Sickle cell disease (SCD) is an inherited defect in the synthesis of hemoglobin characterized by the change of glutamic acid by valine at position 6 in the beta globin chain of hemoglobin. This simple change leads to a disease that affects organs such as the brain, eyes, lungs, kidneys and liver. The disease affects millions of people worldwide with a high prevalence in the Middle East. Type 2 diabetes mellitus (DM) also affects millions of people and is caused by a decreased production of insulin by beta cells in the pancreas. Both diseases have a high prevalence in Bahrain, but the association is rare. Hodgkin lymphoma (HL) is a relatively uncommon disease with a high clinical and epidemiological variability. Its association with SCD has been described in few reports.

We present a case of SCD associated with DM and HL, the first such reported case in Bahrain.

**THE CASE**

A sixty-two-year-old Bahraini female, known to have type 2 DM and SCD presented to with five-month history of multiple lymph nodes gradually increasing in size on the right side of the neck; it was associated with intermittent low-grade fever, night sweats, dizziness and unintentional weight loss of 10-15 kilograms of body weight.

Clinical examination revealed multiple bilateral cervical lymphadenopathies, the largest being 2x2 cm, with mild tenderness on palpation. Conjunctival pallor and congenital anomalies of both hands (dactylitis) were noted.

The investigation revealed anemia of 69 g/L, elevated white cell counts of 24.9 x 10^9/L and thrombocytosis of 803 x 10^9/L. White cell differential count showed 58% neutrophils, 34% lymphocytes, 2.3% eosinophils, 4.4% monocytes and 0.4% basophils.

Inflammatory markers were found to be high: CRP was 117 mg/dL and ESR 120 mm/h. Total protein was 92 g/dL (high), IgG and IgA were elevated at 2,658 mg/dL and 499 mg/dL respectively, IgM was found to be low.

No monoclonal bands were detected by serum protein electrophoresis nor 24-hour urine protein electrophoresis and immunofixation. β-2 microglobulin was slightly high at 7.7 mcg/mL. LDH was high at 279 U/dL. Total bilirubin was 21 mg/dL.

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The aim of this presentation is to report a case of a patient with SCD and type 2 DM, who was diagnosed with HL.
mg/dL, and direct bilirubin was 8 mg/dL. Coagulation profile was normal except for elevated fibrinogen (597 mg/dL). Iron profile showed elevated ferritin.

Echocardiogram revealed grade I diastolic dysfunction with an ejection fraction of 55% and posterior annular mitral calcification.

Ultrasound of abdomen and pelvis revealed a sizeable well-defined enlarged lymph node posterior to the pancreas; most likely to be in the mesenteric group measuring 3.3x2 cm, and another suspected above the level of the pancreas measuring 1x2.6 cm.

Ultrasound of the neck showed bilateral cervical lymph nodes with 10-12 mm long axis and preserved normal shape and echo pattern, but the largest lymph node was on the left side, measuring 19 mm with hypoechoic echo pattern.

Chest X-Ray was normal. CT chest with contrast revealed multiple enlarged non-calcific, non-necrotic, variable in size left supraclavicular, pre-tracheal (21 mm), pre-vascular (21 mm), anterior carinal (17.5 mm), sub-carinal (28 mm), posterior mediastinal/right para-esophageal (30 mm) and paracardiac (12 mm) lymph nodes. Left lower lobe anterior basal segment showed a solitary non-calcific, non-cavitary nodule (9 mm).

CT abdomen and pelvis with contrast revealed hepatomegaly (17.5 cm), cholecystectomy and splenectomy were performed, multiple enlarged non-calcific, non-necrotic coeliac, retro-pancreatic (33.5 mm), left para-aortic, aortal-caval, right para-caval, external iliac (27 mm) and inguinal lymph nodes. Bone marrow aspiration and biopsy showed reactive marrow changes with no morphologic evidence of neoplastic cell infiltration.

The excisional lymph node biopsy showed effaced architecture and patchy necrosis. There were occasional scattered large atypical mononuclear lymphocytes with a prominent nucleolus. The background showed diffuse sheets of histiocytes, lymphocytes and rare eosinophils.

Immunohistochemical studies revealed the following: the atypical lymphocytes were positive for CD30, MUM-1 and BOB-1, while negative for CD3, CD5, CD20, CD15, ALK-1, PD-1 and PAX-5. The background T-cells were positive for CD3 and CD5. The atypical cells were negative for EBV stain.

The patient was diagnosed with mixed cellularity classical Hodgkin’s lymphoma, and she was started on the ‘ABVD’ regimen (Adriamycin, Bleomycin, Vinblastin, and Dacarbazine).

DISCUSSION

Several studies have a lower incidence of DM in the SCD population. This fact has led to hypothesis of a possible protective genetic mechanism in these patients. A cross-sectional study performed in Bahrain showed that the age- and sex-standardized prevalence of DM was 8.3%, which was still lower as compared to the expected figure of 15.4% among the general population.

Patients with SCD were more likely to die at a younger age; consequently, a smaller number of patients survived to express the manifestation of diabetes clinically; both β-globulin and insulin genes were expression on the short arm of chromosome 11. Nonetheless, there is no solid evidence as to whether the proximity of these genes has any inhibitory effects on the pattern of inheritance. Few studies highlighted the possible association between DM and SCD; however, a definitive link has not yet been established.

The first ever reported case of HL was in a patient with SCD. However, there are various other hematological malignancies apart from HL that could occur in SCD patients such as acute myeloid leukemia, multiple myeloma, acute lymphoblastic leukemia, malignant histiocytosis, B and T cell non-Hodgkins lymphoma, chronic lymphocytic leukemia and hairy cell leukemia.

A study reported seven-year-old Nigerian boy with SCD and HL (mixed cellularity subtype). The reported cases of patients with HL in SCD patients were scattered evenly within the age of 8 to 23 years.

HL is a disease with a bimodal distribution. The incidence peaks between 20-40 years, and the second peak occurs in more than 55 years. Nodular sclerosis classical HL is the most common type followed by mixed cellularity. A case report confirmed the occurrence of SCD, type II DM and multiple myeloma in fifty-eight-year-old Cuban patient.

Up to December 2016, there have been ten reported cases of chronic myeloid leukemia in patients with SCD. However, the occurrence of hematological malignancies in SCD patients is quite rare. It has been hypothesized that this could be attributed to the comparatively shorter life expectancy of SCD patients. Nevertheless, due to advancements in medicine, the average lifespan of a patient with SCD has increased from 14 years to 42 years; therefore, increasing the likelihood and incidence of such malignancies. Furthermore, there are various risk factors that could increase the likelihood of hematological malignancies in SCD such as HIV, hepatitis C virus, stem cell transplantation, persistent transfusion-related immunomodulation and chemotherapeutic agents, including hydroxyurea, commonly used for the treatment of SCD.

There have been reported cases of secondary malignancies with long-term use of hydroxyurea, which could be a possibility in this case report. However, the incidence of hematological malignancy in SCD patients who have been on hydroxyurea for a long period is unknown, an interesting topic for future research in Bahrain.

Other proposed hypotheses include high oncogenic expression due to stimulated erythropoiesis, as demonstrated in a study using rats. Furthermore, in SCD, bone marrows have higher mitotic rates which lead to higher incidence of defects in the chromosomes; therefore, resulting in high incidence of malignancies.

A study highlighted the possibility of some other cancers in SCD affected patients. The study demonstrates that there are higher rate ratios in hematological malignancies such as...
Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, multiple myeloma, lymphoid leukemia and myeloid leukemia and a greater risk in other malignancies including colon, kidney, thyroid, prostate and non-melanoma skin cancer. However, there were certain other malignancies that did not show a higher incidence, namely: cancer of the esophagus, stomach, rectum, bladder, liver, pancreas, bone and cartilage, malignant melanoma, chronic and acute lymphoid leukemia, ovary, uterus and testis.

It is thus imperative to study the relationship between SCD, DM and hematological malignancies.

**CONCLUSION**

The concurrence of diabetes mellitus, sickle cell disease and Hodgkin’s lymphoma has not previously been reported, to the best of our knowledge. There is a possibility of an underlying genetic association between these diseases. A prospective study is advised to highlight such association.

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