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Hematological Malignancies in Sickle Cell Disease Patients: Report of Four Cases in Togo and Literature Review

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Abstract

Background: Hemopathies were rarely observed in major sickle cell disease patients some thirty years ago, probably due to the high mortality rate among the latter as a result of progressive complications. Thanks to advances in the management of sickle cell disease, patients' life expectancy has increased considerably, exposing them more frequently to neoplasia, including hematological malignancies. The increased risk of leukemogenesis is multifactorial and linked to the pathophysiological mechanisms of the clinical manifestations of sickle cell disease. **Study Setting:** The clinical haematology department of campus teaching hospital and the paediatric onco-haematology unit of Sylvanus Olympio teaching hospital in Lomé were used as study settings. **Observations:** Four hematologic malignancies were collected in a cohort of 5847 major sickle cell syndromes. The median age of the patients was 31.25 years (extremes: 14 and 58 years) and they were predominantly female (sex ratio M/F = 0.25). Two were on background therapy with hydroxyurea. Among the four patients, there were two cases of acute lymphocytic leukemia, including ALL3 in a 58-year-old SS woman and T-ALL2 in a 12-year-old SC. Then, a case of lymphocytic lymphoma in a 20-year-old SS man was reported and finally a case of chronic myelocytic leukemia in a 33-year-old woman of Sβ+ thalassaemia phenotype. **Conclusion:** To further report this coexistence, it is therefore essential to systematically consider hematological malignancies during major sickle cell syndromes even if there are similarities in the symptomatology of these two serious pathological situations.

Keywords

Hematological Malignancies, Sickle Cell Disease, Lomé-Togo

1. Introduction

Sickle cell anemia is an inherited disorder of the hemoglobin structure characterized by the replacement of glutamic acid by valine in position 6 of the globin beta chain [1]. This mutation characterizes hemoglobin S (HbS) whose essential characteristic is gelation, responsible for sickle cell disease [1]. Sickle cell homozygous SS and composite forms (SC, S-Beta thalassemia, SD, SO Arab...) constitute major sickle cell syndromes (MSS). It is the most frequent hemoglobin anomaly in sub-Saharan Africa, and the leading cause of hemolytic anemia in black Africa, where it poses a public health problem as its course is fraught with complications. Its treatment is increasingly well codified, and among the therapeutic advances, the administration of hydroxyurea (HU) represents a notable development in improving the survival of major sickle cell patients [2].

Hematological malignancies were rarely observed in major sickle cell patients some thirty years ago, probably due to the high mortality rate among the latter as a result of progressive complications [3]. Thanks to advances in the management of sickle cell disease, patients' life expectancy has increased considerably, exposing them more frequently to neoplasia, including hematological malignancies [4]. Thus, since James D Herrick's description of sickle cell disease (SCD) in Chicago at 1910 [5], a wide variety of malignancies, including hematological malignancies, have been reported in the course of SCD. Indeed, the increased risk of leukemogenesis is thought to be multifactorial and linked to the pathophysiological mechanisms of the clinical manifestations of sickle cell disease. Chronic hemolysis and secondary hemochromatosis may cause increased chronic inflammation, leading to persistent bone marrow stress, which could be at the origin of genetic instability of hematopoietic stem cells, generating genomic damage and somatic mutations during the course of sickle cell disease [6]. The first description of the coexistence of SCD with acute myeloid leukemia (AML) was reported by Goldin and al. in 1953 in a 38-year-old black man [7]. Subsequently, several Western [4] [6] and African [8] [9] studies have reported hematological malignancies during SCD, and a synthesis of some 30 studies reporting 52 cases together was made by Giovanna Cannas and al in 2023 [6].

In Togo, to our knowledge, no hematologic malignancies have yet been reported during SCD. The aim of this study is firstly to describe four cases of hematological malignancies during SCD in Togo and then make a review of literature.

2. Results/Observations

Four cases of hematologic malignancies were identified in a cohort of 5847 SCD. The median age of the patients was 31.25 years (extremes: 14 and 58 years) and

they were predominantly female (sex ratio M/F = 0.25). Two were on HU-based background therapy. Among the four patients, there were two cases of acute lymphocytic leukemia (one is a 58-year-old SS woman and another one is a 14-year-old SC teenager), one case of lymphocytic lymphoma (in a 20-year-old SS man) and one case of chronic myeloid leukemia (in a 33-year-old Sβ+ thalassmia woman).

2.1. Observation N˚1

Mr K.K., aged 20, student, single without children, referred on March 10, 2023 from the Centre National de Recherche et de Soins aux Drépanocytaires (CNRSD) for management of a lymphocytic lymphoma. The onset would date back some seven months earlier with the appearance of a right inguinal adenopathy, painless and progressively increasing in size. He consulted various doctors' surgeries, where treatments of an unknown nature were instituted without success. Four months later, his general condition deteriorated and he developed splenomegaly. There was no evidence of night sweats or long-term fever. A lymph node biopsy with histological and immunohistochemical examination revealed CD20 and CD55 lymphoma cells; absence of cyclinD1, Bcl2 and CD30 compatible with lymphocytic lymphoma. He has sickle cell anemia (SS), discovered at the age of 06. He has been transfused several times with packed red blood cells. His baseline hemoglobin is 6.5 g/dl. His vaccination was not up to date. He was on background treatment with folic acid and hydroxyurea (HU).

Initial examination revealed an axillary temperature of 37.2 degrees Celsius (˚C), a weight of 39 kilograms (kgs), a height of 147 cm, an estimated body surface area of 1.26 m^2, and an altered general condition with a World Health Organization (WHO) status performance index of 2. Physical examination revealed an anemic syndrome and a tumor syndrome consisting of Hackett's type V splenomegaly and a right inguinal adenopathy measuring 4 cm along its long axis. Thoracic-abdominal-pelvic computed tomography (TAP-CT) revealed splenomegaly associated with multiple adenopathies of variable size, in hilar splenic, lombo-aortic, mesenteric, aorto-caval, ilio-pelvic and bilateral inguinal locations, and osteolytic lesions of the pelvis. Osteomedullary biopsy showed an absence of lymphoid and myeloid hyperplasia. The patient was classified as Ann Arbor stage IIIs. Fibrinemia was 8.8 g/l; protidogram showed hypoalbuminemia at 22.3 g/l. HIV and hepatitis B and C serologies were negative; liver and kidney functions and blood ionograms were normal. Immunochemotherapy based on the protocol: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP), 6 cycles of 21 days, was recommended. The first course of treatment was started on May 4, 2023, the 6th on august 17, 2023 with good clinical and biological tolerance. After 6 treatments, there is complete remission. Monitoring is ongoing.

2.2. Observation N˚2

Mrs. A.A., aged 58, shopkeeper, single without children, referred from the CNRSD

for acute lymphocytic leukemia (ALL) type 3 diagnosed in October 2022 during her follow-up for homozygous sickle cell disease SS. The onset would date back to October 2022, marked by asthenia, dizziness and shortness of breath lasting more than a week with no other associated signs. This prompted a blood count showing peripheral pancytopenia (anemia 6.9 g/dl, neutropenia 1000/mm^3, thrombocytopenia 70,000/mm^3) with lymphoblasts at 29%. A myelogram revealed 65% of lymphoblasts, most of which contained vacuoles in their cytoplasm compatible with Franco-American-British (FAB) type 3 acute lymphocytic leukemia (ALL 3). Immunophenotyping and molecular biology could not be performed due to technical and financial difficulties. Her SS sickle cell disease was discovered at the age of 07. She is irregularly monitored. Her vaccination was not up to date. She had several episodes of vas occlusive crises (CVO) and was transfused at least 3 times a year. Her baseline hemoglobin was 6.2 g/dl. She presented other complications, notably infectious, such as bilateral coxarthrosis with common germs, followed by secondary ischemic osteonecrosis of the bilateral femoral heads. She was undergoing background treatment with hydroxyurea and folic acid, taken irregularly (due to financial difficulties). Examination on 19th October 2022 revealed an axillary temperature of 37.5˚C, an altered general condition with a WHO performance status index of 3, and a decompensating anemia syndrome. Pre-therapeutic assessment was in progress for a treatment proposal when the patient died in January 2023. Death occurred in a context of worsening bone marrow failure syndrome with severe sepsis and anemic decompensation for which there was no transfusion yield.

2.3. Observation N˚3

Mrs O.A. aged 33, seamstress, single without children, referred from Anié hospital (locality located 176 km from Lomé) on 18th june 2019 for hyperleukocytosis at 258,540/mm^3. The onset would date back to approximately 07 months earlier with a sensation of heaviness in the left hypochondrium and secondary appearance of splenomegaly, which prompted a consultation during which the hyperleukocytosis was highlighted. Her sickle cell disease Sβ+ thalassaemia had been known since she was 8 years old but had not been followed up. She developed no progressive complications. Her vaccination was not up to date. Baseline hemoglobin is 10.5 g/dl. She is not taking any background treatment. Initial examination revealed an axillary temperature of 37.1˚C, good general condition with a WHO performance status index of 0, Hackett type III splenomegaly and hepatomegaly. The lymph nodes were free. Examination of the other systems, notably the cardiovascular and pleuropulmonary systems, was unremarkable. The haemogram showed a haemoglobin level of 10.9 g/dl, a hyperleukocytosis of 258,540/mm^3 with a neutrophilic predominance of 220,562/mm^3 and a polymorphic, significant and harmonious myelimia. The bone marrow aspiration showed granular hyperplasia (93%), and the bone marrow karyotype performed at the CERBA laboratory (France) revealed a translocation t (9; 22)

(Philadelphia chromosome) compatible with chronic myeloid leukemia (CML) chronic myelocytic stage. Human Immunodeficiency Virus (HIV) and hepatitis B and C serologies were negative, and renal and hepatic function were normal. The patient was started on a tyrosine kinase inhibitor (TKI), initially imatinib (400 mg/d), which was poorly tolerated, followed by dasatinib (100 mg/d). At the May 15, 2023 follow-up, a good hematological response was noted. Molecular testing has not yet been performed (technical platform and financial difficulties).

2.4. Observation N˚4

Adolescent B.P. aged 12, born 26th March 2006, student, referred on 4th April 2018 from Campus teaching hospital to the pediatric hemato-oncology unit Sylvanus Olympio teaching hospital for acute lymphocytic leukemia (ALL) on sickle cell SC background. The onset would date back to about a month earlier with headache, fever and abdominal pain. This prompted a consultation at a local clinic, where she was transfused with packed red blood cells, and a hemoglobin electrophoresis revealed composite double heterozygous SC sickle cell disease. A blood count showed anemia at 5.8 g/dl, thrombocytopenia at 80,000/mm^3 and marked hyperleukocytosis at 186,000/mm^3, with lymphoblasts present on the smear. The myelogram showed a medullary proliferation of 63.5% large and small lymphoblasts compatible with FAB type 2 acute lymphocytic leukemia. Immunophenotyping of the blast population at CERBA revealed an intermediate CD45 population expressing the CD3 marker intracytoplasmically, as well as the CD5, CD7 markers. B lymphoid markers (CD19, CD22) were negative, as were myeloid markers apart from CD33, all consistent with T-type ALL 2.

Her sickle-cell SC was discovered concomitantly with the signs of her leukemia. The patient was up to date with her vaccinations. Examination on admission to Sylvanus Olympio teaching hospital revealed an infectious syndrome (axillary temperature 40.2˚C, superficial polypnoea 31 cycles per minute, tachycardia 180 beats per minute); a weight of 35 kgs and height of 147 cm with a body surface area of 1.2 m^2; altered general condition with a WHO status performance index of 4, anemia syndrome, tumor syndrome (Hackett type II splenomegaly, subclavicular and axillary adenopathy and hepatomegaly). Examination of other systems, notably odontostomatological and neurological, was unremarkable. Hepatitis B and C serologies were negative. Transaminases and renal function were normal. In view of the poor prognostic factors (type T ALL, tumor syndrome and hyperleukocytosis), the French-African Pediatric Oncology Group (GFAOP) ALL protocol was chosen, with the Lomé proposal for the high-risk arm. Progression was marked by cortico-resistance, followed by complete remission in June 2018. Consolidation treatment was then started. The occurrence of an infectious syndrome led to treatment discontinuation during this phase on two occasions. Death occurred in 2019 during the consolidation phase in severe sepsis. **Table 1** shows the summary of the 4 patients's observations.

Table 1. Summary of the four patients' observations

N°	Sex	Sickle cell disease	Background treatment	Basal haemoglobin	Malignant hemopathy	Age (years odl)	Treatment	Mortality
1	M	SS	HU	6.5	NHL	20	chemotherapy	On going
2	F	SS	HU	6.2	ALL 3	58	No one	Death (volution)
3	F	Sβ+	No one	10.5	CML	33	Tyrosine kinase inhibitor	Hematological remission
4	F	SC	No one	-	ALL T	12	chemotherapy	Death (consolidation)

3. Discussion

The occurrence of neoplasia in SCD has long been reported by several authors in small series [10] [11] [12]. The annual incidence of cancer in SCD has been estimated at 1.74 new cases per 1000 patients, according to the results of a study carried out in an institution in the USA [13]. These neoplasia consist mainly of hematological malignancies, in particular acute leukemia. In the 1970s, Jackson reported that out of 58 children treated for ALL, there were 4 cases of ALL and 3 cases of AML in patients with sickle cell trait S (AS), and one case of ALL in an SS homozygote [10]. In black Africa, a study in Nigeria reported the association of acute leukemia with myelodysplastic syndrome (MDS) in 8.6% of cases [9]. Three recent epidemiological studies have demonstrated the prevalence of neoplasia in SCD [14] [15] [16]. The first study used a standardized incidence ratio to compare people with SCD with the general population. One hundred and fourteen out of 6423 people with SCD developed cancer, including 6 cases of AML and 3 cases of ALL [14]. In the second study, 8 cases of AML out of 7512 people with SCD were reported. Among hematological malignancies, risks were high for all pathologies studied, with the exception of chronic lymphocytic leukemia (CLL) [15]. The third study identified 52 cases of cancer in 49 patients among 16,613 major sickle cell patients [16]. The most frequent hematological malignancies were acute leukemias (8 cases). The prevalence of hematological malignancies in our series of major SCD (4 cases among 5847 major sickle cell syndromes) seems similar to the majority of data in the literature [14] [15] [16]. Acute leukemia and in particular ALL, was also the most frequently reported hematological malignancy in our series (half of the cases), particularly in patients 2 and 4. None of our patients had developed CLL. Sickle cell disease therefore appears to be a major leukemogenic factor. Olena O Seminog and al in England, in a study of administrative data, showed that within the black race, major sickle cell patients had a higher risk of developing cancer than a control cohort for cancers in general and particularly for hematological malignancies, but also for certain solid tumors [15]. In fact, the risk of hematological malignancy in sickle cell disease is 2 to 11 times as high as in the general population [6]. In fact, the increased risk of leukemogenesis in major sickle cell disease is thought to be multifactorial. Chronic hemolysis and secondary hemochromatosis could cause increased chronic inflammation, leading to persistent bone mar-

row stress, which could be at the origin of genetic instability of hematopoietic stem cells, generating genomic damage and somatic mutations during the course of sickle cell disease [6].

Long-term hydroxyurea has been suggested by some authors as an etiological factor in the occurrence of hematological malignancies in SCD. Recently, hydroxyurea has become an essential pillar in the management of sickle cell disease. Based on the specific pathophysiology of sickle cell disease, hydroxyurea is the first treatment to have had an impact on the natural course of the disease, reducing the frequency of CVO and extending patients' life expectancy [2]. Initially chosen for its ability to reactivate fetal hemoglobin synthesis, this molecule has proved capable of acting via multiple other mechanisms too. These include reducing excessive adhesiveness of stress reticulocytes, increasing nitric oxide, modulating inflammatory processes, and reducing leukocytes involved in inflammatory phenomena [2]. The question of whether acute leukemia in major sickle cell disease patients on HU-based background therapy is coincidental or therapy-related has been debated in numerous studies. The leukemogenic risk could theoretically increase with the duration of drug exposure. The DNA damage index in peripheral blood leukocytes of HU-treated sickle cell patients was found to be higher than in controls, and this phenomenon was confirmed to be influenced by the duration and dose of HU treatment, as well as by HbS genotype [17] [18]. The leukemic risk of HU has never been confirmed in major sickle cell patients with chronic myeloproliferative diseases [19] [20], and no increased risk of malignancy has been reported in large studies of myeloproliferative syndromes in major sickle cell patients [21] [22] [23]. This is confirmed in our series, as the only patient (patient 3) with a myeloproliferative syndrome (CML) was never been taking HU as background therapy, and even had minor hemolysis as evidenced by her high baseline hemoglobin level.

Of the 278 children with sickle cell disease receiving long-term HU, only one developed acute leukemia [24]. While a study of children with SCD treated with HU showed that genotoxicity increased with HU administration [25], it was demonstrated that individuals may have different susceptibilities to HU, and that this event occurred in a patient population that may already have a high risk of malignancy initially assessed by a higher index [26]. Overall, the effects of genotoxicity clearly demonstrate that HU is not directly linked to DNA and is not mutagenic [27]. This finding was recently confirmed in France by Flevari P *et al* [28], who reported, in a large cohort, a case of myelodysplastic syndrome in a 40-year-old patient after 17 years of HU treatment. This was the largest European cohort of 1903 adults and children treated with HU who were followed prospectively over 10 years, representing a total exposure of 7309.5 patient-years. Comparing this single case with similar previously published cases, they drew no significant conclusions due to the rarity of this event. In vitro, HU can lead to accumulation of somatic mutations and chromosomal damage due to interference with DNA repair, but the number of mutations was not increased in patients on long-term HU [29]. On the other hand, HU treatment may mitigate the risk of

chronic hemolysis by increasing fetal hemoglobin in the blood and potentially reduce accompanying stress marrow hemoglobin in these patients. Our results are similar to those reported in the literature, as only two of our four patients had been treated by HU. This is particularly true of these two patients, who were not regularly on HU due to their financial difficulties in paying for this background treatment on an ongoing basis.

Hematological malignancies can occur at any age during the course of major sickle cell disease syndromes. The median age of 31.25 years and the predominance of females in our series are similar to those reported by Guiraud Chaumeil J *et al.* [4] in France, with a mean age of 34 years and a sex ratio (M/F) of 0.6. Female predominance was also found by Kamara *et al* in Côte d'Ivoire [8], but the median age was over 65 for the two cases of multiple myeloma reported. Indeed, multiple myeloma preferentially affects subjects aged over 40, with a peak in frequency between 63 and 70. Hemopathies can develop during all major forms of sickle cell disease. Acute leukemia has been described in all these major forms in France [6]. The homozygous SS form was the most common in our series. Our results are contrary to those of Guiraud Chaumeil J *et al* [4] with a predominance of the composite heterozygous double form SC. The Sβ+ thalassemia major form found in our series (patient 3) was also the form of sickle cell disease found during multiple myeloma in Côte d'Ivoire [8].

From a therapeutic standpoint, the authors report that the co-existence of sickle cell disease and oncological pathology appears to be a limiting factor in the optimal management of cancer: oncological therapies that cause vaso-occlusive crises and thoracic syndromes (corticosteroids); modification of the therapeutic plan in the face of sickle cell disease organ damage and/or a state of post-transfusion immunization [4]. In our series, three (03) patients out of 04 had started chemotherapy, two of them in the induction phase and one in the consolidation phase. Indeed, in the course of acute leukemia and lymphoma, chemotherapy is the most accessible treatment in Togo, given the inadequate technical platform and the low socio-economic status of patients. These three patients were all at an advanced stage of the disease and all had unfavorable prognostic factors. The progression was unfavorable for the two ALL patients who died, one of whom was in the consolidation phase. Guiraud and al in 2021 found a death rate of almost 60% [4]. This 50% death rate could be explained by a higher risk of death in subjects with sickle cell anemia from hematological malignancies than from other cancers. Indeed, according to a study carried out by Brusson and al in 2019 in England, the risk of death was five times higher during hematological malignancies than during other cancers in patients with sickle cell disease [30]. Patient 3 benefited from tyrosine kinase inhibitor (TKI) treatment thanks to Max Foundation, which has been providing free TKIs to CML patients in Togo since 2003.

4. Conclusion

This study reported the first observations of haematological malignancies in

SCD in Togo and reviewed the literature. It revealed a predominance of women, and a large majority of young adults. Both homozygous and heterozygous forms of sickle cell disease were found. HU intake was not recognized as an etiological factor. Acute leukemias were the most common. Chemotherapy was the first-line treatment for ALL and lymphomas. Complete remission was achieved in only one patient on TKI for CML. In order to report this coexistence, it is therefore essential to systematically consider hematological malignancies during sickle cell disease, even if there are similarities in the symptomatology of these two serious pathological situations.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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