Lesson of the Week: In the Nick of Time!

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Introduction

Management of diabetes lends itself very well to several classical rules of good clinical practice, an elaboration of which is out of the scope of this short story. However, a couple of these are noteworthy. "Diagnosis should precede treatment as much as possible except for measures of resuscitation" applies to diabetes as to all other conditions. In diabetes, diagnosis and classification are the same. Hence, a serious attempt to classify diabetes at the time of diagnosis or as soon as possible after that is mandatory.[1] In particular, when the patient's characteristics are atypical, or events do not follow the expected course, making assumptions under these circumstances can be very dangerous.[2] In this vignette, an unusual case of diabetes in a young woman is presented and discussed with an analysis of lessons to be learned. The present case report exemplifies several themes of "not expecting the expected," "not making unfounded assumptions," and "ignoring several alert signals."

In the Merriam-Webster dictionary, the idiom "in the nick of time" means just before the last moment when something can be changed or something terrible will happen.[3] Many examples are medical, for instance, "The ambulance arrived in the nick of time" or "The doctor arrived in the nick of time. The patient's life was saved". Hence, the choice of the title is not for fun, but it is perhaps the best description of the case as the story unfolds.

Case Report

The Scene

On a very busy Thursday, the on-call endocrinologist was about to start seeing his patient in the diabetic clinic when the clinic nurse at the door asked if he could accommodate the 9 am patient who arrived late at 11:30 am from another town 265 km. His cellular phone and clinic phone rang at the same time. He pretended to be in control while trying to sort out all these issues simultaneously; he apologized to the patient for the distraction, accepted to see the late patient, rejected the cellular call, and responded to the switchboard calls. This last one proved the most exciting and challenging and would be the subject of this case report. A primary care doctor asked wanted to discuss the case of a young diabetic patient. Taking into consideration the time pressure, only a short discussion was possible. However, after seeing the patient who was in the room, he felt that it was better to see the patient himself on the same day, so he called back the primary care doctor and asked her to send the patient along to be seen as a walk-in patient.

Case History

A 23-year-old native Emirati single female was diagnosed with diabetes 2 years previously (2016). She initially presented with classic osmotic symptoms; her initial hemoglobin A1c (HbA1c) was 10.9%. Despite her young age, typical symptoms, high HbA1c on presentation, and not particularly morbidly obese, she was assumed to have type 2 diabetes mellitus (T2DM). She was started on metformin 1g twice daily. Her blood glucose monitoring values improved reasonably promptly, and her A1c went down to 6.1% within 6 months. She sustained this level throughout 2017. However, her diabetes started to deteriorate, reflected in her self-monitoring of blood glucose (SMBG) values and HbA1c (10.1% in January 2018). Sitagliptin was added in combination with metformin but her HbA1c 3 months later rose to

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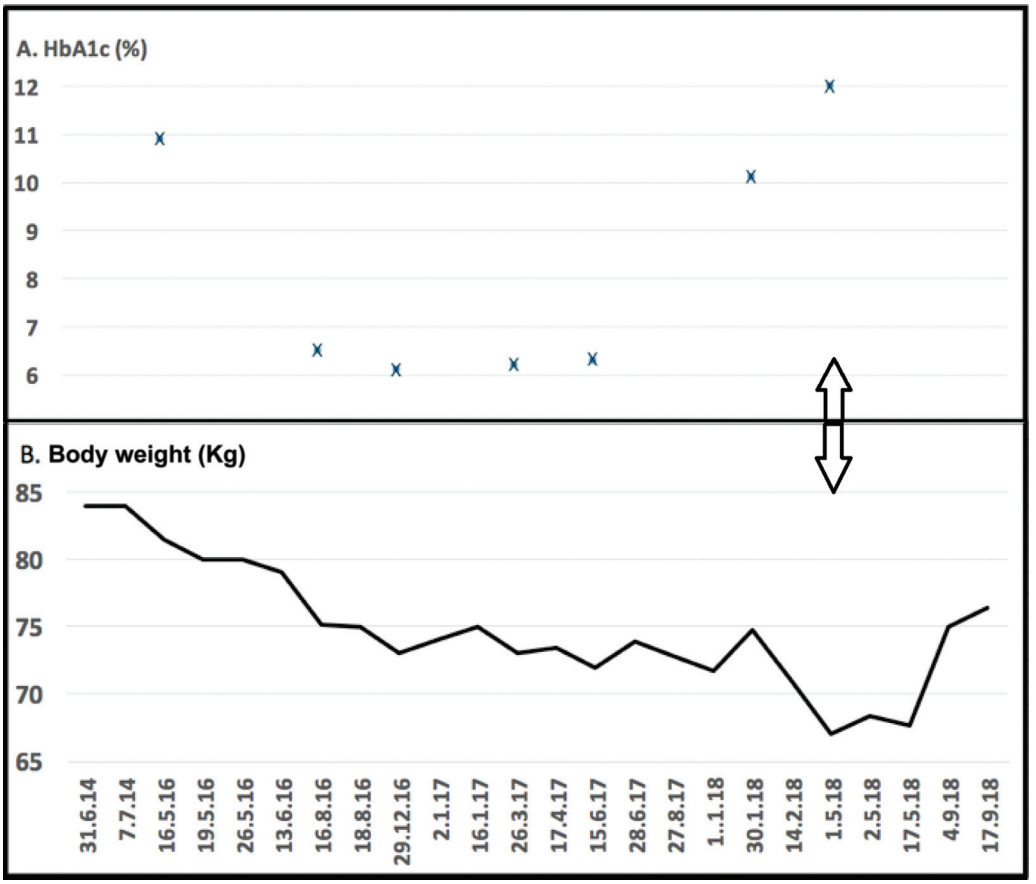

Fig. 1 The time course of the hemoglobin A1c (HbA1c) (**A**) and body weight (**B**) from diagnosis till presentation. The dates on the X-axis apply to both **A** and **B**. Minimal variations in the weight measurements at different care facilities are expected. The blue arrow marks the nadir of the weight corresponding to the initiation of insulin therapy. Note the U-shape of the HbA1c curve and the dissociation between the two curves.

12%. On May 2, 2018, she changed to gliclazide 60 mg daily, dapagliflozin 10 mg daily, and vildagliptin 50 mg combined with metformin 1,000 mg twice daily as she remained reluctant to start insulin. For 1 week before the presentation, she had been feeling vaguely well, tired, and constantly nauseated. She thought it could be a large number of tablets, and she decided to seek help from her physician, who referred her to the endocrine clinic.

She confirmed the history as documented above. No other medical problems were found. There was a family history of T2DM in her mother but no family history of type 1 diabetes mellitus (T1DM), thyroid disease, or other autoimmune diseases. She looked unwell and miserable. She was clinically euthyroid with no goiter, no vitiligo, or alopecia. The unintentional weight loss of more than 10 kg and her HbA1c were noted (►**Fig. 1**). The comparison of her random blood glucose and details of her urinalysis on presentation and now were fascinating (►**Table 1**).

At this stage, it became apparent that the diagnosis must be T1DM rather than T2DM. This was explained to the patient. Investigations to support the diagnosis of T1DM were requested. However, a complete physiological insulin regimen was initiated immediately using insulin degludec (Tresiba, Novo Nordisk, Denmark) 10 U daily subcutaneously and insulin Humalog Lispro (Eli Lilly, United States) 8 U thrice daily. All other medications were discontinued. The exemption from Ramadan fasting for T1DM for newly diagnosed people was explained to the patient. She was seen, and arrangements were made to see her in 1 week jointly with a diabetes educator to review the response and review the results. Investigations confirmed her low bet cell reserve and autoimmune background consistent with T1DM (►**Table 2**). The patient made a speedy recovery regarding blood glucose and weight (►**Fig. 1**).

Final Diagnosis and Assessment

1. T1DM presenting with hyperglycemia and no ketosis—obesity proposed the diagnosis of T2DM.

Table 1 Comparison of serum blood glucose and urinalysis at the initial presentation in 2016 and the current presentation in 2018

Investigations	Initial (2016)	Current (2018)
Serum glucose (mmol/L)	12.3	6.4
Urine specific gravity	1.020	1.020
Urine glucose + (mmol/L)	Negative; 0	4+ 56
Urine ketone + (mmol/L)	Negative; 0	2+ 5.0

The dichotomy between plasma glucose and urinary chemistry reflects the stage of diabetes and the impact of SGLT2 inhibitors.

Table 2 The investigations requested to confirm the diagnosis of T1DM

Investigation	Patient's results	Comments
Urinary ketones	5 mmol/L (2 +)	? Starvation or insulin deficiency
Serum C-peptide	0.32 nmol/L	Low; normal range: 0.37–1.47
Serum insulin level	6.5 milli IU/L	Normal, but does not exclude T1DM
Anti-GAD antibodies	>250 IU/mL	Extremely high, normal <4.9

Abbreviations: Anti-GAD, anti-glutamic acid decarboxylase autoantibodies; T1DM, type 1 diabetes mellitus.
Serology for celiac disease and autoimmune thyroid disease were negative.

2. The initial improvement in glycemia is compatible with a "honeymoon" phenomenon rather than the effect of metformin.
3. The deterioration in blood glucose, weight, and development of ketosis is part of the natural history of diabetes supported by the lack of response to oral antidiabetic medications.
4. The average blood glucose on presentation despite high HbA1c and heavy ketonuria is most likely induced by fasting of Ramadan and the injudicious use of Sodium-Glucose co-Transporter-2 (SGLT2) inhibitor inferred from the heavy glycosuria. It suggests that a "euglycemic diabetic ketoacidosis" was imminent if action was taken.

Discussion

When I received this referral, I merely wanted to advise the doctor to start the patient on basal insulin and send her to the diabetes clinic as soon as possible. Honestly, I initially only offered to see her on a different day. However, after I cleared all the mayhem in the clinic, I thought I could have made a significant error of judgment by leaving the patient in the hands of a doctor who was calling for help and feeling out of her depth. I do not doubt that such a patient must be assessed by an advanced care provider, namely specialist diabetes care team. Perhaps the patient's refusal of insulin therapy could have distracted the physicians from addressing the fundamental question: what type of diabetes does she have? The answer to this question could have empowered their arguments in favor of starting insulin as an essential measure rather than merely one option out of many.[4]

There are a couple of learning opportunities in this case report. Her management deviated from the principles of good practice for a young patient with newly diagnosed diabetes.[4,5] Although admittedly, an attempt was made soon after diagnosis to assess her for ketonuria, no serious effort was made to explore her autoimmune status and beta-cell reserve.[1]Her body mass index of 32 kg/m^2 on presentation could have made the physicians from further investigations. However, obesity is prevalent in children, adolescents, and adults in the Gulf, and she was not exceptionally obese.[6] The family history of T2DM in the mother could have been another red herring. However, when the patient's glycemic control started to deteriorate, the care providers persevered with the same treatment plan, and clinical features of T1DM were not sought or ignored. Indeed, there she was treated as T2DM with no evidence thereof. The risk taken by ineffective therapies such as sulphonylureas, changing her Dipeptidyl-peptidase 4 (DPP4) inhibitor, or even potentially dangerous treatments such as SGLT2 inhibitors in a young patient with T1DM has not been excluded.[7]

T1DM is an autoimmune condition resulting from destroying beta cells in the pancreas. Some patients regain beta cell activity transiently as part of the natural history. This phenomenon is referred to as the 'honeymoon period' or remission of T1DM.[8–10] This is a very likely scenario for our patient. However, this usually occurs after a short period of insulin therapy. During this period, patients manifest improved glycemic control with reduced or no use of insulin or antidiabetic medications.[8–10] Metformin does not cause hypoglycemia, so no need was felt to reduce its dose. However, the improvement was falsely attributed to metformin, although the magnitude reduction in HbA1c from greater than 10% down to 6.3% is not typical for metformin action. The honeymoon period has been more extensively studied in the pediatric population than the adult population, leading to limited information regarding the honeymoon phase available to providers of patients with T1DM diagnosed in adulthood. Known factors predicting remission include high age at onset, male sex, mild initial metabolic derangement, and absence of frank ketoacidosis.[8–10] Some of these do exist in our patients.

Latent autoimmune diabetes in adults (LADA) can be diagnosed by the cooccurrence of three traits, adult-onset non-insulin-requiring diabetes, an islet autoantibody such as glutamic acid decarboxylase autoantibodies or cytoplasmic islet cell autoantibodies, and no need for insulin treatment for several months postdiagnosis.[1,2] In the present patient, over 18 months passed before she presented again with severe hyperglycemia. This suggests that possible diagnosis of LADA. Similar to T1DM, patients with LADA often carry other autoantibodies associated with celiac disease and adrenal and thyroid disorders, but these were not detected in our patients. It is widely agreed that LADA may represent one end of a continuum of autoimmune diabetes, with classic T1DM occupying the other end of the spectrum.[2] Interestingly, the mode of the present patient's unintentional weight loss is not typical of T1DM, that is, it was neither rapid nor associated with poor glycemic control (►**Fig. 1**). However, the magnitude of the weight loss should have alerted the physicians to consider the possibility of T1DM.

Soon after the introduction of this class, the risk of diabetic ketoacidosis (DKA) after initiation of SGLT2 inhibitors has been suggested by several case reports, including cases of T1DM.[11–14] Also, analysis of an extensive database of commercially insured patients[15] suggested that SGLT2

inhibitors were associated with twice the risk of DKA as were DPP4 inhibitors. However, cases of DKA leading to hospitalization were infrequent. It has been recommended that the increased risk of DKA with SGLT2 inhibitors is among the factors to be considered at the time of prescribing and throughout therapy if patients present with symptoms suggestive of DKA. This was not observed in the present case. Risks and benefits were not weighted carefully when SGLT2 inhibitors were prescribed. Two weeks later, the patient was presumably at the prink of euglycemic DKA revealed in her urinary and plasma chemistry, most likely resulting from the natural progression of her diabetes, Ramadan fasting, and SGLT2 inhibitors. Fortunately, the patient was seen and started on insulin in the very nick of time.

Conclusions

The present case highlights the need to consider T1DM and its variants in young patients with atypical attributes and an unusual course of events at the time of diagnosis or soon after that. The label of the type of diabetes should be reviewed if the course changes or when new data become available—injudicious usage of medications that may be ineffective or potentially carry a risk of harm. Finally, from an organizational point of view, the management of complex or unusual cases of diabetes remains the remit of advanced care providers in specialized centers, which should allow a seamless patient flow at the time of their need.

Patient's Consent

The author confirms that the patient provided consent for publication on totally anonymous basis. None of the published details can provide any identification of the reported case.

Author Contributions

Single author responsible for all the aspects of the article.

Compliance with Ethical Principles

Not required for single case reports made on totally anonymous basis.

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Conflict of Interest

None declared.

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