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Diabetic Ketoacidosis in Type 1 DM: A Novel Presentation of CML

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Abstract

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes characterized by metabolic acidosis, hyperglycemia, and ketosis. It most commonly occurs secondary to a precipitating event such as an infection, non-infectious illness, or insulin non-compliance. We report a case of a 28-year-old male with a history of well-controlled type 1 diabetes mellitus who began having frequent and repeated episodes of DKA. Evaluation for compliance lapses was negative. The further review noted a worsening white blood cell count over the same period, despite repeated negative infectious workups. A bone marrow biopsy revealed a hypercellular marrow with granulocyte and megakaryocyte proliferation. Testing for the BCR-ABL fusion gene was positive in 92% of cells. This led to a final diagnosis of chronic myeloid leukemia as the precipitator for repeated presentation with DKA. The two diseases do not commonly present simultaneously due to differences in median age. No previous reports of adults with DKA precipitated by CML are present in the literature. However, worsening hyperglycemia has been reported with other hematologic malignancies, particularly in the setting of acute lymphoblastic leukemia in the pediatric population. This is thought in some instances to be due to the leukemic process itself, potentially through cytokine release.

Keywords

Hematologic Malignancy and DKA, Type 1 DM and CML

1. Introduction

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus (DM) characterized by metabolic acidosis, hyperglycemia, and ketosis. It

usually occurs secondary to a precipitating event such as infection, a non-infectious illness, or insulin non-compliance [1]. Chronic myelogenous leukemia (CML) is a myeloproliferative neoplastic disorder of pluripotent stem cells characterized by the presence of an abnormal t(9; 22) translocation forming what is known as the Philadelphia or BCR-ABL chromosome [2]. It results in increased numbers of mature myeloid cells, including neutrophils, basophils, monocytes, and eosinophils. The two diseases commonly occur in different age groups; however, here, we present a young patient with frequent DKA episodes in the newly diagnosed CML setting.

2. Case Presentation

A 28-year-old male with a history of type 1 diabetes on basal-bolus insulin, diabetic gastroparesis, diabetic neuropathy, chronic kidney disease, and hypertension presented to the hospital with chest pain, nausea, and vomiting. His symptoms began on the day of presentation, and the pain was described as a constant, centrally located sensation of tightness. The pain was aggravated by inspiration, and there were no relieving factors. He also noted shortness of breath and multiple episodes of non-bloody non-bilious vomiting. Reviewing his record, this was his 6th presentation with similar symptoms in the last four months. Before these four months, he had rarely been hospitalized. On those five previous admissions, he was found to be in DKA and was managed with an insulin infusion and intravenous hydration. Each time, he was discharged on an appropriate basal-bolus insulin regimen, with which he consistently reported compliance.

Initial vitals were notable for a heart rate of 115 and an elevated blood pressure of 234/125 mmHg. Respiratory rate and temperature were normal. On physical exam, tenderness was noted in the bilateral parasternal areas of the chest. Pulses were equal, and heart sounds were normal. Neurological, respiratory, and abdominal exams were unremarkable.

He was admitted to the intensive care unit and started on an insulin infusion for DKA, with the transition to a basal-bolus regimen once this was resolved. He was initially started empirically on vancomycin, cefepime, and metronidazole, but antibiotics were discontinued once infectious workup returned negative. WBC did not improve throughout the hospitalization. Hematology was consulted and recommended flow cytometry on a peripheral blood sample. Flow cytometry revealed leukocytosis with a left shift. A bone marrow biopsy was subsequently done with histopathology showing a hypercellular marrow with marked granulocyte and megakaryocyte proliferation. Fluorescence in situ hybridization (FISH) testing demonstrated the BCR-ABL fusion gene in 92% of cells analyzed, leading to the final diagnosis of CML. Our patient was discharged with an insulin pump. Hematology and endocrinology follow-ups were arranged. Following the diagnosis, our patient was started on a tyrosine kinase inhibitor and has not been re-admitted with DKA.

3. Discussion

DKA is one of the two serious DM complications and a hyperglycemic hyperosmolar state. It is characterized by the triad of hyperglycemia, metabolic acidosis, and increased blood ketones [1]. DKA arises most commonly in younger patients, with the majority of those affected being between 18 and 44 years old with type 1 diabetes. However, most of those affected have type 2 diabetes [1]. The primary mechanisms underlying DKA include insulin deficiency and an increase in the secretion of counter-regulatory hormones, including glucagon, catecholamines, cortisol, and growth hormone [1] [3]. Patients typically develop this complication in the setting of a risk factor that causes a catecholamine surge or, in the case of type 1 DM, due to previously undiagnosed diabetes or non-compliance with insulin. The most common precipitating factors include infections and noninfectious illnesses, such as acute myocardial infarction, stroke, and pancreatitis [1] [4]. Infection is the most common precipitating cause of DKA worldwide [4]. The initial investigation and management of a patient with DKA often involve appropriate identification and treatment of this precipitating factor. In our patient, the workup for infectious causes, including blood cultures, urine cultures, and imaging, failed to identify a contagious source over multiple admissions. He reported compliance with his insulin regimen.

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder characterized by increased granulocytic cell line proliferation without losing its capacity to differentiate. Consequently, the peripheral blood cell profile shows an increased number of granulocytes and their immature precursors, including occasional blast cells. CML accounts for 20% of all leukemias affecting adults. CML is a myeloproliferative disorder that most commonly affects older adults with an average age of 64. The pathogenesis involves the fusion of ABL1 and BCR genes located in chromosomes 9 and 22, respectively. This results in a chimeric protein with unregulated tyrosine kinase activity that promotes leukemogenesis [5]. Given the significant difference in age between DKA and CML, an overlap of the two conditions is unlikely, with no cases of DKA related to underlying CML reported previously. While neoplasms are not typically cited as a cause of DKA, hyperglycemia has been documented in the pediatric population in the setting of acute lymphoblastic leukemia [6] [7]. This is thought to be due to multiple factors, including treatment with the drug L-asparaginase, glucocorticoids, infections, and the leukemic process. The leukemic process has been theorized to contribute to this due to alterations in cytokine production [6].

Multiple epidemiologic studies show that diabetic patients are more likely to develop cancer [8]. There is also evidence that COVID-19 precipitates DKA due to B-cell destruction from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [7]. Medical, surgical, and emotional stress are listed as factors that precipitate DKA [7], and CML could be one of the unstudied causes under medical conditions.

There was one population-based cohort study done in Australia which tried to

assess the relationship between fasting blood glucose and the incidence of cancer. There was a link between insulin and growth-promoting factor of insulin-like growth factor with colon cancer. Men also positively correlated with NHL and liver cancer [9]. Other than this positive correlation, there was no in-depth study on how these cancers affect the glucose control of patients with these two conditions.

Hyperglycemia and DKA have, however, been documented in pediatric patients during therapy for ALL [3]. This has been attributed to a combination of drugs such as L-asparaginase, glucocorticoids, and leukemic processes [3]. Higher HbA1c values have been seen in these patients with WBC > 20,000 [3]. Perhaps a similar mechanism exists in CML and may explain this patient worsening glucose control. Still, there are no studies done that mention CML or malignancy being the direct precipitants of DKA.

4. Conclusion

CML may contribute to worsening glycemic control and increased risk of DKA; however, overlap in presentation is rare due to differences in the peak incidence of both diseases. Elevated WBC may not indicate infection even in the appropriate clinical scenario. It is known that cancer patients are more prone to poor glucose control due to their propensity for disease and the medications they take, but the direct effect of cancer on glucose control is not well studied. Clinician awareness of the possibility of malignancy being a precipitant of DKA helps to detect underlying illness early.

Conflicts of Interest

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

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