Annals of Hematology (2023) 102:1657–1667
https://doi.org/10.1007/s00277-023-05294-3

ORIGINAL ARTICLE

Sickle cell disease and acute leukemia: one case report and an extensive review

Giovanna Cannas[1,2] · Solène Poutrel[1,2] · Maël Heiblig[3] · Hélène Labussière[3] · Marie-Virginie Larcher[3] · Xavier Thomas[2] · Arnaud Hot[1,2]

Received: 20 March 2023 / Accepted: 22 May 2023 / Published online: 3 June 2023

Abstract

Population-based studies and case reports suggest that there may be an increased risk of acute leukemia associated with sickle cell disease (SCD). Following the description of a new case report, an extensive review of the literature identified 51 previously described cases. Most cases study showed myelodysplastic features confirmed, when available, by genetic markers such as chromosome 5 and/or chromosome 7 abnormalities and *TP53* gene mutations. The increased risk of leukemogenesis is certainly multifactorial and related to the pathophysiologic mechanisms of the clinical manifestations of SCD. Chronic hemolysis and secondary hemochromatosis may cause increased chronic inflammation, resulting in persistent marrow stress, which could potentially compromise the genomic stability of the hematopoietic stem cells generating genomic damage and somatic mutations over the course of SCD and its treatment, resulting in a clone that led to acute myeloid leukemia.

Keywords Sickle cell disease · Acute myeloid leukemia · Treatment · Prognosis

Introduction

Sickle cell disease (SCD) corresponds to an autosomal recessive hemoglobinopathy in which structurally abnormal hemoglobin (HbS) leads to chronic hemolytic anemia and to a variety of severe clinical manifestations. The disorder is caused by a point mutation. A single DNA base change leads to substitution of valine for glutamic acid at the sixth position on β globin chain. Patients with homozygous hemoglobin (SS) often present with severe symptoms, while those with a heterozygous mutant allele (SA) demonstrate minimal clinical symptoms. The combination of hemoglobin S with another type of β subunit gene mutation, such as hemoglobin C or β thalassemia, forms a compound heterozygous hemoglobinopathy (SC or $S\beta^0$). With the exception of the compound $S\beta^0$, the heterozygous genotypes are usually less clinically severe than hemoglobin SS [1].

Since Herrick's description of SCD in 1910 [2], a wide variety of malignancies, including hematological neoplasms, have been reported in both children and adults with SCD. However, the exact incidence of malignancy has not been accurately determined due to a lack of long-term follow-up. The first description of SCD coexisting with acute leukemia has been reported by Goldin et al. in 1953 in a 38-year-old black man with SCD and acute myeloid leukemia (AML) [3]. Since then, the occurrence of acute leukemia has been reported in several cases of patients with SCD.

We reported here a new case of SCD patient who developed AML and reviewed extensively the literature in order to better understand the relationship between the two diseases. This review leads to the hypothesis of a mechanism involving multifactorial causes through the pathophysiologic mechanisms of the clinical manifestations of SCD.

✉ Giovanna Cannas
giovanna.cannas@chu-lyon.fr

1 Internal Medicine, Hospices Civils de Lyon, Edouard Herriot Hospital, 5, place d'Arsonval, Lyon cedex 03, 69437 Lyon, France

2 Constitutive reference center: Major sickle cell syndromes, thalassemias and other rare pathologies of red blood cell and erythropoiesis, Edouard Herriot Hospital, Lyon, France

3 Hematology, Hospices Civils de Lyon, Lyon-Sud Hospital, Pierre-Bénite, France

Patients and methods

Case selection

A sole case of acute leukemia in the setting of SCD was retrieved from the pathology database of the "Centre de Référence Constitutif des pathologies du globule rouge et de l'érythropoïèse" in Lyon (France), including a pool of more than 600 adults and children with SCD. The diagnosis of leukemia was confirmed according to the World Health Organization classification [4]. Informed consent for reporting this case was obtained from this patient in accordance with the declaration of Helsinki. Clinical history and laboratory data, including flow cytometry analysis, cytogenetics, and molecular biology, were collected as well as data regarding SCD history.

Literature data sources

The PubMed database was searched on October 2022 for case reports previously published involving both SCD and acute leukemia. The relevant keywords used were: "sickle cell disease" or "sickle cell anemia", combined with "acute leukemia", or "myelodysplastic syndrome" (MDS). Fifty-one previously published cases were identified since 1972, and the relevant data regarding acute leukemia and SCD were collected and analyzed (Tables 1 and 2). These cases did not included those only mentioned in the epidemiologic reports from California and the United Kingdom [5, 6].

Results

Case report

A 27-year-old woman of African origin with known SCD ($S\beta^0$), previously complicated by recurrent severe vaso-occlusive crisis (VOC) and acute chest syndrome despite hydroxyurea (HU) therapy (1000 mg/day for 7 years) and regular exchange transfusions, presented on May 2022 a progressive bicytopenia with anemia to 50 g/dL (based-hemoglobin level under compliant treatment with HU around 75 g/dL) and thrombocytopenia to 50×10^9/L, leading to HU discontinuation. A suspicion of MDS was confirmed by a first bone marrow sample showing a hypercellular marrow with signs of dyserythropoiesis with demonstration of ring sideroblasts on a Perls'stain, dysmegacaryopoiesis, and dysgranulopoiesis, but no leukemic cells. The patient was referred to the Hematology Department and a repeat bone marrow aspirate, performed sequentially showed a progressive blast increase up to 25% leading to the diagnosis of AML-MRC (myelodysplastic related changes). The immunophenotypic profile was $CD34^{+/-}$ $CD38^{+/-}$ $CD123^{+/-}$, $CD13^{+/-}$ $CD33^{+/-}$ $CD117^{++}$, $HLADR^{+/-}$, $CD36^{+/-}$ $CD71^{++}$, $CD7^{-}$ $CD19^{-}$ $CD56^{-}$, MPO^{-}. Seventeen percent of myeloblasts expressed a multipotent progenitor-like leukemia stem cell (LSC) profile $CD34^{+}$ $CD38^{-}$ $CD90^{++/-}$ $CD45RA^{+/-}$ CLL1/TIM3/$CD97^{+/-}$. Cytogenetic analysis showed a complex karyotype: 44–46, XX, der(1)t(1;12)(q31;q15)add(1)(p11), − 3, der(5)t(5;7)(q13;q31), − 7, del(12)9q21), der(15)t(?3;15)(q21;p13), add(16)9p13), − 22, + 3-6mars[cp18]/46, XX [2]. Molecular study by next-generation sequencing (NGS) identified the presence of a *TP53* mutation c.1024C > T with a variant allele frequency (VAF) of 0.64. The patient received induction chemotherapy with Vyxeos (daunorubicin/cytarabine) at a dose of 44 mg/m^2 on days 1, 3, and 5. On day 22, peripheral blood showed 18% blasts signing remnant leukemia. Salvage chemotherapy combined mitoxantrone 6 mg/m^2/day, etoposide 80 mg/m^2/day, and intermediate-dose cytarabine 1 g/m^2/day from day 1 to day 6. Salvage chemotherapy was complicated by infections including inguinal cellulitis requiring large spectrum antibiotics and white blood cell infusion therapy, pericarditis, and posterior reversible encephalopathy syndrome (PRES) leading to a transitory hospitalization in intensive care unit. Cytological remission was achieved, but measurable residual disease (MRD) remained positive at 0.09% based on leukemia associated immunophenotype (LAIP)/LSC. Allogeneic phenol-identical hematopoietic stem cell transplantation (HSCT) with one mismatch was performed on January 2022 based on thiotepa-busulfan-fludarabine (TBF) conditioning regimen followed by post-transplant cyclophosphamide and everolimus for graft-versus-host prophylaxis. The hospitalization was complicated by a septic shock (*Klebsiella pneumonia*) and by invasive pulmonary aspergillosis and severe hepatosplenic candidosis (*Candida glabrata*). Bone marrow evaluation at one month and two months post-transplant confirmed the cytological remission with MRD negativity assessed by multi-parameter flow cytometry and total donor chimerism.

Review of the literature

Fifty-two cases of acute leukemia in SCD patients (including our case report) were identified in the literature since 1972 (Tables 1 and 2). Among patients with available data, male/female sex ratio was 0.45. Median age was 23.5 years (range: 3 – 61 years). Thirteen patients (25%) had acute lymphoblastic leukemia (ALL), one patient an undifferentiated acute leukemia, and 38 patients (73%) a myeloid neoplasm, including 16 AML, 6 MDS and 16 MDS/AML. Among the 26 patients studied for genetic markers, two patients with ALL showed a Philadelphia chromosome (Ph +) (#9, #49), one patient with AML had a normal karyotype (#12), two had

Table 1 Acute leukemia characteristics and outcome of the 51 patients identified in the literature

Reference	Pt/Age/Gender	Type of AL	Treatment	Outcome (Cause of death)
Jackson (1972) [7]	#1/6/F	ALL	Chemo	CR OS: 17 months (viremia)
Samal (1979) [8]	#2/7/F	AML	None	OS: 4 days
Clinicopathologic conference (1982) [9]	#3/27/F	MDS/AML4	None	OS: 3 days (ARDS)
Johnson (1984) [10]	#4/8/F	AML2	HSCT	OS: 16^+ months
Bigner (1986) [11]	#5/4/F	ALL null (del9p13)	NA	NA
Stricker (1986) [12]	#6/43/M	MDS/AML1 (−3, t13;17, t3;5, 5q−, −7, +8)	Chemo	OS: 1 month (hemorrhage)
Njoku (1988) [13]	#7/22/M	ALL	Chemo	CR OS: 10 months (disease progression)
Sotomayer (1999) [14]	#8/14/M	ALL ($CD10^+$, $CD19^+$, $CD22^+$, DR^+, TdT^+)	Chemo	CR OS: 2.5^+ years
De Montalembert (1999) [15]	#9/10/F	Ph^+ ALL	Chemo	CR OS: 12^+ months
Rauch (1999) [16]	#10/27/F	MDS/AML	NA	NA
Wilson (2000) [17]	#11/42/F	MDS/AML (−5, −7, del17)	Chemo	OS: 13 months
Al-Jam'a (2002) [18]	#12/25/F	AML1 (Normal karyotype)	Chemo	CR OS: NA (aspergillosis)
Schultz (2003) [19]	#13/14/F	ALL	NA	NA (Alive)
	#14/5/NA	ALL	NA	NA (Alive)
	#15/7/NA	ALL	NA	NA (Alive)
	#16/8/NA	AML	NA	NA (Alive)
	#17/8/NA	ALL	NA	NA (Alive)
	#18/17/NA	ALL	NA	NA (Alive)
	#19/61/NA	ALL	NA	NA (Dead)
	#20/20/NA	AML	NA	NA (Dead)
Ferster (2003) [20]	#21/21/F	AML3v	ATRA + Chemo	CR
Taylor (2011) [21]	#22/33/M	MDS/AML6 (Abn5q, del7q, −15, −22, −Y, mar5)	Chemo Allo HSCT	CR Relapse at 4 months OS: 9 months
Baz (2012) [22]	#23/41/M	MDS/AML (Abn5, del7, −17)	Chemo	OS: 3 months (sepsis)
Zemenides (2014) [23]	#24/55/M	MDS/AML (5q−, 7q−, del17p)	NA	NA
Aumont (2015) [24]	#25/49/M	MDS/AML6 (del17p, del5q, monosomy 20) BM fibrosis	Chemo	OS: 3 weeks (CNS involvement)
Chauhan (2018) [25]	#26/25/F	AML3	NA	NA
	#27/19/M	AML2	NA	NA
Janakiram (2018) [26]	#28/31/F	MDS/AML (5q−, add5p, −7, t2;5, *TP53*$^+$, *NRas*$^+$)	Azacitidine	OS: 12 months (sepsis)

Table 1 (continued)

Reference	Pt/Age/Gender	Type of AL	Treatment	Outcome (Cause of death)
Li (2019) [27]	#29/59/F	MDS (del4, 5q−, 7q−, −15, −16, *TP53*$^+$)	Decitabine	OS: 2 months (progression to AML)
	#30/27/M	MDS/ AML (11q23, +3, +19, +21, *KMT2A*$^+$)	ChemoAllo HSCT	OS: 7 months
	#31/37/F	MDS (del1, del5, t3;6, −17, +3, *TP53*$^+$)	Lenalidomide + prednisone	OS: 5$^+$ months
	#32/34/M	MDS (7q22, del20, −2, Inv9)	Matched sibling HSCT	OS: 21$^+$ months
Eapen (2019)* [28]	#33/19/NA	AML	NA	NA
	#34/37/NA	MDS	NA	NA
	#35/32/NA	AML	NA	NA
	#36/37/NA	MDS	NA	NA
Regan (2019) [29]	#37/26/F	MDS/AML (5q−, +8, del17, *TP53* deletion)	Chemo	OS: 4 months
Aworanti (2020) [30]	#38/15/M	AL mixed lineage	None	Death before any treatment
	#39/21/F	ALL	None	Discharged at day5CR after 2 lines
	#40/15/M	AML4	Chemo	Discharged after CRDeath 4 weeks after
	#41/3/M	AML	None	Discharged after diagnosis
	#42/15/F	AML5	Chemo	OS: 2 months(sepsis)
Yadav (2020) [31]	#43/29/F	AML6 (5q−)	Chemo	OS: few months (AML progression)
Ghannam (2020) [32]	#44/39/M	MDS/AML7 (complex cytogenetics, *TP53*$^+$, BM fibrosis)	Decitabine Azacitidine	OS: 12 months (pulmonary hypertension)
	#45/39/M	MDS/AML(complex cytogenetics, *TP53*$^+$)	Haplo HSCT	OS: 7 months(intracranial hemorrhage)
	#46/49/F	MDS/AML(7q−, BM fibrosis)	NA	NA
Chellapandian (2020) [33]	#47/14/F	AML CNS$^+$ (*FLT3-ITD*$^+$)	Chemo + sorafenib Haplo HSCT	CR OS: 8$^+$ months
Hsieh (2020) [34]	#48/42/M	MDS/AML (−7, 19p abnormality, *RUNX1*$^+$, *KRAS*$^+$, *PTPN11*$^+$)	Azacitidine Decitabine Chemo Haplo HSCT	CR after Haplo OS: 6$^+$ months
Ahmed (2021) [35]	#49/19/M	Ph$^+$ ALL	Chemo + imatinib	OS: 6 months (meningoencephalitis)
Goyal (2022) [36]	#50/31/F	AML0 (−7, 11p−, *WT1*$^+$, *RUNX1*$^+$, *PTPN11*$^+$)	Chemo Haplo HSCT	CR (MRD$^+$) OS: 12 months (AML progression)
Flevari (2022) [37]	#51/40/M	MDS (complex cytogenetics, 5q−, 3p, 7p, −16, −7, −18)	None	OS: 3 months (severe cytopenia)
Our case report	#52/27/F	MDS/AML (−3, t5;7, −7, del12, −22, *TP53*$^+$)	Vyxeos MEC HSCT	CR MRD$^-$ after HSCT OS: 12$^+$ months

Abbreviations: Abn, abnormality; AL, acute leukemia; ALL, acute lymphoblastic leukemia; Allo, allogeneic; AML, acute myeloid leukemia; ARDS, Acute respiratory distress syndrome; ATRA, all-*trans* retinoic acid; BM, bone marrow; Chemo, intensive chemotherapy; CNS, central nervous system; CR, complete remission; F, female; Haplo, haplo-identical; HSCT, hematopoietic stem cell transplantation; NA, not available; M, male; MEC, chemotherapy combining mitoxantrone, etoposide, and cytarabine; MDS, myelodysplastic syndrome; MRD, measurable residual disease; OS, overall survival; Ph$^+$, Philadelphia chromosome-positive; Pt, patient number

*This reference is based on registry data. The patients may therefore overlap with others reported in the table

Table 2 SCD characteristics of the 51 patients identified in the literature

Reference	Pt/Diagnosis/Origin	Age at diagnosis	Treatment	Clinical features
Jackson (1972) [7]	#1/SS/Afr.Am	NA	No HU	NA
Samal (1979) [8]	#2/SS/NA	Infancy	Transfusions	NA
Clinicopathologic conference (1982) [9]	#3/SS/NA	NA	Transfusions	Hemosiderosis
Johnson (1984) [10]	#4/SS/Afr.Am	Infancy	NA	NA
Bigner (1986) [11]	#5/SS/NA	At birth	NA	NA
Stricker (1986) [12]	#6/SC/Afr.Am	NA	NA	Aseptic necrosis humeral head
Njoku (1988) [13]	#7/SS/Nigerian	NA	NA	NA
Sotomayer (1999) [14]	#8/SS/Afr.Am	Infancy	No HU	VOC
De Montalembert (1999) [15]	#9/SS/NA	Infancy	HU (1.5 m)	VOC (3 to 7/year)
Rauch (1999) [16]	#10/SS/NA	NA	HU (8y)	VOC
Wilson (2000) [17]	#11/SS/NA	NA	HU (6y)	NA
Al-Jam'a (2002) [18]	#12/SS/Saudi Arabian	NA	HU (2y)	VOC (6/year) Hepatitis C
Schultz (2003) [19]	#13/SS/NA	Infancy	HU (3 m)	NA
	#14/SS/NA	Infancy	No HU	NA
	#15/SS/NA	Infancy	No HU	NA
	#16/SS/NA	Infancy	No HU HSCT	NA
	#17/SS/NA	Infancy	No HU	NA
	#18/SS/NA	NA	No HU	NA
	#19/SS/NA	NA	No HU	NA
	#20/SS/NA	NA	No HU	NA
Ferster (2003) [20]	#21/SS/NA	NA	HU (8y)	VOC Osteonecrosis ACS
Taylor (2011) [21]	#22/SS/Afr.Am	NA	HU (5y) Transfusions	VOC Priapism ACS
Baz (2012) [22]	#23/SS/Afr.Am	21	Exchange transfusions HU (15y)	VOC (14 to 3/year)
Zemenides (2014) [23]	#24/SS/Jamaican	NA	No HU	Pulmonary hypertension
Aumont (2015) [24]	#25/SS/NA	NA	HU (14y) Transfusions	VOC Hip necrosis Retinopathy Infections Ischemic stroke Cholelithiasis Iron overload
Chauhan (2018)[25]	#26/SS/Indian	NA	Transfusions HU	NA
	#27/SS/Indian	NA	HU	NA
Janakiram (2018) [26]	#28/SS/Afr.Am	Childhood	HU (5y) Haplo HSCT (8 m)	VOC
Li (2019) [27]	#29/SC/NA	NA	HU Exchange transfusions	HHV8
	#30/SS/NA	NA	Exchange transfusions	VOCMyocardial infarctionHIV^{+}
	#31/SS/NA	Infancy	Exchange transfusions	VOC
	#32/Sβ^{0}/NA	NA	Exchange transfusionsHU (9y) Matched HSCT (7y)	VOCPriapismArterial anevrysmIntracranial bleeding

Table 2 (continued)

Reference	Pt/Diagnosis/Origin	Age at diagnosis	Treatment	Clinical features
Eapen (2019)* [28]	#33/NA/NA #34/NA/NA #35NA/NA #36/NA/NA	NA NA NA NA	Haplo HSCT (3.6y) Haplo HSCT (9 m) Haplo HSCT (1y) Matched sibling HSCT (2.6y)	NA NA NA NA
Regan (2019) [29]	#37/SS/Afr.Am	Childhood	Transfusion/Exchange HU (2y)	VOC Pulmonary fibrosis Pneumonia Hips necrosis Peritonitis
Aworanti (2020) [30]	#38/SS/Nigerian #39/SS/Nigerian #40/SC/Nigerian #41/SC/Nigerian #42/SS/Nigerian	2 years 4 years Childhood et al. diagnosis NA	No HU Transfusion No HU Transfusion No HU Transfusion None No HU	None VOC (1/year) VOC (1/2 years) None NA
Yadav (2020) [31]	#43/SS/NA	NA	HU (5y)	VOC
Ghannam (2020)[32]	#44/SS/NA #45/SS/NA #46/SS/NA	NA NA NA	HU Haplo HSCT (2y) HU Sibling HSCT (2.5y) HU Haplo HSCT (5y)	Stroke VOC CRI VOC Diastolic dysfunction ESRD Pulmonary hypertension
Chellapandian (2020) [33]	#47/Sβ^0/Haitian	At birth	HU (9y)	VOC
Hsieh (2020) [34]	#48/SS/NA	NA	HU (8y) Gene therapy (LentiGlobin) (3y)	VOC Iron overload Leg ulcers Hypertension Gallbladder disease
Ahmed (2021) [35]	#49/SS/Nigerian	At 1 year	Transfusions No HU	VOC (> 4/year)
Goyal (2022) [36]	#50/SS/NA	NA	HU (6y) Gene therapy (LentiGlobin) (5.5y)	VOC Hip necrosis Deep-vein thrombosis
Flevari (2022) [37]	#51/SS/NA	NA	HU (17y) Exchange transfusions	VOC Priapism Pulmonary hypertension
Our case report	#52/Sβ^0/African	Childhood	HU (7y) Exchange transfusions	VOC ACS Cholelithiasis Retinopathy COVID-19

Abbreviations: ACS, acute chest syndrome; Afr.Am, African-American; AL, acute leukemia; CRI, chronic renal insufficiency; ESRD, end-stage renal disease; Haplo, haplo-identical; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplantation; HU, hydroxyurea; LentiGlobin, Gene therapy consisting of autologous hematopoietic stem and progenitor cells transduced with the BB305 lentiviral vector encoding the β^{A-T87Q}-globin gene designed to produced anti-sickling hemoglobin (HbA^{Y87Q}); m, months; NA, not available; Pt; patient number; VOC, vaso-occlusive crisis; y, years

*This reference is based on registry data. The patients may therefore overlap with others reported in the table

acute promyelocytic leukemia (#21, #26), and 20 patients with MDS and/or AML displayed unfavorable cytogenetics [−5, −7, del(17), 11q23, chromosome 3 abnormality] and/or molecular abnormalities of poor prognosis [*TP53*, *KMT2A*, *RAS*, *RUNX1*, *PTPN11*] (#6, #11, #22–25, #28-#32, #37, #43–46, #48, #50, #51, #52). Most of the patients (84%) displayed a SS homozygous hemoglobin, while only 9% were SC and 7% Sβ^0. Data were available in 38 patients regarding the potential use of long-term SCD therapy with HU: 16 (43%) did not receive any HU, while 22 (57%) received HU

prior to acute leukemia diagnosis (median duration of treatment: 6.5 years; range: 0.05 – 17 years). Ten patients underwent allogeneic HSCT, after conditioning regimen including alkylating agents and/or total body irradiation, as treatment of SCD. Four patients were allografted from a matched sibling donor (#16, #32, #36, #45) and six patients from a haploidentical donor (#28, #33–35, #44, #46) (Table 2). The median time between HSCT and acute leukemia diagnosis was 2.5 years (range: 0.26 – 7 years). Two cases of AML developed in SCD patients who had been treated by gene therapy with LentiGlobin [34, 36], which required myeloablation with an alkylating agent.

Overall acute leukemias in SCD patients were of dismal outcome with overall survival (OS) ranging from few days to 2.5^{+} years (median in patients with available data: 7 months).

Discussion

Historically, the development of malignancy in children and adults patients with SCD has been documented by several small series [7, 12, 38]. On the basis of a single institution study, the cancer incidence in SCD patients has been estimated to be 1.74 cases per 1,000 patient-years [39]. Malignancies mainly included hematological neoplasias, especially acute leukemias. In the 1970s, Jackson reported, among 58 black children treated for acute leukemia, 4 ALL and 3 AML with sickle cell trait, and one ALL with homozygous HbS [7]. In a low-income country, the association of acute leukemia with SCD was even reported in 8.6% of cases [30]. Actually, the risk of hematologic malignancies is 2 to 11 times as high as that in the general population. This was established by three recent epidemiology reports [5, 6, 19]. The first study used a standardized incidence ratio (SIR) to compare individuals with SCD to the general population. One hundred and fifteen on 6423 SCD individuals were diagnosed with cancer, with a total of 6 AML cases (SIR, 3.59; 95% confidence interval: 1.32–7.82) and 3 cases of ALL (1.83; 0.38–5.35) [5]. In the second study, 8 cases of AML on 7512 individuals with SCD were reported (11.05; 3.86–30.17). Among hematological malignancies, the risks remained elevated for all conditions studied, except for lymphoid leukemia [6]. The third study identified 52 cases of cancer in 49 patients among 16,613 individuals with SCD, 40% of cases occurring in children [19]. The most frequent malignancy was acute leukemia (8 cases).

The vast majority of SCD patients receive conservative therapy. In this setting, HU has greatly improved the survival of SCD patients in developed countries, due to its efficacy in preventing VOC via an inhibitory effect on HbS polymerization by increasing the synthesis of fetal hemoglobin, and an improvement of blood flow in the microcirculation through the expression or activity of several adhesion molecules on red blood and endothelial cells [40, 41]. Three randomized placebo controlled trials have demonstrated the efficacy of HU in SCD, with an excellent safety profile and up to a 40% reduction in mortality after 9 years of follow-up [42–44]. HU is an inhibitor of DNA synthesis that may theoretically lead to an accumulation of acquired DNA mutations and eventually leukemic transformation. Whether acute leukemia in SCD patients with long-term exposure to HU is a co-incidental or related to therapy has been a major issue debated in many reports. The leukemogenic risk could theoretically increase with the duration of drug exposure. The index of DNA damage in peripheral blood leukocytes from HU-treated patients with SCD was demonstrated higher than in controls and was confirmed influenced by the duration and the dose of HU treatment, and by the HbS genotype [45, 46]. The leukemic risk of HU has never been confirmed in patients with chronic myeloproliferative diseases [47, 48], and no increased risks of malignancy were reported in large series of SCD patients [49–51]. Among 278 SCD children receiving long-term treatment with HU, only one developed acute leukemia [15, 52, 53]. If one study in pediatric SCD patients treated with HU showed that genotoxicity increased with HU administration [54], it was demonstrated that individuals may have different susceptibilities to HU, and that this occurred in a patient population that may already have an elevated risk for malignancy evaluated at baseline by a greater Damage Index [55]. Overall the genotoxicity results clearly demonstrate that HU does not directly bind DNA and is not mutagenic [56]. In vitro, HU can result in the accumulation of somatic mutations and chromosomal damages due to interference with DNA repair, but the number of acquired mutations did not increase in patients with long-term exposure to the drug [57]. On another hand, HU therapy can alleviate the risk of chronic hemolysis by increasing the fetal hemoglobin content in the blood, and potentially reduce the accompanying marrow stress in these patients. The recent prospective observational study ESCORT-HU (NCT02516579), which evaluated the long-term safety and effectiveness of HU in SCD patients across several European centers, confirmed the benefit-to-risk ratio of HU in children and adults [58]. Only one incident hematological malignancy was reported.

In contrast to life-long supportive care measures, HSCT offers a curative option but may be followed by various severe complications. It is therefore being reserved to patients who are refractory to conventional therapy. The 5-year OS ranges from 91 to 95% in children who underwent HLA-identical HSCT after myeloablative conditioning, while disease-free survival, rate of rejection, and incidence of chronic graft versus host disease are approximately 82%, 8%, and 12%, respectively [59, 60]. Nine percent of patients died of complications related to transplantation [59].

Peripheral blood stem cells, which would come from AA or AS donors, have also been proposed as a source of stem cells for allogeneic HSCT. The results after related (5-year OS: 97%) and unrelated (2-year EFS: 90%) donor umbilical cord transplantation (UCT) have also been encouraging [61]. However recent results were more discouraging showing a high incidence of graft rejection (50% to 62%) after unrelated UCT [62], although updated data using a reduced intensity conditioning combining HU, alemtuzumab, fludarabine, thiotepa, and melphalan were more impressive [63]. Haploidentical-related donor transplantations are under study. It is becoming a viable alternative curative option for SCD, extending the availability of HSCT as a treatment option to eligible SCD patients. Overall survival was high (91%) in all studies included in a recent meta-analysis [64]. One study has suggested that HSCT for SCD does not increase the risk of developing acute leukemia, compared with patients who have not undergone SCT [60]. However, transplanted patients are generally exposed to alkylating agents and ionizing radiation as part of a conditioning regimen, and intervals, found in the literature, between the procedure and the diagnosis of leukemia are falling in the range of latency reported in other diseases. Furthermore, therapy-related MDS/AML is a well known event after autologous transplantation for lymphomas, with cumulative risks as high as 15%.

Trials in gene therapy are under way and also offer great promise. However, the largest lentiviral vector-mediated β-globin replacement gene therapy trial in SCD reported two cases of adult patients diagnosed with AML [34, 36, 65, 66]. These two cases shared similar cytogenetic and molecular abnormalities with monosomy 7 and *RUNX1* and *PTPN11* mutations, which were not found in patients pre-conditioning bone marrow samples. The first case was considered to be related to busulfan conditioning [34]. The second case showed vector present in leukemia blast cells, which suggests that blast cells originated from a transduced hematopoietic stem cell and not from residual host cells exposed to busulfan [36]. However, several lines of evidence showed that the development of this case of AML most likely occurred independently of insertional oncogenesis [36].

If a coincidental event between acute leukemia and SCD could be evocated in several cases from the literature that resemble de novo acute leukemia, an increased risk for acute leukemia is suggested by the significant underlying MDS features of most reported cases compared to leukemic patients from the general population of the same age. Extensive literature review demonstrates at least 18 patients with presence of complex structural rearrangements involving complete or partial loss of chromosome 5 and/or chromosome 7 and/or 17p deletions. *TP53* gene mutations have also been shown frequently implicated [67]. Furthermore, several cases were classified as AML6 or AML7 and/or presented bone marrow fibrosis. Those facts are not in favor of a simple coincidence between the occurrence of acute leukemia and SCD, but are generally considered as a marker of secondary leukemia.

The exact underlying connection between acute leukemia and SCD is not clearly understood. Beside therapy for SCD, other potential cancer risk factors might exist for SCD patients and have been discussed in a recent published commentary [68]. Red blood cell transfusions can lead to increased iron levels and non-specific immunomodulation that could increase the risk of malignancy. However, heavily transfused patients with thalassemia only show a few cases of cancer [69]. Chronic inflammation implies the potential involvement of inflammasomes in SCD pathogenesis [70]. Chronic organ damage with inflammation could also cause cellular damage with subsequent malignant transformation. The pro-tumorigenic role of inflammasomes is associated with promoting cell proliferation, inhibition of apoptosis, and an immunosuppressive effect on the immune cells. Constant hematopoietic hyperplasia, stimulated by a hemolysis-induced cytokine storm, may increase the risk of somatic mutations, resulting in transformation of myeloid precursors [71]. Other factors associated with the increased risk include increased risk of infections, and increased bone marrow turnover, which form the pathophysiologic mechanisms of the clinical manifestations of SCD [5, 72]. The accumulation of multiple genetic abnormalities over years, due to a high degree of proliferative activity of bone marrow cells, may be responsible of the increased risk of cancer.

After myeloablation, the bone marrow niche undergoes extensive proliferation of hematopoietic stem cells, generating proliferative stress that may lead to mutations as part of the normal engraftment process [73]. After HSCT, myeloid malignancy was only seen within patients who did not engraft [28, 32]. In case of graft failure, the need for more replication cycles is required to repopulate the bone marrow, increasing the probability of acquiring a mutation that could lead to AML. *TP53* mutations were detectable in blood before transplantation and increase until therapy-related myeloid malignancy diagnosis [32]. The progression of baseline high-risk *TP53* clonal abnormalities into AML in patients with SCD has been reported after unsuccessful allogeneic HSCT. It has been previously demonstrated that the *TP53* mutated clones specially expanded after chemotherapy exposure [74]. Because of erythropoietic stress and systemic inflammation, SCD patients may have been predisposed to developing clonal hematopoiesis. As these clones may be more resistant to radiation and/or chemotherapy, it has been suggested that they may preferentially expand after a failed transplant, leading to the myeloid malignancy detected after graft rejection.

TP53 is the most commonly mutated gene in therapy-related MDS/AML. Low folic acid, associated with an increased risk for leukemia, can make cells vulnerable to mutagenesis and can affect the genetic and epigenetic integrity of *TP53* [75]. *TP53* plays a central role in regulating cellular responses to genotoxic stress, and loss of *TP53* provides a selective advantage for neoplastic growth [76]. The specific *TP53* mutation has been shown to be present at low frequencies (0.003–0.7%) in blood leucocytes in some cases 3–6 years prior to the development of therapy-related MDS/AML and prior any chemotherapy [74]. *TP53* mutations have also identified in small populations of peripheral blood cells of healthy chemotherapy-naïve elderly individuals. Chromosomal aberrations were demonstrated in some SCD patients with no evidence of hematological disease [27]. Furthermore, murine bone marrow chimeras containing wild type and $TP53^{+/-}$ hematopoietic stem/progenitor cells preferentially expanded after exposure to chemotherapy [74]. These data suggest that *TP53* mutations precede the development of AML and the acquisition of other mutations, such as *TET2*, *NUP98*, or *RUNX1*.

Despite limitations coming from the retrospective nature of our study involving missing data and biases related to cases reported over an extended period, our review of the literature tend to suggest that chronic hemolysis, increased iron levels, and increased bone marrow turnover, which form the pathophysiologic mechanisms of the clinical manifestations of SCD are mainly responsible for a situation in which cells are undergoing constant hematopoietic hyperplasia, leading to the increased risk of acute leukemia by inducing genomic damage and somatic mutations [77]. The effects of SCD on progenitor cells have not been fully determined [78]. SCD may promote accelerated aging of hematopoietic cells and oncogenic somatic mutations [79]. Further studies are needed to identify risk factors for developing acute leukemia by pre-screening individuals with SCD. Next-generation DNA sequencing can be used to detect expanded peripheral blood progeny of a mutant clone and clonal hematopoisis of indeterminate potential (CHIP), which is a risk factor for subsequent hematologic malignancy [80]. Recent large studies have tried to address clonal hematopoiesis in SCD [81, 82]. Despite different conclusions related to the technique used, the control cohort chosen, and the value of VAF defined for considering clonal hematopoiesis, a small percentage of cases were identified as having somatic variants of *TP53*, *DNMT3A*, *ASXL1*, and/or *TET2*.

In conclusion, several cases of MDS/AML have been reported in SCD leading to the hypothesis that SCD may lead to the development of hematopoietic malignancies, even in the absence of disease-modifying treatments. The increased risk of leukemogenesis is certainly multifactorial and related to the pathophysiologic mechanisms of the clinical manifestations of SCD, which may promote accelerated aging of hematopoiesis. A prevalence of clonal hematopoiesis in SCD patients should demonstrate a higher risk than in the general population.

Author contributions GC treated the patient, interpreted the data, and wrote the manuscript; SP, MH, HL, and MVL treated the patient; XT collected and interpreted the data, and wrote the manuscript; and AH reviewed the manuscript. All authors gave final approval of the version to be submitted.

Funding None.

Data availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethical approval All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from the individual included in the study.

Conflicts of interests The authors do not have any competing financial interest in relation with the work described.

References

1. Piel FB, Steinberg MH, Rees DC (2017) Sickle cell disease. N Engl J Med 376:1561–1573
2. Herrick JD (1910) Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. Arch Intern Med 6:517–521
3. Goldin AG, Kelty KC, Beard MF (1953) Sickle cell anemia terminating in acute myeloblastic leukemia. Ann Intern Med 39:920–928
4. Arber DA, Orazi A, Hasserjian R et al (2016) The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 127:2391–2405
5. Brunson A, Keegan THM, Bang H et al (2017) Increased risk of leukemia among sickle cell disease patients in California. Blood 130:1597–1599
6. Seminog OO, Ogunlaja OI, Yeates D et al (2016) Risk of individual malignant neoplasms in patients with sickle cell disease: English National Record Linkage Study. J R Soc Med 109:303–309
7. Jackson RE, Short BJ (1972) Frequency and prognosis of coexisting sickle cell disease and acute leukemia in children. Clin Pediatr 183:183–185
8. Samal GC (1979) Sickle cell anemia with acute myeloid leukemia – (a case report). Indian Pediatr 16:453–454
9. Conference C (1982) Left elbow pain and death in a young woman with sickle-cell anemia. Am J Med 73:268–282
10. Johnson FL, Look AT, Gockerman J et al (1984) Bone marrow transplantation in a patient with sickle-cell anemia. N Engl J Med 311:780–783
11. Bigner SH, Friedman HS, Kinney TR et al (1986) 9p− in a girl with acute lymphocytic leukemia and sickle cell disease. Cancer Genet Cytogenet 21:267–269
12. Stricker RB, Linker CA, Crowley TJ, Embury SH (1986) Hematology malignancy in sickle cell disease: report of four cases and review of the literature. Am J Hematol 21:223–230

13. Njoku OS, Johnson SB, Kulkarni AG, Mba EC (1988) Acute lymphoblastic leukaemia in a Nigerian adult with sickle cell anaemia. Centr Afr J Med 34:158–160
14. Sotomayer EA, Glasser L (1999) Acute lymphoblastic leukemia in sickle cell disease. Arch Pathol Lab Med 123:744–745
15. De Montalembert M, Bégué P, Bernaudin F et al (1999) Preliminary report of a toxicity study of hydroxyurea in sickle cell disease: French Study Group on Sickle Cell Disease. Arch Dis Child 81:437–439
16. Rauch A, Borromeo M, Ghafoor A et al (1999) Leukemogenesis of hydroxyurea in the treatment of sickle cell anemia. Blood 94(suppl.1):415a
17. Wilson S (2000) Acute leukemia in a patient with sickle cell anemia treated with hydroxyurea. Ann Intern Med 133:925–926
18. Al-Jam'a AH, Al-Dabbous IA, Al-Khatti AA, Esan FG (2002) Are we underestimating the leukemogenic risk of hydroxyurea. Saudi Med J 23:1411–1413
19. Schultz WH, Ware RE (2003) Malignancy in patients with sickle cell disease. Am J Hematol 74:249–253
20. Ferster A, Sariban E, Meuleman N (2003) Malignancies in sickle cell disease patients treated with hydroxyurea. Br J Haematol 123:368–369
21. Taylor JG, Darari DS, Maric I et al (2011) Therapy-related acute myelogenous leukemia in a hydroxyurea-treated patient with sickle cell anemia. Ann Intern Med 155:722–724
22. Baz W, Najfeld V, Yotsuya M et al (2012) Development of myelodysplastic syndrome and acute myeloid leukemia 15 years after hydroxyurea use in a patient with sickle cell anemia. Clin Med Insights Oncol 6:149–152
23. Zemenides S, Erblich T, Luqmani A, Bain BJ (2014) Peripheral blood features of acute myeloid leukemia with myelodysplasia-related changes developing in a patient with sickle cell anemia. Am J Hematol 89:1010
24. Aumont C, Driss F, Lazure T et al (2015) Myelodysplastic syndrome with clonal cytogenetic abnormalities followed by fatal erythroid leukemia after 14 years of exposure to hydroxyurea for sickle cell anemia. Am J Hematol 90:E131–E132
25. Chauhan S, Swain SK, Sahu MC (2018) Incidence of hematological malignancies in sickle cell patients from an Indian tertiary care teaching hospital. Asian J Pharm Clin Res 11:205–209
26. Janakiram M, Verma A, Wang Y et al (2018) Accerated leukemic transformation after haplo-identical transplantation for hydroxyurea-treated sickle cell disease. Leuk Lymphoma 59:241–244
27. Li Y, Maule J, Neff JL et al (2019) Myeloid neoplasms in the setting of sickle cell disease: an intrinsic association with the underlying condition rather than a coincidence; report of 4 cases and review of the literature. Modern Pathol 32:1712–1726
28. Eapen M, Brazauskas R, Walters MC et al (2019) Impact of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in patients with sickle cell disease: a retrospective, cohort study. Lancet Haematol 6:e585–e596
29. Regan S, Yang X, Finnberg NK et al (2019) Occurrence of acute myeloid leukemia in hydroxyurea-treated sickle cell disease patient. Cancer Biol Ther 20:1389–1397
30. Aworanti OW, Fasola FA, Kotila TR et al (2020) Acute leukemia in sickle cell disease patients in a tertiary health facility in Nigeria: a case series. Afri Health Sci 20:1304–1312
31. Yadav DK, Paul T, Alhamar M et al (2020) Pure erythroid leukemia in a sickle cell patient treated with hydroxyurea. Case Rep Oncol 13:857–862
32. Ghannam JY, Xu X, Maric I et al (2020) Baseline *TP53* mutations in adults with SCD developing myeloid malignancy following hematopoietic cell transplantation. Blood 135:1185–1188
33. Chellapandian D, Nicholson CL (2020) Haploidentical bone marrow transplantation in a patient with sickle cell disease and acute myeloid leukemia. Pediatr Transplant 24:e13641
34. Hsieh MM, Bonner M, Pierciey FJ et al (2020) Myelodysplastic syndrome unrelated to lentiviral vector in a patient treated with gene therapy for sickle cell disease. Blood Adv 4:2058–2063
35. Ahmed IO, Ochogwu LO, Owojuyigbe TO et al (2021) Philadelphia chromosome-positive B-cell acute lymphoblastic leukemia with e1a3 *BCR-ABL1* transcript in a Nigerian with sickle cell anemia: a case report. J Med Case Reports 15:504
36. Goyal S, Tisdale J, Schmidt M et al (2022) Acute myeloid leukemia after gene therapy for sickle cell disease. N Engl J Med 386:138–147
37. Flevari P, Voskaridou E, Galacteros F et al (2022) Case report of myelodysplastic syndrome in a sickle-cell disease patient treated with hydroxyurea and literature review. Biomedicines 10:3201
38. Paydas S (2002) Sickle cell anemia and hematological neoplasias. Leuk Lymphoma 43:1431–1434
39. Dawkins FW, Kim KS, Squires RS et al (1997) Cancer incidence rate and mortality rate in sickle cell disease patients at Howard University Hospital: 1986–1995. Am J Hematol 55:188–192
40. Green NS, Barral S (2014) Emerging science of hydroxyurea therapy for pediatric sickle cell disease. Pediatr Res 75:196–204
41. Steinberg MH, Barton F, Castro O et al (2003) Effect of hydroxyurea on mortalityand morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMA 289:1645–1651
42. Charache S, Terrin ML, Moore RD et al (1995) Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med 332:1317–1322
43. Ferster A, Vermylen C, Cornu G et al (1996) Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. Blood 88:1960–1964
44. Wang WC, Ware RE, Miller ST et al (2011) Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). Lancet 377:1663–1672
45. Da Silva Rocha LB, Dias Elias DB, Barbosa MC et al (2012) DNA damage in leukocytes of sickle cell anemia patients is associated with hydroxyurea therapy and with HBB*S haplotype. Mutat Res 749:48–52
46. Maia Filho PA, Pereira JF, Almeida Filho TPD et al (2019) Is chronic use of hydroxyurea safe for patients with sickle cell anemia? An account of genotoxicity and mutagenicity. Environ Mol Mutagen 60:302–304
47. Kiladjian JJ, Chevret S, Dosquet C et al (2011) Treatment of polycythemia vera with hydroxyurea and pipobroman: final results of a randomized trial initiated in 1980. J Clin Oncol 29:3907–3913
48. Lanzkron S, Strouse JJ, Wilson R et al (2008) Systematic review: hydroxyurea for the treatment of adults with sickle cell diseases. Ann Intern Med 148:939–955
49. Steinberg MH, McCarthy WF, Castro O et al (2010) The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: a 17.5 year follow-up. Am J Hematol 85:403–408
50. Voskaridou E, Christoulas D, Bilalis A et al (2010) The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). Blood 115:2354–2363
51. Castro O, Nouraie M, Oneal P (2014) Hydroxycarbamide treatment in sickle cell disease: estimates of possible leukaemia risk and of hospitalization survival benefit. Br J Haematol 167:687–691
52. Kinney TR, Helms RW, O'Branski EE et al (1999) Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. Blood 94:1550–1554
53. Ferster A, Tahriri P, Vermylen C et al (2001) Five years of experience with hydroxyurea in children and young adults with sickle cell disease. Blood 97:3628–3632

54. Flanagan JM, Howard TA, Mortier N et al (2010) Assessment of genotoxicity associated with hydroxyurea therapy in children with sickle cell anemia. Mutat Res 698:38–42
55. Rodriguez A, Duez P, Dedeken L et al (2018) Hydroxyurea (hydroxycarbamine) genotoxicity in pediatric patients with sickle cell disease. Pediatr Blood Cancer 65:e27022
56. Ware RE, Dertinger SD (2021) Absence of hydroxyurea-induced mutational effects supports higher utilization for the treatment of sickle cell anaemia. Br J Haematol 194:252–266
57. Hanft V, Fruchtman S, Pickens C et al (2000) Acquired DNA mutations associated with in vivo hydroxyurea exposure. Blood 95:3589–3593
58. De Montelembert M, Voskaridou E, Oevermann L et al (2021) Real-life experience with hydroxyurea in patients with sickle cell disease: Results from the prospective ESCORT-HU cohort study. Am J Hematol 96:1223–1231
59. Vermylen C (2003) Hematopoietic stem cell transplantation in sickle cell disease. Blood Rev 17:163–166
60. Gluckman E, Cappelli B, Bernaudin F et al (2017) Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. Blood 129:1548–1556
61. Locatelli F, Rocha V, Reed W et al (2003) Related umbilical cord blood transplant in patients with thalassemia and sickle cell disease. Blood 101:2137–2143
62. Kamani NR, Walters MC, Carter S et al (2012) Unrelated donor cord blood transplantation for children with severe sickle cell disease: results of one cohort from the phase II study from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). Biol Blood Marrow Transplant 18:1265–1272
63. Abraham A, Cluster A, Jacobsohn D et al (2017) Unrelated umbilical cord blood transplantation for sickle cell disease following reduced-intensity conditioning: results of a phase I trial. Biol Blood Marrow Transplant 23:1587–1592
64. Aydin M, Dovern E, Leeflang MMG et al (2021) Haploidentical allogeneic stem cell transplantation in sickle cell disease: a systematic review and meta-analysis. Transplant Cell Ther 27:1004.e1-1004.e8
65. Jones RJ, DeBaun MR (2021) Leukemia after gene therapy for sickle cell disease: insertional mutagenesis, busulfan, both, or neither. Blood 138:942–947
66. Kanter J, Walters MC, Krishnamurti L et al (2022) Biologic and clinical efficacy of LentiGlobin for sickle cell disease. N Engl J Med 386:617–628
67. Christiansen DH, Andersen MK, Pedersen-Bjergaard J (2001) Mutations with loss of heterozygosity of p53 are common in therapy-related myelodysplasia and acute myeloid leukemia after exposure to alkylating agents and significantly associated with deletion or loss of 5q, a complex karyotype, and a poor prognosis. J Clin Oncol 19:1405–1413
68. Ribeil JA (2022) Primary myelofibrosis in untreated sickle cell disease: Are adult patients at higher risk for developing hematological myeloid neoplasms? 97:4–6
69. Forni GL, Gianesin B, Musallam KM et al (2023) Overall and complication-free survival in a large cohort of patients with β-thalassemia major followed over 50 years. Am J Hematol 98:381–387
70. Tomasik J, Basak GW (2022) Inflammasomes – New contributors to blood diseases. Int J Mol Sci 23:8129
71. Alves PM, Martins PRJ, Dias FDL et al (2008) Sensitivity to cisplatin-induced mutations and elevated chromosomal aberrations in lymphocytes from sickle cell disease patients. Clin Exp Med 8:31–35
72. Crusz SM, Balkwill FR (2015) Inflammation and cancer: advances and new agents. Nat Rev Clin Oncol 12:584–596
73. Nawas MT, Schetelig J, Damm F et al (2021) The clinical implications of clonal hematopoiesis in hematopoietic cell transplantation. Blood Rev 46:100744
74. Wong TN, Ramsingh G, Young AL et al (2015) Role of *TP53* mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature 518:552–555
75. Kim YI, Pogribny IP, Basnakian AG et al (1997) Folate deficiency in rats induces DNA strand breaks and hypomethylation within the p53 tumor suppressor gene. Am J Clin Nutr 65:46–52
76. Hollstein M, Sidransky D, Vogelstein B, Harris CC (1991) P53 mutations in human cancers. Science 253:49–53
77. Gondek LP, Sheedan VA, Fitzhugh CD (2022) Clonal hematopoiesis and the risk of hematologic malignancies after curative therapies for sickle cell disease. J Clin Med 11:3160
78. Tolu SS, Wang K, Yan Z et al (2020) Characterization of hematopoiesis in sickle cell disease by prospective isolation of stem and progenitor cells. Cells 9:E2159
79. Platt OS (2000) Sickle cell anemia as an inflammatory disease. J Clin Invest 106:337–338
80. Snetsinger B, Ferrone CK, Rauh MJ (2019) Targeted, amplicon-based, next-generation sequencing to detect age-related clonal hematopoiesis. Methods Mol Biol 2045:167–180
81. Pincez T, Lee SSK, Ilboudo Y et al (2021) Clonal hematopoiesis in sickle cell disease. Blood 138:2148–2152
82. Liggett LA, Cato LD, Weinstock JS et al (2022) Clonal hematopoiesis in sickle cell disease. J Clin Invest 132:e156060