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RECURRENT HYPOGLYCEMIA IN A PATIENT WITH HODGKIN'S LYMPHOMA: A CASE REPORT WITH REVIEW OF LITERATURE

Gautam Rawal [1,✉], ***Raj Kumar*** [1], ***Sankalp Yadav*** [2], ***Amrita Singh*** [3]

[1] Respiratory Intensive Care, Max Super Specialty Hospital, Saket, New Delhi, India
[2] Department of Medicine & TB, Chest Clinic Moti Nagar, North Delhi Municipal Corporation, New Delhi, India
[3] Gen-X Diagnostics, MadhuVihar, New Delhi, India

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Abstract

A rare complication associated with the Hodgkin's lymphoma is the occurrence of persistent or recurrent hypoglycemia. Although few cases have been reported in the literature, describing its pathophysiology to be multifactorial, it is difficult to determine the exact cause. We present the case of a 26 year old patient diagnosed with Hodgkin's lymphoma who developed recurrent episodes of hypoglycemia and also discuss the various causes for its pathogenesis. In this case the serum insulin and C-peptide levels were found to be low, suggesting the presence of insulin like growth factors (IGF) secreted by the cancer cells. Also, we performed a ^{18}F-2-fluoro-2-deoxy-d-glucose positron emission tomography that showed a massive tumor load. The published reports in literature have similary suggested the presence of IGF or auto-antibodies secreted by the tumor cells and also the Warburg effect in patients with high tumor load. Further research is required to clearly diagnose and define the exact etiopathogenesis of the hypoglycemia occurring in a patient with Hodgkin's lymphoma.

key words: *Chemotherapy, hypoglycemia, Hodgkin lymphoma, Warburg effect*

Introduction

Hypoglycemia is a rare complication associated with Hodgkin's lymphoma. There are few cases reported in the literature, but the exact pathophysiology causing this phenomenon is not clearly understood [1,2]. We present the case of a young (26 year old) male who was diagnosed with recurrence of high grade Hodgkin's lymphoma. He also developed recurrent episodes of hypoglycemia and required repeated infusions of 25% dextrose. The work-up for hypoglycemia showed low levels of serum insulin and C peptide, consistent with the presence of insulin like factor and also a high tumor burden, with suspected Warburg effect in the patient may have been the contributing factors.

Case report

A 26 year male, diagnosed with recurrence of non-sclerosing type Hodgkin's lymphoma (post chemotherapy) with a rapid progression of the disease was transferred to the Intensive Care Unit (ICU) of Max Super Specialty hospital, New Delhi, for respiratory distress, generalized weakness and difficulty in swallowing. The

✉ Flat No. 417, Dhruva Apartments, Plot no. 4, I P Extension, Patparganj, Delhi, India, Pin-110092.
Mobile no.: +91 9868371857; *corresponding author e-mail*: drgautamrawal@hotmail.com

patient was diagnosed as Hodgkin's lymphoma two years prior to the present admission with initial complaints of low grade pyrexia, night sweats, weight loss and clinical findings of multiple cervical lymph nodes and was confirmed on lymph node biopsy. He was initially treated with ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) chemotherapy protocol and showed good response in the first year, but the symptoms and lymph nodes size again increased in the second year suggesting recurrence. He had a rapidly growing tumor mass involving the left anterior chest wall, neck mass (left more than right), and also lymph node masses in bilateral axillary and inguinal regions.

On clinical examination the patient was conscious, oriented, afebrile, hemodynamically stable, oxygen saturation of 95% on oxygen at 4 liters/minute, chest auscultation-bilateral lower zone decreased air entry (left more than right), heart sounds-normal.There was soft tissue swelling over the left anterior chest wall, bilateral cervical region (left>right), and bilateral inguinal multiple enlarged lymph nodes. The weight of the patient was 70 kg with a body mass index of 27 kg/m^2. His random blood sugar was 68mg/dL and was immediately infused intravenously with 100ml of 25% dextrose. Despite the dextrose he continued to have recurrent episodes of hypoglycemia requiring continuous infusion of dextrose. In a span of 48 hours he had six episodes of asymptomatic hypoglycemia (blood sugar ranging from 60 to 68 mg/dL). The differential diagnosis for the causes of recurrent hypoglycemic events were thought to be sepsis, liver infiltration by the malignant cells, insulinoma, insulin like growth factors (IGF), and Warburg effect.

Chest radiograph showed bilateral pleural effusion with mediastinal widening. His blood investigations did not show evidence of sepsis, and the liver function tests were normal with no evidence of liver metastasis on abdominal ultrasonography. The acid-base analysis of the arterial blood showed type 1 respiratory failure with mild increase in lactates to 3.0 (normal range 0.5-1.6 mmol/Litre) and normal pH of 7.38 (normal range 7.35-7.45). The computer tomography (CT) for neck and thorax showed soft tissue extending from the skull base to the mediastinum encasing the major blood vessels and esophagus, along with bilateral pleural effusion (left more than right). Patient's respiratory distress got relieved upon aspiration of the left pleural effusion.

We requested a ^{18}F-2-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET/CT) (that was earlier delayed due to the recurrent hypoglycemic episodes), which showed active FDG uptake in bilateral neck mass, left anterior chest wall, bilateral axillae and inguinal areas and right iliac crest, indicating a massive tumor load (Figure 1A and 1B).

The patient was further evaluated for recurrent hypoglycemia and his cortisol level was normal (patient value=14.94, normal range= 6.7-22.6 µg/dL) with low insulin (patient value= 1.29, normal range= 1.9-23 µIU/ml) and C peptide (patient value=0.7, normal range=1.1-4.4 ng/ml) levels. The patient was initiated on the ESHAP (Etoposide, Methlyprednisolone, Cytrabin, Cisplatin) chemotherapy protocol. The infusion of methylprednisolone resulted in resolution of his hypoglycemia and his blood sugars stabilized. He was then transferred to the regular oncology ward and continued chemotherapy.

An informed consent was obtained from the patient for using the medical information and the clinical images.

Figure 1A. *PET scan showing cell activity*

Figure 1B. *PET scan showing exact location of increased cell activity*

Discussion

Hypoglycemia associated with Hodgkin's lymphoma has been reported previously in a few cases for which various mechanisms have been postulated. The exact pathophysiology has not been described, as there may be more than one mechanism playing role in causing recurrent hypoglycemia [1,2]. These various mechanisms are: **a)** the cachexia or the malnutrition associated with the malignant disease and critical illness [3,4], **b)** increased basal serum levels of growth hormone together with high level of Substance Immunologically Cross-Reactive with Insulin (SICRI) [1,2], **c)** synthesis of insulin-like substances (IGF) by the malignant cells (more commonly in patients with cachexia and liver infiltration) [1,2], **d)** production of autoantibodies that mimic the insulin effect (by binding to the insulin receptors) and cause hypoglycemia in the patients of Hodgkin's lymphoma [1,2], **e)** extensive liver infiltration by the lymphoma [1,2,5], **f)** stimulation of the insulin secretion from the pancreatic islet cells by the tumor cells causing hyperinsulinemia [1,2], **g)** the Warburg effect, that is characterized by excessive glucose consumption with increased lactate production by the cancer cells even under the aerobic condition [6],and also **h)** the increased glucose uptake by massive tumor burden [7].

The presence of multiple etiologies for occurrence of hypoglycemia in a patient of lymphoma makes it not only difficult to manage but can be a life threatening phenomenon.

Conclusion

In our case presentation, the patient had Hodgkin lymphoma with a massive tumor burden evidentiated by the PET-CT scan associated with recurrent hypoglycemia. The mechanism that maybe responsible for the recurrent hypoglycemic episodes could be insulin-like growth factors (as the insulin and C-peptide levels were low), production of autoantibodies (as the hypoglycemia was abolished on initiating high dose methylprednisolone), and the excessive consumption of glucose by the cancer cells. The limitation of our case is that the measurement of the levels of insulin receptor antibody, growth hormone, and insulin like factors was not done in our patient. Further research is recommended to describe the prevalence and to know the exact pathology causing the occurrence of hypoglycemia in the patients of Hodgkin's lymphoma for its effective and early management.

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