General Medicine

Review Article

Subcutaneous Panniculitis in Sickle Cell Disease (SCD): A Rare Disease Complication

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- Received Date: 08 Nov 2023
- Accepted Date: 20 Nov 2023
- Publication Date: 27 Nov 2023

Keywords
subcutaneous panniculitis; sickle cell disease; rare disease

Abstract

Objective: *To delineate the explore potential etiological contributions to subcutaneous panniculitis-like T-cell lymphoma (SPTCL) in adults with sickle cell disease. Sickle cell disease (SCD) is an inherited hematologic disorder where standard treatment may enhance risk of the development of rare co-morbidities like SPTCL.*

Methods: *We reviewed the scientific literature and only found one case report detailing the development of SPTCL in an adult with SCD.*

Results: We reviewed 1 case reports and the general literature on hematolymphoid disorders. We discovered that there are several potential mechanisms to explain SPTCL in SCD but no conclusive evidence to support either. We reported radiographic, serological, immune, and hematological finding from the previous case.

Conclusions: *SPTCL is a complex disorder with a likely multifactoral etiology. The development of the disease in adults with SCD is rare but possible as evidenced by a published case report. We advocate for additional attention to the intersection of these two diseases for the purpose of better understanding their etiology and epidemiology. More research is needed.*

Introduction

Lymphoma is a type of cancer typically localized in the lymphatic system that results from the uncontrolled growth of lymphocytes [1-2]. There are two broad categories of lymphomas- Hodgkin and non-Hodgkin lymphomas [3]. When comparing Hodgkin lymphomas (HL) and non-Hodgkin lymphomas, HL refers to when lymphatic cells within the body's network of immune channels grow uncontrollably in conjunction with the presence of Reed Sternberg (RS) cells, with symptoms often including edema in the lymphatic system, notably around cervical, axillary, and inguinal lymph nodes, fever, excessive fatigue, and pruritis [5]. By contrast, in non-Hodgkin lymphoma, lymphocytes grow to produce tumors throughout the body but without the presence of RS cells [6].

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare, slow velocity variant of non-Hodgkin lymphoma [7]. Individuals with SPTCL develop multiple painless nodules in the adipose layer of the skin, producing panniculitis or edema in the

Citation: Scott S, Edwards CL, Boggan M. Subcutaneous Panniculitis in Sickle Cell Disease (SCD): A Rare Disease Complication. Gen Med. 2023;1(2):1-5

subcutaneous fat layer [8]. Like many cancers associated with the lymphatic system, the etiology of SPTCL is multifactoral and likely includes a genetic susceptibility combined with environmental exposure [1]. SPTCL is most common among women aged 40 to 60, who frequently have pre-existing autoimmune diseases [9].

Although the epidemiological risk of SPTCL is unspecified at this time, there is evidence that the disease can occur among individuals with hematological disorders like Sickle Cell Disease (SCD). In the following paper, we review the rare case of a patient with SPTCL and SCD for the purpose of better understanding comorbid risk factors associated with the two diseases, as well as delineating potential future research associated with this important set of disorders [8].

Genomic features

Few studies have explored the genomic features associated with SPTCL. Notably, some studies have concluded that germline HAVCR2 mutations were overexpressed in their respective patient populations, and were identified by whole-exome sequencing (WES) [10,11]. The HAVCR2 gene is responsible for encoding the T cell immunoglobulin mucin 3 (TIM-3), which has been implicated as a potential target for cancer therapies due to some literature suggesting that it plays a role in tumor suppression [12]. Gayden et al. also stated that in patients with SPTCL, elevated serum levels of IFN-γ–induced CXCL10, soluble CD25, interleukin-18, tumor necrosis factor-alpha (TNF-α), and IL2 were observed [11]. Contrarily, a separate study conducted by Li et al. used WES to determine that their patient with SPTCL did not exhibit HAVCR2 or CXCL10 overexpression but did observe low expression of IL2, IL18, TNF, and CD25 [13].

A number of studies have also explored chromosomal copy number abnormalities in patients with SPTCL. Hahtola et al. conducted comparative genomic hybridization (CGH) and found consistent DNA copy number losses in chromosomes 1p, 2p, 2q, 5p, 7p, 9q, 10q, 11q, 12q, 16, 17q, 19, 20, 22. There were also DNA copy number gains in chromosomes 2q, 4q, 5q, 6q, and 13q [14]. Li et al. furthered these findings, noting that DNA copy number gains were observed in chromosomes 6p, 12p, and 14p within the malignant cells [13]. Additionally, researchers have identified gene expression programs (GEPS) that may be determinant of the expression profiles of specific cells. Consensus non-negative matrix factorization (cNMF) algorithms revealed that malignant cells primarily had one GEP, with predominant gene expression including the chemokines family (CCL5, CCR5, CXCR3, CXCR6), cytotoxic proteins (NKG7, GZMA, GZMB, GZMH, GNLY, and PRF1), and immune checkpoint genes (LAG3, CD27, TIGIT, HAVCR2, PDCD1, and CTLA4) [13].

Specific genotypic profiles have been outlined in patients belonging to specific demographic groups, primarily within Asian, Polynesian, and European populations, which have been more adequately reported in the literature. For example, Polprasert et al. conducted a study that included 13 patients from Japan and Thailand that had SPTCL. Within their sample, 11 patients were positive for the HAVCR2 mutation. Within those patients, 10 patients had the homozygous p.Y82C mutation, and the other patient had the compound heterozygous p. Y82C and p.T101I mutation. They further noted that the p.Y82C allele is more prevalent in East Asians, whereas the p.T101I allele is more prevalent in South Asians [10]

A separate study conducted by Gayden et al. included 27 patients, 16 of which were positive for the HAVCR2 gene mutation. Within the participants that were positive for HAVCR2, WES revealed that 12 Polynesian and East Asian patients had the homozygous p.Y82C mutation, two of three European patients had the homozygous p.I97M mutation, one of three European patients had the compound heterozygous mutation, and one North African patient had the compound heterozygous p.Y82C and p. I97M mutation [11]. Together, these reported findings demonstrate that specific genotypic profiles have been more readily published on patients with Asian, Polynesian, and European origins rather than those with African origins.

Diagnostic criteria and ICD-10 codes for SPTCL

MDue to the rarity of SPTCL, there are no standardized diagnostic criteria available. Diagnosis relies on clinical presentation, histopathologic findings from subcutaneous tissue excisional biopsies, immunohistochemical staining, and molecular features. Notably, in 2001, the World Health Organization (WHO) recognized SPTCL as a specific type of non-Hodgkin Lymphoma. However, SPTCL can be further classified by the phenotype of the T-cell receptor (TCR) implicated and the resulting immunophenotype of the cells that form the mass [7]. The TCRαβ phenotype is most commonly CD4-, CD8+, CD56-, and presents with multiple or recurrent painless tumors and has the best clinical prognosis. By contrast, the TCR gamma-δ phenotype is primarily CD4-, CD8-, CD56+, and has a much poorer prognosis with higher mortality rates [7]. Among both phenotypes, lymphocytes are usually positive for CD2, CD3, CD7, CD8, beta F1, T-cell intracellular antigen (TIA-1), perforin, and Granzyme B [15]. The remainder of the current paper will refer to TCRαβ SPTCL.

The clinical presentation of SPTCL includes one or more subcutaneous lesions or deep plaques, frequently observed in the extremities, trunk, and in fewer cases, the neck, face, and back [7]. Upon examination, the affected areas may appear as multidiameter contusions [16]. These nodules are typically painless, may begin to heal without medical intervention, and very rarely involve dermal ulceration. Accompanying symptoms can include rigors, pyrexia, cachexia, and asthenia. More than half of patients with SPTCL will also have comorbid cytopenia [7].

Histopathological findings from excised biopsies often demonstrate infiltrates within the deep subcutaneous layer with a lobular pattern. Abnormal lymphocytes are typically small-to-medium in size with atypical hyperchromatic nuclei. Plasma cells, histiocytes, and small lymphocytes may also be observed. Additionally, neoplastic T-lymphocytes are commonly found rimming individual adipocytes [16]. Immunohistochemical staining is beneficial for identification of cell phenotypes. For example, neoplastic T-lymphocytes surrounding adipocytes are frequently CD8+, CD3+, CD4-, and CD56-. The cytotoxic granular proteins, including TIA-1, perforin, and Granzyme A, are expressed by the tumor cells, with the vast majority of SPTCL cases presenting positive for beta F1 [7].

With respect to the lack of outlined diagnostic criteria,

diagnosis of SPTCL should also include appropriate differential diagnosis to distinguish between similar features present in other panniculitides and T-cell lymphomas. Three main diagnoses should be ruled out prior to an SPTCL diagnosis and include 1) primary cutaneous γ/δ T-cell lymphoma, 2) extranodal natural killer (NK)/ T-cell lymphoma, and 3) lupus panniculitis.15 Primary cutaneous γ/δ T-cell lymphoma can be differentiated from SPTCL by epidermal ulcerations and the positive expression of CD56 and TCR-γ. Extranodal NK/ T-cell lymphoma is distinct in that it may progress beyond subcutaneous tissue, is CD8-, negative for TCR, CD56+, and is frequently associated with Epstein-Barr viral infection. Finally, lupus panniculitis can be distinguished by the presence of T-cells, B-cells, multiple plasma cells, alterations in the connective tissue without atypical cells, positive expression of CD4 and CD8 cells, and is negative for TCR [15].

The International Statistical Classification of Diseases and Related Problems, 10th revision (ICD-10) provides independent coding for sickle cell diseases and SPTCL. Coding should include the specific genotype of SCD, modified by "with other specified complication," in addition to the code for SPTCL. See table 1 for the ICD-10 codes applicable to patients with SCD and SPTCL.

***Table 1**. ICD-10 codes for SCD and SPTCL*

ICD-10 Code	Disorder
D57.09	Hb-SS disease with other specified complication
D57.218	Sickle-cell/ Hb-C disease with other specified complication
D57.418	Sickle-cell thalassemia, unspecified, with other specified complication
D57.438	Sickle-cell thalassemia beta zero with other specified complication
D57.458	Sickle-cell thalassemia beta plus with other specified complication
D57.818	Other sickle-cell disorders with other specified complication
C86.3	Subcutaneous panniculitis-like T-cell lymphoma

Review of case report

We are aware of only one published case report of SPTCL in SCD. The case involved a 25-year-old African American male diagnosed with hemoglobin SS disease (HbSS/sickle cell anemia) with an extensive medical history resulting from vaso-occlusive crises (VOCs) complications [8]. In sequence of the longer-term management of crises, the patient was prescribed 500 mg of Hydroxyurea (Hydroxycarbamide)(HU) daily, and two months later developed a mass on the left side of his neck. Excisional biopsy revealed dense connective and fibroadipose tissue with granulomatous inflammation and no evidence of clonal TCR cell rearrangement. Treatment included 5 mg Prednisone daily, which resolved the mass within one month. Although there were no indications of major depressive disorder or other psychiatric disorders secondary to treatment with immunosuppressive agents in this case of SCD, there should always be awareness that steroids can induce psychiatric disturbances that may alter interventional outcomes [17].

Following acute care for the mass, the patient continued SCD-related supportive care, where his HU dosage was increased to 1000 mg a Day. Two years later, the patient presented with right buccal swelling. A lobular pattern of inflammation within dense connective and adipose tissue was observed. Infiltrates included medium-sized lymphocytes, histiocytes, and a minority of plasma cells. Lymphocytes were atypical, found rimming individual adipocytes, and were positive for CD2, CD3, CD5, CD7, beta F1, Granzyme A, and TIA-1.

An excisional biopsy was also conducted, followed by immunohistological staining, which yielded results suggestive of SPTCL. Few cells were positive for Epstein-Barr virus-encoded RNA, which is more frequently negative in patients with the TCRαβ phenotype. Clonal TCRγ gene rearrangement was negative. The patient was again treated with Prednisone 5mg daily, which successfully resolved the lesion [8]. See table 2 for an overview of the patients' medical history, medication use, and presenting symptoms; see table 3 for the patients' excisional biopsy results, MRI results, treatments, and supportive care and; see table 4 for histopathological findings, immunohistochemical findings, and patient outcome.

In alignment with what is known about TCRαβ SPTCL, the patient had a recurrent episode of left buccal swelling less than one year after the initial two episodes, which responded with the same treatment course.

***Table 2.** Medical history, medications at hospital admission, and presenting symptoms.*

Reference	History	Medications at Time of Hospital Admission	Presenting Symptoms
Ma et al., 2019 [8] 25-year-old, M	- HbSS - Multiple VOCs - Priapism - ACS - Hepatic sequestration - Episodic lower back pain - Bilateral knees, elbows, and ankles - Essential hypertension - Asthma - Community acquired pneumonia	- Hydroxyurea (HU) 500 mg/ daily since 23 years of age	- Two months after the start of HU, developed mass on the left side of the neck - Two years following resolution of mass on the left side of the neck, developed right buccal swelling

***Table 3**. Biopsy and MRI results, treatment, and changes in supportive care*

Reference	Basic Excisional Biopsy Results	MRI Results	Treatment	Changes in Supportive Care
Ma et al., 2019 [8] 25-year-old, M.	Mass on the left side of the neck: - Dense connective and fibroadipose tissue with granulomatous inflammation -Negative for clonal lymphoproliferative process Right buccal lesion: - Ovoid, pink-reddish fibroadipose tissue - Homogenous, firm, tan-gray, and lobulated cut surface	Mass on the left side of the neck: - N/S Right buccal lesion: - 3.7 X 2.7 cm - Located in the right masticator space and infratemporal fossa - Heterogeneous enhancement	Mass on left side of the neck: - Prednisone 5 mg/daily Right buccal lesion: - Initially treated with antibiotics, without resolution - Prednisone 5 mg/daily	Following resolution of the mass on the left side of the neck: - HU dose increase to 1000 mg/daily - Supportive care included hydration, blood transfusions, and antibiotic prophylaxis

Radiographic and Biopsy results

***Table 3**. Biopsy and MRI results, treatment, and changes in supportive care*

Reference	Histopathological Findings	Immunohistological Findings	Outcome
Ma et al., 2019 [8] 25-year-old, M	Right buccal lesion: - Lobular pattern of lymphohistiocytic inflammation in dense connective and fatty tissue - Infiltrates contained heterogeneous cell populations including medium-sized lymphocytes, histiocytes, and few plasma cells - Small aggregates of epithelioid histiocytes in focal areas - Lymphoid cells were cytologically atypical with irregular nuclear contours - Rimming of lymphoid cells around individual adipocytes	Right buccal lesion: - CD2, CD3, CD5, CD7, and beta F1 expressed on majority of lymphoid cells - Ratio of CD4+ cells to CD8+ cells was 1:3 - Rimming of adipocytes primarily by CD8+ cells - Significant number of lymphoid cells positive for Granzyme B1 and TIA-1 -Ki-67 staining showed a proliferative index of 25-30% of total mononucleated cells with positive cells rimming adipocytes - Acid fast bacilli and Gömöri methenamine silver stains were negative - Epstein-Barr virus-encoded RNA (EBER) in situ hybridization was positive in rare cells - TCRγ gene rearrangement analysis was negative for clonal product - TCRβ gene rearrangement analysis showed clonal proliferation	Right buccal lesion: - Prednisone resolved lesion Ten months after right buccal lesion, patient presented with left buccal lesion which again, resolved with prednisone

Abbreviations: TIA-1: T-cell restricted intracellular antigen-1; RNA: ribonucleic acid; TCR: T-cell receptor

Summary and conclusion

With such a small sampling, as represented by the literature, the true etiology of hematolymphoid neoplasms in patients with SCD is relatively unknown. Various etiological theories would explain SPTCL in SCD with chronic inflammation resulting from recurrent VOCs, possible infections transmitted by routine blood transfusions, immunomodulation associated with blood transfusions, and cytotoxic medications such as HU [8]. Each of these seemingly legitimate theories to explain a possible mechanism of SPTCL in SCD can and should be explored scientifically. Each would suggest a very different path to modifying

the risk for hematolymphoid lesions. For example, better identification and screening of pathogens that are associated with infection from transfusion is quite different from assessing and potentially relabeling the risk of side effects associated with HU. Given that many patients with moderate to severe SCD are exposed to multiple risks for SPTCL, having a better understanding of what is most associated with the development of comorbid non-Hodgkin lymphomas seems warranted.

The current paper reviews the only known published case of SPTCL in a patient with SCD; thus, conclusive statements comparing the morbidity and prognosis will not be proffered. We view the review of the case study to remind clinicians and researchers that hematolymphoid lesions do exist and should be screened for as a part of the standard of care when appropriate symptoms present. Understanding that our treatments for and management of SCD may elevate the risk of developing non-Hodgkin lymphomas may increase interest in the intersection of these two disorders in a manner that others begin to publish on this topic. Only through this mechanism of increased literature presence can we obtain a better understanding of the epidemiology and diverse presentations of SPTCL [18-21].

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