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Severe Insulin Resistance secondary to insulin antibodies induced by Insulin Glargine

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ABSTRACT

Background: Medical literature well-documents insulin resistance related to insulin antibodies (IAs), particularly in patients treated with human insulin or insulin analogs.

Case report: We report a case involving a 25-year-old female patient with a 7-year history of type 1 diabetes mellitus (DM) who required hospital admission due to a poorly controlled glycemic state (HbA1C 10.0%) despite escalating insulin dosages, reaching four units per kilogram per day before admission and concomitant progressive weight loss. The presence of circulating anti-insulin antibodies was identified upon investigation, leading to severe insulin resistance. The patient responded positively to the replacement of insulin glargine with insulin detemir.

Conclusion: This case highlights the importance of recognizing immunological factors, specifically anti-insulin antibodies, as potential contributors to insulin resistance in individuals with type 1 diabetes mellitus.

Keywords: Diabetes mellitus; Detemir; Insulin dosage; Glargine

INTRODUCTION

Insulin resistance (IR) in type 1 diabetes mellitus (T1DM) is usually associated with metabolic factors like obesity or insulin receptor mutations. However, in rare cases, it can be caused by immunological responses, particularly the development of anti-insulin antibodies (IA)[1]. These antibodies can neutralize the effects of

exogenous insulin, rendering it less effective or ineffective. Over the years, insulin therapies have evolved from animal-derived insulins to recombinant human insulin and insulin analogs, significantly reducing IA occurrence[2,3]. However, some patients still develop insulin antibodies, leading to clinically significant insulin resistance, as seen in this case. Here, we report a young woman with T1DM who developed IA-induced insulin resistance, successfully managed by changing her insulin therapy.

CASE REPORT

A 25-year-old female with a 7-year history of type 1 diabetes mellitus (T1DM) presented with poorly controlled blood glucose levels, evidenced by an HbA1C of 10.0%, despite escalating her insulin dosage to 4U/kg/day. She was initially diagnosed with T1DM at age 18 after an episode of diabetic ketoacidosis (DKA). At that time, she was placed on an intensive insulin regimen, including insulin glargine at bedtime and insulin aspart at mealtimes, which initially resulted in adequate glycemic control. Her childhood growth and development were average, with the onset of puberty at age 14.

Her glycemic control had been stable with home self-monitored blood glucose (SMBG) averaging around 8.0 mmol/L. However, there was an abrupt rise in SMBG to around 24 mmol/L starting three months before admission. Frustrated by the lack of improvement, she sought medical help. Despite recommendations to gradually increase her insulin dosage, her condition did not improve, prompting her admission for closer monitoring.

Upon admission, the patient was underweight but fully conscious and oriented. Her vital signs included a blood pressure of 110/60 mmHg, a temperature of 37.0°C and a heart rate of 102 beats per minute. Her body mass index (BMI) was 13.8, significantly below the normal range of 18.5-23. Physical examination revealed no acanthosis nigricans and normal findings in the chest and cardiovascular systems, but there was abdominal tenderness with noticeable loss of abdominal wall fat without organ enlargement.

Laboratory investigations showed a fasting blood glucose level of 24 mmol/L (normal range: 4-5.6 mmol/L; target for T1DM: 5-7 mmol/L) and an HbA1C of 10.0% (target <6.5%) with bicarbonate 19 mmol/L (20-30 mmol/L), anion gap 12 and negative urine ketone. Despite high basal/bolus insulin (70 units of insulin glargine at bedtime and 100 units of insulin aspart at mealtimes), her plasma glucose levels remained persistently elevated, ranging from 28 to 12 mmol/L. (Table 1) provides her blood glucose and electrolyte levels during admission and follow-up and (Table 2) presents her urine analysis results.

Table 1: Shows her Blood Glucose and Electrolyte levels during admission and follow-up.

Date	Sodium 136 ~ 145 mmol/L	Potassium 3.5 ~ 5.1 mmol/L	Chloride 98 ~ 107 mmol/L	Glu R 2.9 ~ 7.8 mmol/L	BUN 2.5 ~ 6.7 mmol/L	Creatinine 50 ~ 98 umol/L	CO2 22 ~ 29 mmol/L
22/02	128	4.6	97	27.5	6.3	64	18
22/02	131	4.6	101	23.3	8	66	19
23/02	131	4	108	25.3	4.3	49	17
23/02	128	4.2	99	23.2	5.1	52	19
24/02	129	4.3	96	21	4.8	57	19
25/02	135	4.3	104	19	3.5	43	18
26/02	134	5.1	103	20	3.5	53	20
27/02	133	4.5	100	24	4.7	51	19
28/02	138	4.3	103	18	5	44	20
1/03	131	4.1	97	27	7.6	50	18
2/03	131	3.6	100	14	5.5	46	21
3/03	132	3.7	99	7	4.8	48	23
4/03	133	3.8	101	5	6.3	47	25
5/03	133	3.8	100	7	6.3	49	24
6/03	134	3.9	102	5	6.2	43	25

Table 2: Displays her Urine Analysis upon Admission.

Test	Result
UA Color	STRAW
UA Spec Grav	1.028
UA pH	5
UA Glucose	>1000
UA Ketones	Trace
UA Blood	Negative
UA Leuk Est	Negative
UA Nitrite	Negative
UA Bili	Negative
UA Urobilinogen	NORMAL
UA Protein	Negative

The patient strictly adhered to dietary therapy throughout her hospital stay and was closely monitored. Further investigations revealed elevated levels of anti-insulin antibodies (IA), confirming the diagnosis of insulin resistance due to IA. (Tables 3-6) summarize her laboratory findings. In response, her insulin regimen was adjusted by switching from insulin glargine to insulin detemir, resulting in a marked improvement in her plasma glucose levels.

Table 3: Endocrine Hormones

Exam. Name	Reference Value	Results
TSH	0.35 ~ 4.94 mIU/L	1.50
Free T4	9.0-19.0 pmol/L	15.8
Insulin	12-150 pmol/L	>21520
C-Peptide	0.9 – 7.10 NG/ML	<0.1
Glucagon	59-177 pg/ml	62
Total 25-OH Vit D	nmol/L	73
PTH	1.6-7.2 pmol/L	3.38

Table 4: Lipid & Calcium

Exam. Name	Reference Value	Results
Cholesterol Total	Desirable: < 5.18 mmol/L	3.5
LDL	<1.8 mmol/L	2.1
HDL	>1.5 mmol/L	0.87
Triglyceride	<=1.70 mmol/L	2
Adj Ca	2.1 ~ 2.55 mmol/L	2.31
Phosphorus	0.74 ~ 1.52 mmol/L	1.13

Table 5: Serology

Exam. Name	Reference Value	Results
Insulin Ab to human insulin IgG	>5000+	<0.4 U/ml
Endomys IgA Ttr	<1:10	<1:10
tTG-IgG	< 20 UNIT	2.6

Table 6: CBC

Test	Result
WBC	5.1
RBC	5.18
Hgb	142
Hct	0.397

MCV	26.8
MCH	27.8
MCHC	356
RDW	14.9
Platelet	347
MPV	7.9

After appropriate titration of insulin detemir, the patient's plasma glucose levels stabilized between 6.5 and 6.8 mmol/L. (Figure 1) illustrates her glucose monitoring during her hospital stay. The patient was subsequently discharged in an improved condition.

Figure 1: Illustrates her glucose monitoring during admission

DISCUSSION

This case illustrates a rare but clinically significant cause of insulin resistance in T1DM due to the development of anti-insulin antibodies. While insulin therapy has evolved from animal-derived insulin to recombinant human insulin and analogs, anti-insulin antibodies (IAs) remain detectable in a substantial percentage of insulin-treated diabetic patients, as highlighted by Fineberg et al., who found that IAs are present in 40-60% of these patients[4]. Although the presence of IAs does not always correlate with poor glycemic control[5], reports since the early 2000s have described cases of insulin resistance linked to IAs[6], leading to severe clinical events, including recurrent diabetic ketoacidosis (DKA)[7] and hypoglycemia[8]. Kronmal et al. further established a strong

correlation between immune-reactive insulin levels and IA levels[9].

In this case, differential diagnoses such as non-compliance, anorexia nervosa and lipodystrophy were considered. However, these were ruled out based on clinical findings and diagnostic tests. Elevated IA levels and a literature review pointed to IA-induced insulin resistance, likely triggered by insulin glargine. Although IA formation in response to glargine is rare, it has been reported. A study by Hattori and Shimatsu found that approximately one-third of patients treated with insulin glargine developed IAs[10]. The structural substitution of asparagine for glycine in the insulin glargine molecule has been hypothesized to increase antibody formation[11]. However, clinically significant insulin resistance due to these antibodies remains rare.

Managing IA-induced insulin resistance is complex and often requires a multifaceted approach. Switching insulin preparations, as done in this case, is a common strategy[12]. The patient responded well to switching from insulin glargine to insulin detemir, an insulin analog with a lower immunogenic profile[12]. Studies have shown insulin detemir is less likely to induce antibody formation than insulin glargine. Other potential therapeutic strategies in severe cases include immunosuppressive therapy, plasmapheresis[13] and even temporary insulin discontinuation[14]. However, immunosuppressive agents, such as corticosteroids, azathioprine or rituximab, pose significant risks, especially in immunocompromised patients. Plasmapheresis, though effective in reducing circulating antibodies, offers only temporary relief and is not a sustainable long-term solution.

Emerging therapies, such as IGF-1 and GLP-1 receptor agonists, have shown promise in reducing insulin dependence in IA-induced insulin resistance[15,16]. However, more research is required to confirm their efficacy and safety in managing this condition.

CONCLUSION

This case highlights the importance of recognizing immunological factors, such as anti-insulin antibodies, in diagnosing insulin resistance in patients with T1DM. As demonstrated in this case, a timely switch in insulin preparations can significantly improve glycemic control. Further research is needed to understand the immunogenicity of different insulin analogs better and to develop more targeted treatments for patients with IA-induced insulin resistance.

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