachycardia, hypotension, and lethargy.[27] Severe episodes may lead to hypovolemic shock and death from cardiovascular collapse within just a few hours.[27] The precise sequence of pathogenetic events leading to ASSC is not precisely known but may be precipitated by febrile infection that may trigger or amplify red cell sickling in the splenic red pulp.[27] Accumulation of sickled red cells that lie in a zone close to major tributaries of the splenic vein are thought to cause mechanical obstruction of venous blood flow, which causes intra-splenic stasis, congestion, and hypoxia, that leads to amplification and extension of red cell sickling within the enlarged organ.[27] This acute event may be self-limited and transient or persistent, leading to extensive infarctions (causing tender splenomegaly), massive sequestration and eventual haemolysis of red cells (causing severe anaemia) and reduction of circulating blood volume (causing hypovolemic shock).[27]

ASSC is a medical emergency that requires immediate restoration of Hb levels and blood volume by whole blood or red cell concentrates with intravenous fluids as well as treating any associated triggering infection.[27] The trapped sickled red cells in ASSC are invariably haemolysed by splenic macrophages, which leads to gradual reduction in the size of the organomegaly.[27] Recurrent episodes of ASSC are very life-threatening and must be mitigated by chronic transfusion, or splenectomy as a last resort.[27,128] The use of splenectomy is controversial, as it may predispose patients to post-splenectomy infections, which must be prevented by peri-operative vaccinations coupled with post-operative chemoprophylaxis.[129] However, a Cochrane review found no evidence in favour of splenectomy vis-à-vis conservative management in improving survival of SCD patients with recurrent ASSC, which calls for randomized studies in order to define the best management strategy for ASSC.[130]

2b. Chronic Splenomegaly: Hypersplenism and Hyperhaemolysis

Chronic hypersplenism is characterized by splenomegaly, a reduction of one or more cellular elements of the blood leading to anaemia, leucopenia, thrombocytopenia, or any combination of these, and a reactive compensatory hyperplasia of the respective marrow precursors of the deficient cell.[131] These cytopenias occur as a result of pooling of blood cells in the vasculature of the enlarged spleen resulting in hyperhaemolysis of red cells with simultaneous destruction of leucocytes and platelets.[131] Moreover, splenomegaly is usually associated with increase in the volumes of plasma and whole blood, and the magnitude of the rise in both plasma and whole blood volumes is closely correlated with the degree of splenic enlargement.[132] Therefore, the anaemia in hypersplenism is essentially bi-factorial,[133] and is characterised by dilutional[134] and hyperhaemolytic[131] components; but the hyperhaemolytic component is the most important cause of the anaemia in hypersplenism.[131] In patients with SCD and chronic hypersplenism, the extent of hyperhaemolysis and anaemia is judged by the trend in transfusion requirements, and surgical intervention is usually contemplated if conservative intervention such as chronic transfusion fails to shrink the spleen, and transfusion requirement exceeds 250 ml/kg of packed red cells per year and/or the fall in Hb concentration exceeds 0.5 g/week.[135,136] Although the first line of therapy for hypersplenism often includes an increasing number of blood transfusions,[135,136] the long term benefits of blood transfusion have to be weighed against the attendant risks of alloimmunization and transmission of blood-borne infections, hence the need to consider splenectomy.[135,136] As in the case of recurrent ASSC, splenectomy for chronic hypersplenism should only be considered as a last resort due to the high risk of post-splenectomy infection, which should be pre-empted by ensuring optimum peri-operative vaccinations with complementary post-operative chemoprophylaxis.[129] Moreover, in order to obviate the risks of total splenectomy, it can be substituted with 'less radical interventions' such as partial splenectomy, embolization or per-cutaneous intra-luminal occlusion of the splenic artery.[135,136]

Conclusion and Recommendations

Although autosplenectomy and splenomegaly are anatomically mutually exclusive, they are nonetheless concordant in the causation of hyperhaemolysis in SCD. Autosplenectomy is an 'indirect and covert' cause of hyperhaemolysis via loss of immune pitting and culling functions (thus increasing susceptibility to erythrocytopathic infections) on the one hand, and via loss of peripheral immune tolerance (thus increasing

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propensity to produce autoantibodies against red cells) on the other hand. In contradistinction, splenomegaly is a 'direct and overt' cause of hyperhaemolysis via acute sequestrations and chronic hypersplenism. Therapeutically rational combinations of transfusion, antimicrobial therapy, and/or immune suppression provide short-term solution for severe hyperhaemolysis due erythrocytopathic infections, red cell autoantibodies, and acute sequestration or chronic hypersplenism. However, in order to achieve long-term preventive measures against autosplenectomy-associated hyperhaemolysis, SCD caregivers should counsel patients on personal and environmental hygiene, vector control, routine chemoprophylaxis for locally endemic erythrocytopathic infections, and immunization for vaccine-preventable infections as a sustainable preventive strategy against infections. Moreover, the use of hydroxyurea as a potential therapeutic tool in the prevention or reversal of autosplenectomy should be carefully considered by SCD physicians since hydroxyurea may 'inadvertently' cause splenomegaly and hypersplenism. Surgical splenectomy as a long-term solution to hyperhaemolysis should only be considered for cases of life-threatening recurrent acute sequestration crisis or severe recalcitrant chronic hypersplenism; even then, the risk of post-splenectomy infection should in all cases be pre-empted by ensuring optimum peri-operative vaccinations with complementary post-operative chemoprophylaxis.

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