Clinical Case Report

Medicine®

OPEN

Fulminant type 1 diabetes mellitus

Two case reports

Wei You, MM, Jianming Yang, MM*, Yanqun Liu, MB, Wen Wang, MB, Li Zhu, MB, Wei Wang, MM, Jun Yang, MM, Fangyuan Chen, MM

Abstract

Rationale: Fulminant type 1 diabetes mellitus (FT1DM) is a new subtype of type 1 diabetes mellitus that was first proposed by the Japanese scholar Imagawa in 2000. In the 2 patient cases described in this study, gastrointestinal symptoms were the first symptoms reported, and the initial blood glucose levels were very high. However, the glycosylated hemoglobin (HbA1c) levels were not very high, the islet β-cell function was almost completely lost in a short time, and the metabolic disorder was severe; the patients' islet β cells demonstrated complete and irreversible functional damage, and the prognosis was poor.

Patient concerns: We report a 37-year-old and 48-year-old male patients. The first patient was addmited with emesis and diarrhea for 2 days and the second patient had stomachache for 8 days, emesis and dyspnea for half an hour before admission. Both patients had no history of hypertension, coronary heart disease, or hyperglycemia.

Diagnosis: Two patients had same scenario: acute onset, hyperglycemia, ketoacidosis, β cell function deficiency, and HbA1c <8.5%.

Interventions: After admission, the administration of adequate liquid infusion, the intravenous injection of regular insulin to reduce the blood glucose levels, and the correction of electrolyte disturbance and acid-base imbalance were conducted.

Outcomes: Subsequently, the blood glucose level of the patients was gradually reduced, the acidosis was corrected, and the disease conditions gradually stabilized. For both patients, the long-term insulin replacement therapy of "insulin aspart plus insulin glargine" was selected.

Lessons: FT1DM is a new subtype of type 1 diabetes mellitus. The onset of this disease is rapid, and the function of islet β cells is almost completely lost in a short time period. This metabolic disorder is severe, and the clinical manifestations are nonspecific. Unless a timely and accurate diagnosis is made, and patients receive prompt treatment, it is difficult to control the disease and the risk of death is high.

Abbreviations: DKA = diabetic ketoacidosis, FT1DM = fulminant type 1 diabetes mellitus, HbA1c = glycosylated hemoglobin.

Keywords: blood glucose, c peptide, diabetes ketoacidosis, glycosylated hemoglobin, type 1 diabetes mellitus

1. Introduction

Fulminant type 1 diabetes mellitus (FT1DM) is a new subtype of type 1 diabetes mellitus. The onset of this disease is rapid, and the function of islet β cells is almost completely lost in a short time period. This metabolic disorder is severe, and the clinical manifestations are nonspecific. Unless a timely and accurate diagnosis is made and patients receive prompt treatment, it is difficult to control the disease, and the risk of death is high. Because FT1DM is relatively rare and case reports are limited, the clinical data of the 2 FT1DM patients treated in the Department of Endocrinology in our hospital were summarized and analyzed, and a literature review was conducted to provide a reference to improve the knowledge level of clinicians diagnosing and treating this class of rare disease with the aim of avoiding misdiagnoses and missed diagnoses.

2. Case descriptions

Case 1: a 37-year-old male patient was hospitalized in the endocrinology department of our hospital due to emesis and diarrhea for 2 days; no previous hypertension, coronary heart disease, or diabetes history was reported. Furthermore, no hepatitis or tuberculosis history was reported. Moreover, the patient reported that he had no history of trauma surgery, no food and drug allergies, and no family history of diabetes. After admission, a physical examination was conducted: temperature (T), 36.7°C; pulse rate (P), 102 bpm; respiratory rate (R), 18/min; blood pressure (BP) and 100/58 mmHg. The patient was lucid but in low spirits. There was no obvious yellow in the skin and sclera. Clear breathing was heard in both lungs (obvious rhonchus and

Editor: N/A.

WY and JY contributed equally to this article.

This research was supported by the Yichang Scientific Research and Development Project (No. A12-301-23 and No. A18-301-32).

The authors report no conflicts of interest.

Department of Endocrinology, The People's Hospital of China Three Gorges University & The First People's Hospital of Yichang, Yichang, Hubei Province, China.

* Correspondence: Jianming Yang, Department of Endocrinology, The People's Hospital of China Three Gorges University & The First People's Hospital of Yichang, Yichang, Hubei Province, China (e-mail: jimyoung71@163.com).

Medicine (2019) 98:5(e14319)

Received: 17 August 2018 / Received in final form: 2 January 2019 / Accepted: 9 January 2019

http://dx.doi.org/10.1097/MD.0000000000014319

Table 1

Comparison of data before and after treatment in 2 cases.

Case	Urine ketone	WBC (10^9/L) (RV)	Scr (μmol/L) (RV)	K (mmol/L) (RV)	BG (mmol/L) (RV)	PH (arterial blood) (RV)	HbA1c (%) (RV)
Case 1							
BT	3+(–)	27.3 (4–10)	247 (57–97)	6.89 (3.5–5.3)	74.55 (3.3–11.1)	7.13 (7.35–7.45)	6.2 (4–6)
AT	–	5.4	82	4.20	12.38	7.41	
Case 2							
BT	3+	24.3	173	5.80	34.73	7.05	6.1
AT	–	6.8	96	4.13	10.82	7.38	

AT = after treatment, BG = blood glucose, BT = before treatment, HbA1c = glycosylated hemoglobin, K = Serum kalium, PH = Arterial blood gas pH value, RV = Reference Values, Scr = serum creatinine, WBC = white blood cell count.

moist rales were inaudible). The heart rhythm was regular (pathologic murmur was inaudible). The patient presented with a normal abdomen with no obvious tenderness and rebound tenderness; an unaffected liver, spleen and subcostal; no sensitive percussion of either kidney, no hyperactive bowel sounds; and no edema in either of the lower extremities.

After admission, a routine blood examination was immediately conducted: (Table 1), and the patient was diagnosed with diabetic ketoacidosis (DKA). After admission to our department, the relevant examinations were further completed (Table 2). The patient was diagnosed with FT1DM complicated with DKA. After admission, administration of adequate liquid infusion, intravenous injection of regular insulin to reduce blood glucose, and correction of electrolyte disturbance and acid-base imbalance were conducted. Subsequently, the blood glucose level was gradually reduced, acidosis was corrected, and disease conditions gradually stabilized. The relevant examinations and tests were reconducted (Table 1). After the patient was treated with insulin glargine combined with insulin aspart, his blood glucose levels gradually became stable. At discharge, the prescribed blood glucose regulation regimen was as follows: subcutaneous injection of insulin glargine (12 U) before sleep and subcutaneous injection of 4 U, 6 U, and 6 U of insulin aspart before breakfast, lunch, and supper, respectively. The treatment continued after discharge for half year, whereupon relevant examinations and tests were reconducted (Table 2).

Case 2: a 48-year-old male patient was admitted to the ICU of our hospital due to "stomachache for 8 days, accompanied by emesis and dyspnea for half an hour". The patient had received laparoscopic renal cyst excision previously. The patient had no previous history of hypertension, coronary heart disease, or diabetes, and neither did he have a history of hepatitis or tuberculosis. Furthermore, the patent had no family history of diabetes. After admission, a physical examination was conducted: T, 35.9°C; P, 107 bpm; R 36/min; BP, and 150/63 mmHg. The patient presented with orthopnea with heavy breathing sounds in both lungs but inaudible rales. The heart rhythm was regular (no murmur). The patient presented with a normal abdomen with audible borborygmus but with lower left abdomen tenderness and no rebound tenderness. There was no edema in either of the lower extremities.

After admission, the relevant examinations and tests were completed (Table 1). Bedside ultrasonic monitoring indicated that the size of various atrioventricular cavities was not abnormal, a small amount of reflux was present in the mitral valve and tricuspid valve, and the left ventricular diastolic function was reduced but its systolic function was normal. Furthermore, a light fatty liver was present, and the gall bladder demonstrated multiple polyp-like changes, but there were no obvious abnormalities in the pancreas, spleen or either of the kidneys. After admission, adequate fluid infusion was conducted to manage blood glucose, correct acidosis, ensure adequate glucose supply, reduce ketone generation, maintain organ function and maintain homeostasis. After group consultation in our department, the patient was transferred to the other department for treatment. After department referral, the relevant examinations and tests were conducted (Table 2). The patient was diagnosed with FT1DM complicated with DKA. After admission, administration of adequate liquid infusion, intravenous injection of regular insulin for reducing the blood glucose levels, and correction of electrolyte disturbance and acid-base imbalance were conducted. Subsequently, the blood glucose level of the patient was gradually reduced, the acidosis was corrected, and the disease conditions gradually stabilized. The relevant examinations and tests were reconducted (Table 1). At discharge, the subcutaneous injection of insulin glargine (23 U) was prescribed before sleep, and the subcutaneous injection of 8 U, 7 U, and 4 U of insulin aspart were prescribed before breakfast, lunch and supper, respectively. The treatment continued after discharge for half a year, whereupon the relevant examinations and tests were reconducted (Table 2).

3. Ethic statement

Our institutional review board requirements were waived due to the retrospective nature of this study. Informed consent was obtained from the patients for the publication of this case report.

4. Discussion

FT1DM is a special type of type 1 diabetes mellitus that was first proposed by the Japanese scholar Imagawa[1] in 2000. The specific etiology and pathogenesis of FT1DM are unclear and may be related to genetic predisposition, autoimmunity, virus infection, and pregnancy.[2] At present, there are obvious regional and racial differences for FT1DM. According to the available literature reports, this disease is mainly found in the Asian yellow race. The reports of FT1DM are mostly concentrated in the East Asian population. The morbidity is higher in Japan, and reports related to this disease have been increasing in recent years.[3–4] In the included data, both patients denied having a family history of diabetes. FT1DM was first reported by Imagawa and other Japanese scholars. Thus, the analyses of genetic predisposition are mostly based on the Japanese population, and there are no special genotype reports in China and other Asian regions. However, Tanaka et al reported that lymphocyte infiltration was found in the internal and external tissues of the pancreas at autopsy in one case of a dead patient with FT1DM. Therefore, scholars also believe that the immune system is partially involved in the onset of FT1DM.[7] Imagawa et al[1] reported that the vast

Table 2

Comparison of data before and after treatment for half year in 2 cases.

Case	0h (RV)	0.5h (RV)	1h (RV)	2h (RV)	3h (RV)
Case 1					
OGTT, mmol/L					
BT	8.01 (3.9–6.1)	13.34 (7.0–9.4)	19.50 (6.7–10.5)	25.43 (3.9–7.8)	25.62 (3.5–5.6)
Insulin, μU/mL					
BT	4.1 (2.6–24.9)	1.86	1.58	1.04	0.808
AT	3.24	4.25	3.27	2.94	2.68
C peptoide, ng/mL					
BT	<0.010 (1.1–4.4)	<0.010	<0.010	<0.010	<0.010
AT	<0.010	<0.010	<0.010	<0.010	<0.010
IAA					
BT	– (–)				
AT	–				
ICA					
BT	– (–)				
AT	–				
GAD					
BT	– (–)				
AT	–				
Case 2					
OGTT, mmol/L					
BT	19.31	22.86	27.95	32.99	31.29
Insulin, μU/mL					
BT	<0.200 (2.6–24.9)	<0.200	<0.200	<0.200	<0.200
AT	<0.20	<0.20	<0.200	<0.200	<0.200
C peptoide, ng/mL					
BT	<0.0100 (1.1–4.4)	<0.010	<0.010	<0.010	<0.010
AT	<0.010	<0.010	<0.010	<0.010	<0.010
IAA					
BT	– (–)				
AT	–				
ICA					
BT	– (–)				
AT	–				
GAD					
BT	– (–)				
AT	–				

AT = after treatment, BT = before treatment, GAD = glutamate decarboxylase antibody, IAA = insulin autoantibody, ICA = islet cell antibody, OGTT = oral glucose tolerance test, RV = Reference Values.

majority of FT1DM cases tested negative for diabetes autoantibodies, but a small number of patients tested positive, although their antibody titer was low. For the 2 included patients, there were gastrointestinal prodromal infection manifestations before FT1DM onset, and it was hypothesized that onset was possibly related to virus infection. Tetsuro et al,[5] utilizing immunohistochemical methods, discovered that retinoic acid-induced protein 1-like helicase (RIG-1) and TOLL-like receptor (TLRS) play an important role in FT1DM islet-β cell damage induced by enterovirus. Tanaka et al[6] reported that enterovirus infection drives chemokine ligand 10 (CXCL10) expression on islet β cells, activating macrophages which attack the islets and further activate cellular immune responses, resulting in irreparable damage to the islet β cells. Pregnant women are the population susceptible to diabetes and are at especially high-risk of developing this disease. In particular, diabetes onset is more common in the last 3 months of pregnancy and in the 2 weeks after delivery.[8] At present, there are no uniform diagnostic criteria for FT1DM, and the diagnosis is usually based on the criteria proposed by Imagawa et al[1] and Hanafusa and Imagawa.[9] If fully compliant with the following 3 criteria, FT1DM may be definitively diagnosed:

(1) Hyperglycemia symptoms appear within 7 days, and diabetes ketosis or ketoacidosis and positive or increased urine and/or serum ketone occur soon after.
(2) At initial diagnosis, the blood glucose level is more than 16.0 mmol/L or 288 mg/dL, and the glycosylated hemoglobin (HbA1c) level is <8.5%.
(3) The urine C-peptide base value is <0.3 ng/mL (<0.10 nmol/L), and the urine C-peptide value after glucagon stimulation is <0.5 ng/mL (or <0.17 nmol/L). If the above 3 criteria are met, the disease can be diagnosed as FT1DM.

If a patient complies with (2) and (3), and the disease course is longer than one week, FT1DM should be highly suspected. In addition, other common clinical characteristics include the following: ① Islet-related autoantibodies are usually negative; ② Onset often occurs within one week, but some patients fall ill within 1 week, and some patients fall ill within 1 to 2 weeks;③ Serum pancreatic enzyme in 98% patients (including amylase, lipase, elastase -1 and phospholipase) rises to different extents, while pancreas ultrasonography or pancreas CT show no obvious abnormality; ④ 70% of patients present fever, upper respiratory infection or gastrointestinal premonitory symptoms;

and ⑤ disease may occur after pregnancy or delivery. In the reported case studies here, both patients complied with the first 3 criteria and presented with gastrointestinal manifestations, but their serum pancreatic enzyme levels were normal. Some studies[10–11] found the pathological changes in the pancreas through autopsy, but these changes were reported to be different from acute pancreatitis. Tang et al[12] previously found that the total amylase of an FT1DM group was higher than that of a T1DM group, but pancreatic enzyme elevation occurred in both FT1DM patients and patients with type 1 diabetes. Therefore, pancreatic enzyme elevation is not a characteristic manifestation of FT1DM patients. Some scholars speculate that the pancreatic enzyme elevation is possibly related to damage to multiple internal organs caused by strong systemic immune or inflammatory responses induced by various causes (such as virus infection).[13] Some researchers believe that pancreatic enzyme elevation is mainly caused by severe metabolic disorders such as acidosis.[14] For FT1DM patients, the onset is rapid, the metabolic disorder is serious, and the disease is critical. If diagnosis and treatment are not timely, the prognosis is poorer, the fluctuation in glucose levels is greater, and the incidence of serious hypoglycemia is higher.[15] Islet β cells of this type of patient are almost always completely damaged. Therefore, these patients must rely on insulin therapy for long lives, and wearing an insulin pump is a better therapeutic regimen. Due to their respective family economies, the 2 patients in this case report used the "base plus meal" regimen after discharge, conducting multiple subcutaneous injections of insulin for blood glucose control, and the blood glucose fluctuation in the follow-up examination of the patients was large.

5. Conclusion

Because patients with FT1DM have no history of diabetes and because the understanding of this new type of diabetes is lacking, FT1DM may be explained by prodromic infection history and be easily misdiagnosed as a digestive tract infection, upper respiratory infection (URI), pancreatitis or myocardial infarction. Therefore, anti-infection treatment may be conducted blindly, for example, by infusing a large amount of sugary liquid. Therefore, the initial manifestations are upper respiratory and gastrointestinal symptoms. For patients who do not show obvious improvement after conventional treatment, blood glucose should be determined in a timely manner. For patients who initially have diabetes and who rapidly present with ketosis or DKA, the disease history should be obtained to evaluate the possibility of FT1DM onset. As FT1DM patients present serious dehydration at the early stage of onset and even have circulatory disturbance or poor subcutaneous absorption of insulin, insulin pump therapy is not recommended, and intravenous infusion of insulin should mainly be administered. At the same time, damages to the function of multiple organs including the heart, liver, kidney and striated muscle should be prevented. After correction of acidosis, the intensive therapy of premeal quick-acting or short-acting insulin combined with moderate- and long-acting insulin before sleep is the most common long-term therapeutic regimen, and few patients use the continuous subcutaneous infusion of insulin. According to the analysis of the data from the 2 patients diagnosed in our hospital and a review of the relevant literature, clinical workers should improve their understanding of FT1DM to effectively treat this type of patient and avoid multiple organ damage in patients. At the same time, follow-up management of blood glucose to delay the occurrence of complications should be conducted.

Author contributions

Conceptualization: wei you, Jianming Yang, Wen Wang.
Data curation: wei you, Wen Wang.
Formal analysis: Jianming Yang, Li Zhu.
Funding acquisition: Jianming Yang.
Investigation: Yanqun Liu, Li Zhu.
Methodology: Wei Wang.
Project administration: Wei Wang.
Resources: Yanqun Liu, Jun Yang.
Software: Jun Yang.
Supervision: Fangyuan Chen.
Validation: Fangyuan Chen.
Visualization: wei you, Fangyuan Chen.
Writing – original draft: wei you.
Writing – review & editing: wei you.

References

[1] Imagawa A, Hanafusa T, Miyagawa I, et al. A novel subtype of type1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. Osaka IDDM Study Group. New Engl J Med 2000;342:301–7.
[2] Fu J, Shi BY. Fulminant type 1 diabetes. Int J Endocrinol Metab 2013;30:185–8.
[3] Fan Y, Lu B, Yang JL. Clinical analysis of six cases of fulminant type 1 diabetes mellitus. Chin J Diabetes 2014;6:545–7.
[4] Yang Y, Xian Y, Wu YC, et al. Fulminant type 1 diabetes: a case report. Chin J Diabetes 2014;4:377–8.
[5] Tetsuro K, Yoriko N, Shoichiro T, et al. Pethological changes in the pancreas of flulminant type1diabetes and slowly progresslive insulin-dependent diabetes mellitus:innate immunity in fulminant type 1 diabetes and SPIDDM. Diabetes Metab Rea Re 2011;27:965–70.
[6] Luo S, Zhang Z, Li X, et al. Fulminant type 1 diabetes: a collaborative clinical cases investigation in China. Acta Diabetol 2013;50:53–9.
[7] Zhou J, Jia WP. The investigation on fulminant type 1 diabetes still continues. Chin J Diabetes Mellitus 2014;6:77–80.
[8] Shimizu I, Makin H, Imagawa A, et al. Clinical and immunogenetic characteristics of fulminant type 1 diabetes associated with pregnancy. Clin Endocrinol Metab 2006;91:471–6.
[9] Hanafusa T, Imagawa A. Fulminant type 1 diabetes a novel clinical entity requiring special attention by all medical practitioners. NatClin Pract Endocrinol Metab 2007;3:36–45.
[10] Tatsushi M, Takashi Y, Rina K, et al. Diagnosis of fulminant type1 diabetes mellitus in an autopsy case with postmortem changes. Leg Med 2011;13:250–3.
[11] Shibasaki S, Imagawa A, Hanafusa T, et al. Fulminanttype 1 diabetes mellitus: a new class of type 1 diabetes[J]. Adv Exp Med Biol 2012;771:20–3.
[12] Tang LH, Zhong X, Du YJ, et al. Comparison in clinical characteristics between fulminant type 1 diabetes and classical type 1 diabetes. Anhui Med Pharm J 2015;19:1099–102.
[13] Tanaka S, Nishida Y, Aida K, et al. Enterovirus infection, CXC chemokine ligand 10 (CXCLl0), and CXCR3 circuit: amechanism of accelerated beta—cell failure in fulminant type 1diabetes. Diabetes 2009;58:2285–91.
[14] Zhou G, Zheng C. Fulminant type1diabetes mellitus: a king of diabetic emergency should not be neglected. J Intern Intensiv Med 2008;14:169–70.
[15] Murase Y, Imagawa A, Hanafusa T, et al. Fulminant type 1 diabetes as a high risk group for diabetic microangiopathy-a nationwide 5-year-study in Japan. Diabetologia 2007;50:531–7.