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CASE REPORT

Diabetic Ketoacidosis in Klinefelter Syndrome Sans Malignancy with Unusually Elevated Levels of CEA: A Case Report

Xinxin Wo, Xiaoyan Yu, Lingling Miao, Yushan Mao, Keke Tang

Department of Endocrinology, The First Affiliated Hospital of Ningbo University, Ningbo University, Ningbo, People's Republic of China

Correspondence: Keke Tang, Department of Endocrinology, The First Affiliated Hospital of Ningbo University, Ningbo University, Ningbo, People's Republic of China, Email lcyxtkk@126.com

Purpose: Klinefelter's syndrome (KS) is the most common sex chromosome disorder in the male population and is characterized by the presence of one or more X chromosomes. Studies have reported that the proportion of KS patients with diabetes is not low. It is also not uncommon for diabetes patients with poorly controlled blood glucose to have a transient mild increase in their carcinoembryonic antigen (CEA) levels. This study reports the case of Diabetic ketoacidosis (DKA) concurrently with a significant increase in CEA levels (reaching 40.8 ng/mL) in patients with KS.

Methods: This middle-aged KS patient was immediately treated for DKA upon admission. A series of exams were performed to exclude the possibility of malignant tumors, and the patient's glucose and CEA levels were closely monitored.

Results: After excluding the possibility of malignant tumors, the patient's CEA level gradually decreased to normal after good glycemic control.

Conclusion: This is the first report describing significant increases in CEA levels in KS patients with diabetes, which is of great clinical significance for the treatment of diabetes patients.

Keywords: diabetic ketoacidosis, hyperglycemia, Klinefelter's syndrome, carcinoembryonic antigen

Introduction

Klinefelter's syndrome (KS) is the most common sex chromosome disorder in the male population and is characterized by the presence of one or more X chromosomes.[1] In individuals with KS, testicular abnormalities and hypogonadism are well-established characteristic features, the incidence of metabolic disturbances, encompassing diabetes mellitus, dyslipidemia, and metabolic syndrome, is markedly elevated compared to that observed in the general population.[2] Studies have reported that the proportion of KS patients with diabetes is not low.[3] Previous research has demonstrated that the prevalence of diabetes mellitus (DM) among patients with KS varies between 6.8% and 39%, while the incidence of insulin resistance in this patient population ranges from 24.0% to 38.5%.[4] It is also not uncommon for diabetes patients with poorly controlled blood glucose to have a transient mild increase in their carcinoembryonic antigen (CEA) levels. However, cases of Diabetic ketoacidosis (DKA) concurrently with a significant increase in CEA levels (reaching 40.8 ng/mL) in patients with KS has not been reported. This middle-aged KS patient was immediately treated for DKA upon admission, and after excluding the presence of malignant tumors, his CEA level significantly decreased to normal after good glycemic control.

Case Presentation

A 41-year-old Chinese man was admitted to our department for glycemic control of DKA. He usually likes to eat sweets and drink beverages, and he had experienced dry mouth and excessive water intake for 3 months and had lost 10 kilograms in weight within 3 months.

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Table 1 Fasting Blood Glucose and CEA Levels During the Treatment

Time (day)	1	2	9	22	40	Reference Range
Fasting blood glucose (mmol/L)	40.11	15.4	7.4	6.12	5.02	3.89–6.11
CEA (ng/mL)	40.8	40.7	18.7	7.0	3.0	≤5

Abbreviation: CEA, Carcinoembryonic antigen.

At the time of admission, his heart rate was 124 beats/minute, and his skin was dry. Routine urine tests revealed 4+ ketones (normal range:(-)). Arterial blood gas analysis revealed metabolic acidosis (pH 7.0, normal range: 7.35–7.45; base excess −25.9 mmol/L, normal range: −2.0–3.0 mmol/L; bicarbonate 5.4 mmol/L, normal range: 21.0–28.0 mmol/L). DKA indicator levels increased (β-hydroxybutyrate 6.96 mmol/L, normal range: 0.00–0.28 mmol/L; lactate 3.09 mmol/L, normal range: 1.33–1.78 mmol/L). The blood glucose level was as high as 40.11 mmol/L (normal range: 3.89–6.11 mmol/L), and the HbA1c was 13.9% (normal range: 4.0–6.0%). Diabetic antibody profiles (ICA 0.05 COI, normal range: < 0.90 No reaction, 0.90 ≤ Suspicious < 1.10, ≥ 1.10 Reactive; GADA 0.71 IU/mL, normal range: <10.00 No reaction, ≥10.0 Reactive; IAA 0.03 COI, normal range: < 0.90 No reaction, 0.90 ≤ Suspicious < 1.10, ≥ 1.10 Reactive; IA-2A<0.70 IU/mL, normal range: <10.00 No reaction, ≥10.0 Reactive) are negative, consistent with the diagnosis of Type 2 diabetes (T2DM). He was immediately given a large amount of intravenous fluids while receiving continuous low-dose insulin infusion. And then he was switched to subcutaneous insulin injections. After appropriate clinical evaluation, oral hypoglycemic agents were added for glycemic control. In addition, during his hospitalization, we noticed that he was very tall (180 cm, 80 kg) and that his testicles on both sides were very small. His total serum testosterone level was decreased (3.30 nmol/L, normal range: 6.07–27.10 nmol/L), and his gonadotropin levels were increased (FSH 28.56 IU/L, normal range: 1.27–19.26 IU/L, LH 27.46 IU/L, normal range: 1.24–8.62 IU/L). Then, we further reviewed his medical history and learned that he was diagnosed with "congenital infertility" during a physical examination at the age of 19. We suspected that the patient had KS, which is usually caused by at least one extra X chromosome in males. Subsequently, with the patient's consent, we conducted a peripheral blood karyotype analysis, which revealed 47,XXY/46,XY, confirming KS.

Previous studies have shown that diabetes can significantly increase the incidence of malignancy.[5] Considering that the patient was a middle-aged man with a 10-year smoking history and a weight loss of 10 kg within 3 months, we screened him for tumor markers. To our surprise, the tumor marker screening conducted on the day of admission revealed a significant increase in the patient's CEA levels (40.8 ng/mL, normal range ≤5 ng/mL), while several other tumor markers (CA19-9 1.6 U/mL, normal range: <= 25.0 U/mL; PSA - Hyb 0.20 ng/mL, normal range: 0.00–4.00 ng/mL; FreePSA 0.51 ng/mL, normal range: 0.00–0.93 ng/mL; AFP 4.1 ng/mL, normal range: <= 7.0 ng/mL) were normal leading us to suspect the presence of a malignant tumor. However, chest CT, gastroscopy, colonoscopy and other tests did not reveal any evidence of tumor presence. There are also many non-malignant diseases, such as smoking, inflammation, fatty liver etc. which can cause abnormal elevation of CEA. However, during the subsequent hospitalization and outpatient follow-up, the patient's CEA levels gradually decreased to normal as after good blood glucose control was gradually achieved (Table 1). Therefore, we believe that the transient increase of CEA is related to poor glycemic control in diabetes patients.

Discussion

Klinefelter's syndrome (KS) is a sex chromosome syndrome and is usually caused by at least one extra X chromosome in males.[1] The most common karyotype is 47,XXY, with a prevalence of approximately 0.1–0.2%.[3] The clinical features include a tall stature, gynecomastia, small testes, and azoospermia. Extra X chromosomes can lead to genital disorders, hypogonadism and infertility.[1] The prevalence of KS with concomitant diabetes mellitus is approximately 10–39% in Western countries.[6] It was reported that KS patients had an almost four times greater risk of type 2 diabetes than did individuals of the same age.[7] Diabetic ketoacidosis (DKA) is associated with significantly elevated HbA1c levels in diabetes. A study reported HbA1c levels ranging from 10.4% to 16.9% in individuals with DKA presenting as the initial

manifestation of diabetes.[8] There are no reports of the prevalence of DKA in KS patients with diabetes. However, DKA is more common in KS patients with poor glycemic control and severe insulin resistance. We will use major databases to further study the incidence of DKA in patients with Klinefelter's syndrome. However, the mechanism of KS complicated with diabetes is still unclear and is presumably related to insulin resistance due to hypogonadism.[4]

Carcinoembryonic antigen (CEA) is a classical tumor marker widely used in the prediction of malignant tumors, assessment of clinical efficacy, and providing valuable prognostic information. CEA is overexpressed in colorectal, lung, and breast cancers.[9–11] However, elevated CEA is also associated with several other non-malignant conditions, such as inflammation, advanced age, and liver disease. CEA levels >10 ng/mL are more common in patients with malignant tumors, and levels >20 ng/mL strongly suggest malignant tumors or even metastasis.[12] In previous studies, the proportion of diabetic inpatients whose CEA level was higher than normal reached an astonishing 14.3%.[13] The CEA level was positively correlated with the HbA1c value. The highest CEA level was 14.61 ng/mL. All these patients were excluded from malignant tumors during the follow-up examinations. Other researchers also found that CEA levels in diabetic patients were independently and positively correlated with glycemic control status.[14] The mechanism of this phenomenon is still unclear. Studies have shown that hyperglycemia can affect the production of free radicals and increase oxidative stress. Severe oxidative stress and hyperglycemia may lead to increased CEA expression.[15] It may also be due to poor control in diabetic patients, and long-term glucose toxicity damage to the pancreas, resulting in inflammatory changes, destruction, and hyperplasia of the pancreas, which may lead to an increase in CEA.[16] The CEA level of our case was high to 40.8 ng/mL, which is much higher than above research. It finally decreased to normal as after good glycemic control. Several scholars have suggested that CEA levels will return to normal or significantly decrease within 2 weeks of obtaining good blood glucose control.[17] The downward trend of the CEA levels in the patient of this case is consistent with the above research, but cost more time.

Conclusion

To date, this is the first report describing significant increases in CEA levels (reaching 40.8 ng/mL) in KS patients with diabetes, which is of great clinical significance for the treatment of diabetes patients. When patients with poor blood glucose control have higher-than-normal levels of CEA, excessive tumor screening is not necessary until the patient's blood glucose is well controlled, and unnecessary panic should not occur in these cases.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

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We thank the patient for granting permission to publish this information.

Consent for Publication

Written informed consent for publication of their details was obtained from the patient. Publication of case report does not need ethical review in our institution.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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