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Case report

Sequential development of human herpes virus 8-positive diffuse large B-cell lymphoma and chronic myelomonocytic leukemia in a 59 year old female patient with hemoglobin SC disease

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ABSTRACT

Hematolymphoid neoplasms, including lymphoma and myeloid neoplasms, can occur in patients with sickle cell disease (SCD) or equivalent hemoglobinopathy, but an underlying connection between the two conditions has yet to be fully determined. Herein, we report a unique case of sequential development of two separate hematolymphoid neoplasms, human herpes virus 8 (HHV8)-positive diffuse large B-cell lymphoma (DLBCL) and chronic myelomonocytic leukemia, in a 59 year-old African American female with hemoglobin SC disease. While etiology of immunodeficiency is unknown, the potential causes include hydroxyurea therapy, disease related immunomodulation, chronic inflammation, and relatively old age. The leukemia cells demonstrated profound trilineage dysplasia and harbored complex cytogenetic abnormalities with loss of chromosome 5q and 7q, which are often observed in therapy-related myeloid neoplasms. Besides the potential causes listed above, we propose that myeloid leukemia in this setting may result from genomic changes due to excessive hematopoietic replication triggered by a hemolysis-induced cytokine storm. While myeloid neoplasms in the setting of SCD seems to herald a dismal clinical outcome per the literature, the HHV8-positive DLBCL in our case was apparently indolent, opposing the current perception of its clinical outcome.

1. Introduction

Sickle cell disease (SCD) affects about 5 million people globally. The disease is autosomally recessive inherited with a point mutation occurring in the sixth codon of the hemoglobin β subunit gene that results in substitution of glutamic acid with valine [1,2]. This genetic change destabilizes hemoglobin, resulting in its polymerization and increased rigidity of the cell membrane, leading to distortion of red blood cells (sickling). This sickling markedly shortens the life span of red blood cells due to their premature extravascular hemolysis, thus leading to constant anemia in these patients. The frequency of sickling episodes and severity of clinical symptoms varies with inherited genotypes. While patients with homozygous alleles of hemoglobin S (HbSS) often manifest a severe anemia and more significant clinical symptoms, those with a heterozygous mutant allele (HbSA), so called carriers, usually present with mild anemia and minimal clinical symptoms. When a heterozygous HbS is combined with a different type of mutation on the other allele of the β subunit gene, such as hemoglobin C, it forms a compound heterozygous hemoglobinopathy (HbSC) with milder clinical symptoms than HbSS, but more severe than homozygous hemoglobin C (HbCC) [2]. Because of these clinical features, patients with SC hemoglobinopathy are often treated similarly to those with SCD. The management of SCD and equivalent hemoglobinopathy involves lifelong health care, with the vast majority of patients receiving conservative therapy, and stem cell transplant reserved for cases that fail conventional therapy [1]. In addition to supportive care, SCD patients are frequently treated with hydroxyurea (hydroxycarbamide) to prevent episodes of hemoglobin polymerization and alleviate sickling crises. These therapeutic modalities have greatly improved the survival of SCD patients and their quality of life. However, along with the extension of life expectancy, secondary conditions such as malignant neoplasms arise in SCD patients, of which hematolymphoid neoplasms,

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such as lymphoma and leukemia, have become more prevalent [3,4]. The pathogenesis of these hematolymphoid neoplasms in this particular clinical setting are largely unknown, and their clinicopathologic features have not been well documented yet. Herein, we report a case of sequential development of HHV8-positive diffuse large B-cell lymphoma, not otherwise specified (HHV8-positive DLBCL-NOS), and chronic myelomonocytic leukemia (CMML) in a 59 year old female patient who had received long term treatment with hydroxyurea for SC hemoglobinopathy.

2. Case report

2.1. Clinical presentation

The patient was an African American female, initially diagnosed with SC hemoglobinopathy at 18 years of age, when she underwent cholecystectomy due to cholelithiasis. At the time, she was found to have mild normocytic hypochromic anemia, which prompted subsequent laboratory evaluations that resulted in the diagnosis. Since the diagnosis, she had periodically complained of chronic pain which had been treated with narcotics. In addition, the patient suffered from frequent sinus infection and recurrent lower urinary tract infection that were treated with antibiotics and supportive management. At 37 years of age, she developed bilateral retinopathy related to her underlying hemoglobin SC disease and was treated with laser coagulopathy. Since then, she received hydroxyurea therapy with an initial dose of 500 mg per day, which was gradually increased to the current dose of 1500 mg per day. The patient occasionally received blood transfusion. At age of 58 years, the patient presented with a sickling episode. Physical examination demonstrated a right neck mass that extended to the submandibular area, and thus was initially considered to be sialadenitis of the submandibular glands. Computed tomography (CT) scan demonstrated an isolated 1.5 cm round nodule or enlarged node anterior to the right submandibular gland (Fig. 1). Otherwise, there was no significant lymphadenopathy, hepatomegaly or splenomegaly identified by CT scan. Laboratory evaluations demonstrated moderate anemia (hemoglobin: 10.9 g/dL) with elevated reticulocytes (4.46%, reference range = 0.7–2.0%; 45.1% immature fraction, reference range = 3.1–16.0%) and normal counts of peripheral blood leukocytes and platelets. Hemoglobin electrophoresis showed 39.8% hemoglobin S, 33% hemoglobin C, 24.9% hemoglobin F, and 2.3% hemoglobin A2; there was no detectable hemoglobin A. The right neck lesion was subsequently excised (biopsy 1), and demonstrated an enlarged lymph node with features suggestive of HHV8-positive DLBCL that appeared to be completely excised. A blood test for human immunodeficiency virus (HIV) was negative. At the time, the patient denied fever, night sweat, fatigue and significant weight loss. Positron emission tomography/computed tomography (PET/CT) showed no avid foci of the disease, blood lactate dehydrogenase was within normal range, and a staging bone marrow biopsy exhibited trilineage hematopoiesis without lymphomatous involvement or other appreciable abnormalities. Therefore, the patient was followed without additional therapeutic intervention. At nine months after the diagnosis of HHV8-positive DLBCL, while continuing to receive hydroxyurea at 1500 mg daily, the patient suffered from a pulmonary embolism that was treated with heparin and other anticoagulants. Approximately one year after the diagnosis of HHV8-positive DLBCL, the patient developed marked leukocytosis (WBC: 39.3×10^9/L) and moderate to severe anemia (hemoglobin: 7.6 g/dL); her platelet count was normal (203×10^9/L). Bone marrow examination (biopsy 2) demonstrated features consistent with the diagnosis of chronic myelomonocytic leukemia-1 (CMML-1). Despite chemotherapy with decitabine, the disease persisted with increased circulating blasts (10–15%) and appeared to disseminate to organs/tissues beyond the bone marrow. The leukemia likely infiltrated into thoracic cavities and pericardial space, resulting in severe apnea and cardiac tamponade, and cardiac arrest followed. Although the patient was resuscitated, the procedure led to multiple organ damage, including hepatic rupture. The patient's condition deteriorated and she eventually succumbed to multi-organ failure one and a half months after the diagnosis of CMML.

2.2. Pathologic findings

The excisional biopsy of the right submandibular mass (biopsy 1) contained 3 lymph nodes that ranged from 0.6 to 1.9 cm in longitudinal diameter. Microscopic examination of the largest lymph node demonstrated partial effacement of nodal architecture by expansion of perifollicular or interfollicular areas with diffuse proliferation of lymphoid cells in focal areas. This diffuse lymphoid proliferation seemed to have a high turnover rate with a scattered increase in tingible body macrophages seen at low magnification (Fig. 2A). In other areas, lymphoid nodal architecture was preserved with scattered reactive follicles and expanded interfollicular areas (Fig. 2B). At higher magnification, the expanded interfollicular areas consisted of sheets of well-differentiated plasma cells (Fig. 2B, inset) and the effaced areas were composed of homogenous population of large lymphoid cells with plasmablastic morphology (Fig. 2C). The plasmablasts in the effaced areas were positive for MUM1, OCT2, and HHV8 latency associated nuclear antigen (LANA-1) (Fig. 2D). A small subset of the large cells was weakly positive for CD45, EMA and CD30, but they were essentially negative for CD138, CD20, CD19, CD79a, PAX5, T-cell antigens and myeloid antigens. Stains for kappa (Fig. 2E) and lambda (Fig. 2F) light chains

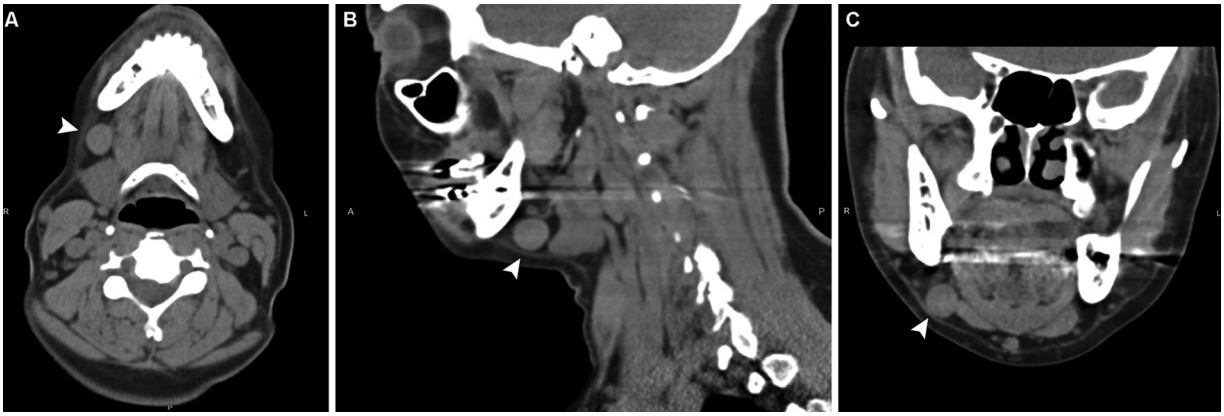

Fig. 1. Computed tomography scan of the neck demonstrating the enlarged submandibular lymph node or amalgamated nodes (arrow heads). A. Axial plane at the level of submandibular gland with the top of the head pointed inside. Note a 1.5 cm nodule is located anterior to the submandibular gland. B. Sagittal plane. C. Coronal plane with anterior facing outside.

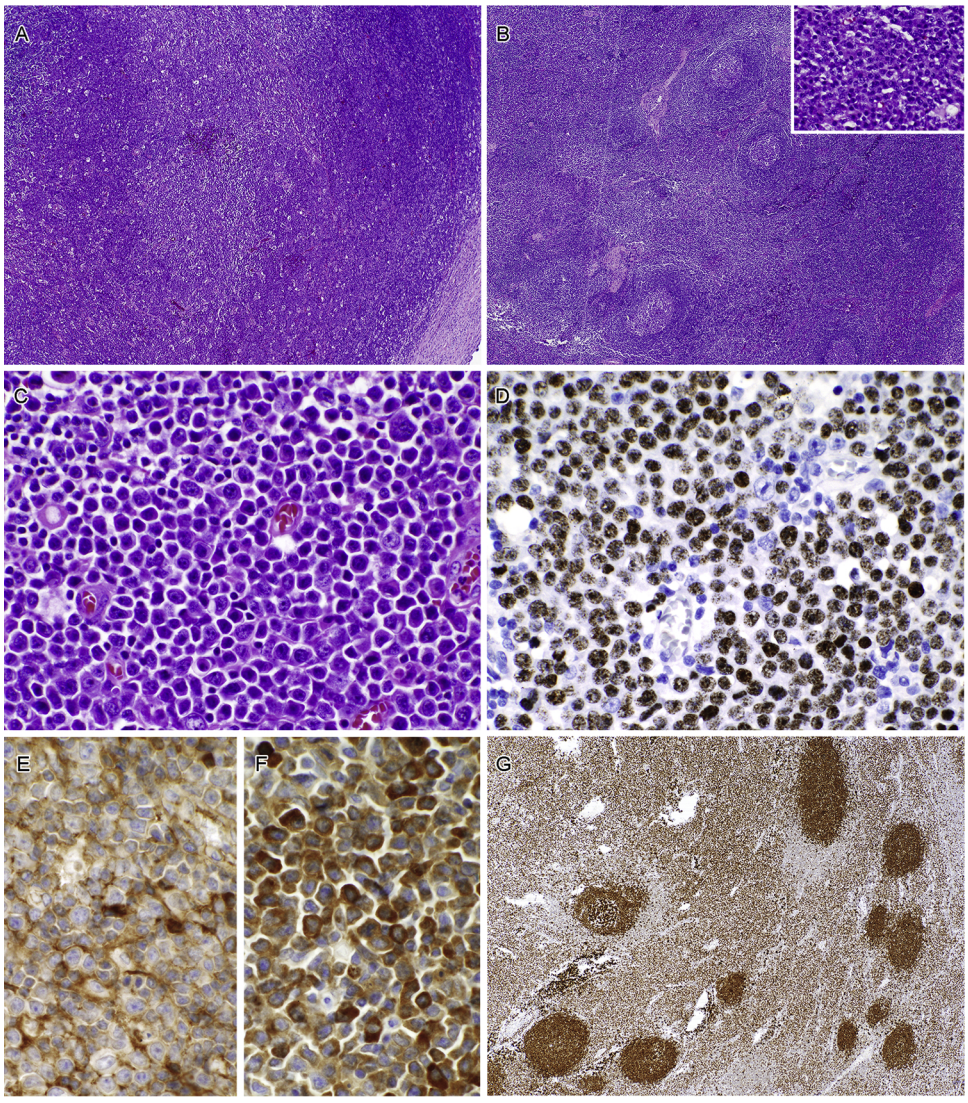

Fig. 2. Histopathologic evaluation of the right submandibular mass lesion (biopsy 1). A, H&E stain shows a focal area with diffuse proliferation of large lymphoid cells that effaces nodal architecture (×40). B, H&E stain of the same section shows another area with preserved nodal architecture demonstrating hyperplastic lymphoid follicles, and expanded interfollicular areas (H&E stain, ×40). Inset exhibits high magnification of interfollicular area with marked increase in well-differentiated plasma cells (H&E stain, ×200). C, A high magnification of area with effaced nodal architecture in Fig. 1A shows confluent growth of large lymphoid cells with eccentric large round nuclei, vesicular chromatin, prominent nucleoli and moderate amount of cytoplasm (plasmablastic morphology) (H&E stain, ×400). D, Plasmablasts are positive for HHV8-LANA-1 with nuclear staining (×400). Plasmablasts are negative for kappa light chain (×400) (E), and positive for lambda light chain (×400) (F). G, Anti−OCT2 stain on the border between the area of diffuse plasmablasts (upper left corner) and the area of preserved architecture with interfollicular plasmacytosis. Note cells at both areas are positive for OCT2, which is weaker than the cells in lymphoid follicles (×40).

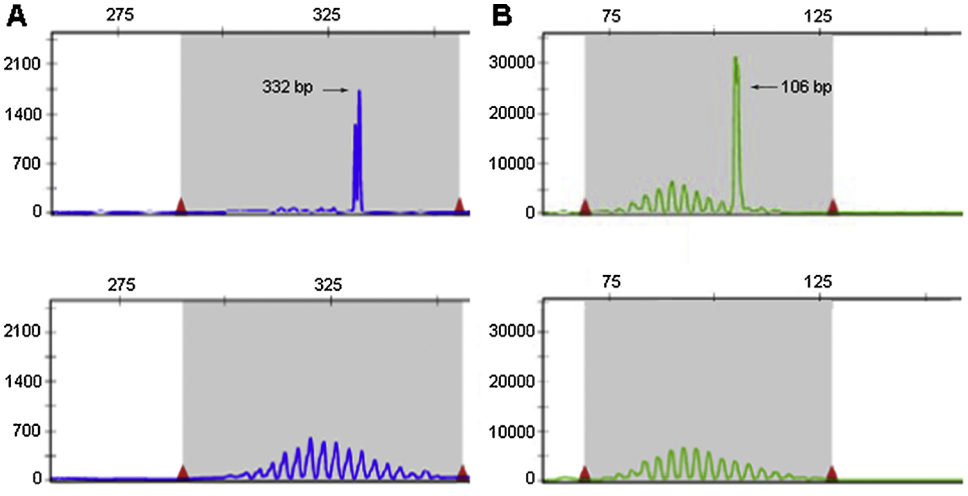

Fig. 3. Detection of clonal rearrangement of *IGH* gene in the right submandibular mass from biopsy 1 using BIOMED-2 primers. Note clonal amplicons were amplified by frame work 1 (A, upper panel, amplicon size = 332 base pairs) and frame work 3 (B, upper panel, amplicon size = 106 base pairs) primer sets. Lower panels in A and B represent reaction from polyclonal samples (negative control reaction). The shaded areas indicate the ranges of anticipated amplicon sizes.

demonstrated restriction to lambda light chain in plasmablasts. In contrast, well-differentiated plasma cells in interfollicular areas were strongly positive for CD138 with membranous staining and were apparently polytypic with regard to the expression of kappa and lambda light chain (data not shown). OCT2 was expressed in both plasmablasts and well differentiated plasma cells (Fig. 2G), in addition to the cells in lymphoid follicles. The proliferation index was high, estimated at 80% of the total nucleated cells in the areas with sheets of plasmablasts, while it was 5–10% in the well differentiated plasma cells in the expanded interfollicular areas. Study for Epstein-Barr virus (EBV), including EBV-latent membrane protein-1 (EBV-LMP1), EBV-nuclear antigen-2 (EBNA2) and EBV-encoded RNA (EBER) in situ hybridization

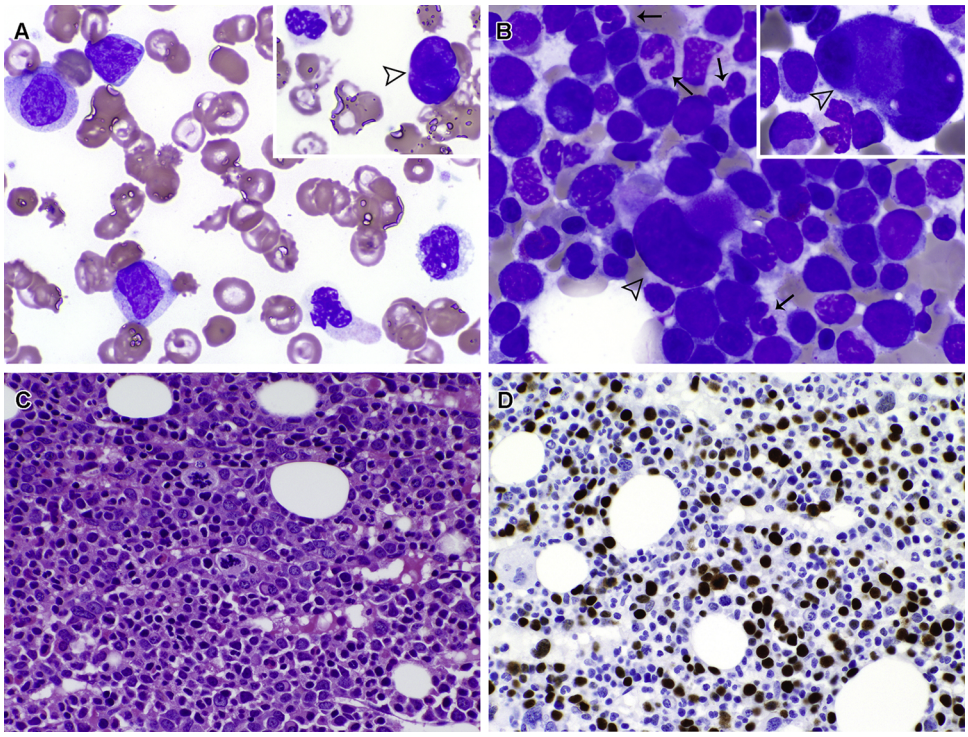

Fig. 4. Morphologic evaluation of bone marrow biopsy (biopsy 2). A, Peripheral blood smear showing one blast, two immature myelomonocytes, one monocyte and one hypogranulated neutrophil in a background of hypochromic red blood cells with anisopoikilocytosis and increased target cells. The inset includes a circulating megakaryocyte with naked nucleus (arrow head) and a hypogranulated neutrophil (Wright-Giemsa stain, ×1000, oil emersion). B, Bone marrow aspirate smears showing dysplastic megakaryocytes (arrow heads), hypogranular neutrophils (solid arrows) and dysplastic erythroid precursor (Wright-Giemsa stain, ×1000, oil emersion). Note the slight increase in blastic cells. Inset indicates a megakaryocyte with nuclear lobe separation (Wright-Giemsa stain, ×1000, oil emersion). C, Bone marrow core biopsy showing hyperplastic hematopoiesis. Note the increased immature precursors and two megakaryocytes in karyorrhexis (center of the image) (H&E stain, ×400). D, Immunohistochemical analysis shows that many hematopoietic precursors are positive for p53 (p53 stain, ×400).

(ISH), was essentially negative. Immunoglobulin gene rearrangement analysis performed on the paraffin embedded tissue demonstrated a clonal rearrangement of heavy chain gene (*IGH*) (Fig. 3). Thereafter, a diagnosis of HHV8-positive DLBCL-NOS was rendered based on morphologic features, immunohistochemical profile, and molecular diagnostic results in this biopsy. The two smaller lymph nodes showed apparently reactive follicular hyperplasia with no appreciable foci of plasmablastic infiltration.

A review of the peripheral blood smear associated with the patient's bone marrow biopsy (biopsy 2) showed marked leukocytosis with increased atypical monocytes (13%), dysplastic neutrophils, circulating erythroid precursors and rare megakaryocytic nuclei; blasts/promonocytes comprised about 3% of the total leukocytes; red blood cells displayed anisopoikilocytosis with many hypochromatic cells, target cells and increased polychromatophilic cells (Fig. 4A), which was consistent with the patient's underlying hemoglobin SC disease. The bone marrow aspirate smear exhibited left-shifted erythroid precursors with dysplasia including megaloblastic changes, nuclear irregularity and nuclear budding; myelopoiesis demonstrated neutrophils or their precursors with hypogranularity and slightly increased blasts/promonocytes (5% of the total nucleated cells in the bone marrow); prominent megakaryocytic dysplasia was also noted, including many small hypolobate forms and rare forms with lobe separation (Fig. 4B). The core biopsy showed a hypercellular bone marrow (about 90%) with hyperplastic hematopoiesis and increased immature forms (Fig. 4C). Megakaryocytes were increased and dysplastic in morphology. Immunohistochemical analysis for p53 showed many hematopoietic precursors were strongly positive for the protein (Fig. 4D). The concurrent flow cytometry demonstrated 61% granulocytes with decreased side scatter and 3% myeloid blasts. Chromosomal analysis showed complex abnormalities with clonal evolution including partial loss of the long arm of chromosome 5 and chromosome 7 in all metaphase cells: 44～45,XX,del(4)(p14p16),der(5;7)(p10;p10),-15,-16,add(18)(q21), +1～2mar [10] /44～45,idem,add(12)(p13) [6] /43～44,idem,+add (4)(p14),-del(4)(p14p16),-12 [4]. Interphase fluorescence in situ hybridization (FISH) analysis on the marrow aspirate smear confirmed interstitial deletion of chromosome 5q and chromosome 7q in 91.5% and 92.5% interphase nuclei, respectively. *BCR/ABL1* fusion was absent by interphase FISH assay. Next generation sequencing (NGS) analysis revealed a pathologic missense mutation in exon 6 of *TP53* gene (NM_000546.5:c.641A > G; NP_000537.3:p.His214Arg) with a variant allele frequency of 0.907 suggestive of homozygous mutation or loss of heterozygosity. Mutations on *JAK2*, *CALR* and *MPL* genes were not identified by our NGS myeloid panel. Thereafter, the diagnosis of CMML-1, proliferative phase, was rendered based on morphologic features and cytogenetic results. Given the absence of *NPM1* mutations and 11q23 abnormalities, rare possibility of acute myeloid leukemia with monocytic differentiation was unlikely in this case.

3. Discussion

The extended life expectancy of today's patients with SCD has unfortunately been accompanied by an increased occurrence of malignant neoplasms [3,4].While the incidence of myeloid leukemia is increased up to 10 times compared to age/ethnic-matched controls, the risk of lymphoma in the setting of SCD has been debated [4]. The literature is limited to sporadic case reports that include DLBCL [5], classic Hodgkin lymphoma [6], small lymphocytic lymphoma [7], B-lymphoblastic lymphoma [8], mycosis fungoides [9], and subcutaneous panniculitis-like T-cell lymphoma [10]. In this manuscript, we report the first case of HHV8-positive DLBCL-NOS in a 58-year old female with hemoglobin SC disease.

HHV8-positive DLBCL is a specific type of HHV8-positive lymphoproliferative disorder that has been associated with immunodeficiency, particularly in patients with HIV infection [11]. Cases of HHV8-positive DLBCL without identifiable cause of immunodeficiency are extremely rare. Its diagnosis requires integration of pathological evaluation with clinical findings and ancillary laboratory studies. Essential pathological features include effaced or partially effaced nodal or splenic architecture by large lymphoid cells with plasmablastic morphology that are positive for HHV8 LANA-1 and demonstrate loss or partial loss of B-cell antigens. The present case exhibited histopathologic features fulfilling the criteria for diagnosis. A solitary extracavitary variant of primary effusion lymphoma (PEL) could possibly display similar morphology and show partial loss of B-cell antigens, however, PEL is often associated with EBV infection, and usually expresses CD138, in contrast to

HHV8-positive DLBCL. Cases of PEL that are negative for EBV latent infection are extremely rare [12,13]. Given the negativity for EBV and CD138 in our case, a diagnosis of HHV8-positive DLBCL was considered more likely than extracavitary PEL. A partial effacement of nodal architecture, absence of constitutional symptoms, and an isolated right submandibular mass with no other detectable lesions seems to suggest an early lymphoma in this particular biopsy of our patient. The possibility of early HHV8-positive DLBCL was supported by the fact that the lymphoma did not recur after one-year observation following its complete excision. On the histologic sections, areas with preserved nodal architecture demonstrated interfollicular plasmacytosis that was polytypic and negative for HHV8 LANA-1. Although the latter feature may suggest a possibility of multicentric Castleman disease (MCD), from which HHV8-positive DLBCL often arises, the absence of constitutional symptoms and other involved sites makes the diagnosis of MCD unlikely in this patient. Alternatively, this polytypic plasmacytosis in interfollicular areas may be mediated by IL6-like molecules released from nearby neoplastic plasmablasts containing latent HHV8, an associated secondary effect rather than a preceding condition [14]. The viral latency in DLBCL prompted a possibility of immunodeficiency in our patient, because the virus is usually kept in check in an immune competent individual. Although HIV tests were negative in our patient at the time of the diagnosis, a few potential causes of immunodeficiency could be present in this patient, including therapy related to SC hemoglobinopathy such as long term use of hydroxyurea (21 years of the treatment), transfusion-related immunomodulation, systemic inflammation in response to chronic hemolysis, and relatively older age (58 years at the diagnosis).

To make the case more complex, our patient developed a second hematolymphoid neoplasm, CMML, one year after the diagnosis of HHV8-positive DLBCL. Could this myeloid neoplasm be a chance of coincidence with the preexisting SC hemoglobinopathy or otherwise, was there an inherent connection between the two conditions in this particular patient? More specifically, does a patient with SCD naturally have an increased risk of myeloid leukemia? While this has been debated, an increased risk of malignancies has recently been demonstrated by epidemiological studies in patients with SCD [3,4]. The risk is particularly higher for myeloid neoplasms than other malignancies with an estimated relative risk from 4 to 10 fold in the setting of SCD compared with an ethnic controlled population. This notion seems to be supported by the pathologic findings in our patient and the cases reported in the literature [15]. In the current case, bone marrow examination showed significant myelodysplasia and complex cytogenetic abnormalities with subclone heterogeneity suggestive of genomic instability in the leukemia clone, as well as a *TP53* mutation with a high mutation burden. All these pathologic characteristics are often associated with secondary myeloid neoplasms per the literature. For instance, myeloid neoplasms related to alkylating agents and/or ionizing radiation tend to have complex cytogenetic abnormalities, many of which contain loss or partial loss of chromosome 7q and/or 5q [16]. Because of a low clinical stage and absence of PET/CT avid lesions, our patient did not receive any treatment pertinent for HHV8-positive DLBCL other than a complete excision of the right submandibular mass, and thus mutagenic regimens such as alkylating agents or ionizing radiation were not readily blamed for leukemogenesis in this case. Sporadic cases of myeloid neoplasm have been described in patients with SCD, and their pathologic features have included morphologic dysplasia and a cytogenetic profile distinct from de novo myeloid neoplasms, as seen in the current case. In their recent article, Li et al [15] reported 4 cases of myeloid neoplasm in SCD patients, and performed a comprehensive review of the literature. By pooling all the reported cases with essential clinicopathological information, the authors demonstrated a younger age at the diagnosis of myeloid neoplasm, a higher proportion of myelodysplastic neoplasms, and a higher fraction of complex cytogenetic abnormalities with -7/7q- and/or -5/5q- within myeloid neoplasms in the setting of SCD than those in de novo myeloid neoplasms. These findings suggest that myeloid neoplasms may have some intrinsic connection to SCD or its treatment. This prompts a consideration of hydroxyurea used in our patient as culprit for the leukemogenesis. While the mutagenic potential of hydroxyurea has been a concern since its approval by the FDA, recent studies demonstrated no evidence of increased risk for myeloid neoplasms at the therapeutic dose for SCD [4], and the majority of SCD patients had no exposure to hydroxyurea before the development of a myeloid neoplasm [15]. Alternatively, SCD is accompanied with chronic inflammation and iron overload owing to constant extramedullary hemolysis and frequent blood transfusion. These factors could increase the risk of developing a myeloid neoplasm by excessive production of reactive oxygen species that potentially induce genomic damage and somatic mutations [17]. Li et al hypothesized that persistent stress on the bone marrow stimulated by chronic hemolysis and episodes of cytokine storm may lead to a disordered proliferation, and thus introduce genomic errors during hematopoietic replication [15]. Furthermore, patients with SCD may have other genetic defects that cause genomic instability and thus hereditary predisposition to myeloid neoplasm. Finally, as discussed above, our patient probably had a deficiency in immunity, which resulted in HHV8 infection leading to an HHV8-positive DLBCL. Her immunodeficiency may have also played a role in the subsequent development of CMML, since a competent immune system continually monitors and controls preneoplastic clones to reduce the incidence of myeloid neoplasms, as has been reported in the recent literature [18]. Nonetheless, the pathogenesis of hematolymphoid neoplasms in the setting of SCD may involve complex pathways and various factors playing multifaceted roles. In this particular case, the two hematolymphoid neoplasms, HHV8-positive DLBCL and a myeloid neoplasm, might have developed via different mechanistic pathways, with immunodeficiency causing the former and other etiologies leading to the latter. The recent advances in genomic analysis provide an opportunity for a comprehensive study of myeloid neoplasms in the setting of SCD against therapy-related myeloid neoplasms and de novo counterparts. Such a genomic profiling could possibly shed light on the pathogenesis of myeloid neoplasms in the setting of this hereditary hematological condition.

While the clinical outcome of HHV8-positive lymphoproliferative disorders varies with its subtypes, HHV8-positive DLBCL has been considered an aggressive disease [11–13]. Our patient showed isolated submandibular lymphadenopathy, and had no evidence of the lymphoma one year after complete excision without additional therapeutic intervention. This indolent biological behavior was in contrast to the current perception of HHV8-positive DLBCL, but may be explained by an early detection of the lymphoma. In addition, recent studies have demonstrated that an unfavorable outcome of HHV8-positive DLBCL can be associated with immunodeficiency, such as HIV-positivity [12,13]. Rare cases occurring in HIV-negative patients, as seen in our patient, have been shown to have relatively better survival than HIV-positive patients, which comprise the majority of cases.

The exact causal mechanism by which SCD or equivalent hemoglobinopathy contributes to the clinical outcome of myeloid neoplasms is unknown at the current time. The coexisting SCD probably complicates the decision for management of myeloid neoplasm because of a concern for potential sickling episode when the patients receive chemotherapeutic agents. Additionally, given its association with high-risk cytogenetic abnormalities and resemblance to secondary leukemogenesis, myeloid neoplasms detected in the setting of SCD might be equivalent to their therapy-related counterparts and therefore indicative of a dismal outcome. This notion seems to be supported by the aggressive clinical course experienced by our patient and the others reported in the literature. In their recent article, Yang et al [15] demonstrated an estimated median survival of only 7 months via Kaplan-Meier survival analysis of SCD patients with myeloid neoplasms. However, the exact biological nature of the disease in this clinical setting remains to be determined with large cohorts of patients in future analyses.

In summary, we reported the sequential development of HHV8-positive DLBCL and CMML within a one-year period, in a 58 year-old female with SC hemoglobinopathy. Localized features and an indolent clinical course of the lymphoma raised the possibility of an early HHV8-positive DLBCL, suggesting an indolent variant of the disease in an HIV-negative patient. Given the features of HHV8-positive DLBCL in this patient and a frequently insidious initial presentation of CMML, the two hematolymphoid neoplasms in our patient might have arisen simultaneously, with the lymphoma caught earlier and CMML remaining undiagnosed until progressing into a more aggressive phase. There is a possible intrinsic connection between these two hematolymphoid neoplasms and the underlying SCD in our patient, with immunodeficiency as a culprit for HHV8-positive DLBCL and other still unknown mechanisms for CMML. The possible pathogenesis for CMML or other myeloid neoplasms in the setting of SCD includes chronic inflammation, iron overload and constant replication of hematopoietic cells, which may increase somatic genomic mutation or aberrations. Interestingly, CMML in our case demonstrated morphologic features, cytogenetic profile, and a molecular signature resembling therapy-related myeloid neoplasms, as did several cases published previously. While the biological behavior of HHV8-positive DLBCL in the setting of SCD may vary with status of HIV infection, the development of myeloid neoplasms associated with SCD herald an unfavorable clinical outcome.

Conflict of interest

None.

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