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Insulin autoimmune syndrome caused by esomeprazole in a Chinese patient

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Insulin autoimmune syndrome (IAS) is a rare cause of spontaneous hypoglycaemia, which is characterized by endogenous hyperinsulinism and high titres of insulin autoantibodies (IAA) despite no prior exposure to exogenous insulin [1]. In Chinese people, it is known to be induced by drugs containing a sulfhydryl group, such as methimazole, captopril, or α -lipoic acid [2]. Here, we report a unique case of IAS after using esomeprazole, a drug not previously known to be associated with hypoglycaemia.

A 58-year-old Chinese man presented to our hospital for recurrent hypoglycaemia episodes including dizziness, shivers, weakness, and sweating over a 2-week period. He started esomeprazole (40 mg/d) to treat gastritis 6 weeks before admission. The patient had no history of diabetes or autoimmune diseases such as hyperthyroidism, systemic lupus erythematosus (SLE), systemic sclerosis, or rheumatoid arthritis. He denied using exogenous insulin and anti-thyroid drugs.

Physical vital signs were as follows: height 172 cm, weight 70 kg, and body mass index (BMI) 23.7 kg/m². He had several episodes of spontaneous hypoglycaemia and the serum insulin level was > 1000 uIU/mL (measured by chemiluminescence assay, using a Roche Elecsys immunoassay analyser, GmbH, Mannheim, Germany). During one such episode, serum glucose was 2.68 mmol/L and the simultaneous serum insulin was 5940 uIU/mL. C-peptide was measured as 3.36 ng/mL and glycated haemoglobin (HbA_{1c}) 5.8% (Tab. 1). Hyperinsulinemia was initially suspected and further confirmed by 75 g oral glucose tolerance test (Tab. 2).

Tests of the insulin-antibody showed positivity for IAA, higher than 50 U/mL, and negativity for glutamic acid decarboxylase antibody (GAD). The results

Table 1. Laboratory data on admission

Parameters	Results	Reference range
Glucose [mmol/L]	2.68	3.9–6.1
Insulin [uIU/mL]	5940	1.9–23.0 (chemiluminescence assay)
C-peptide [ng/mL]	3.36	1.1–4.4
GAD	Negative	Negative
IAA [U/mL]	Positive > 50	Negative (chemiluminescence assay) 0.0–0.40 (radioligand assay)
Haemoglobin [g/L]	132	130–175
ALT [U/L]	15	9–50
AST [U/L]	20	15–40
Creatinine [μ mol/L]	79	44–133
Cortisol [nmol/L]	276.0	171–536
TSH [mIU/L]	3.27	0.27–4.2
HIV	Negative	Negative
ANA	Negative	Negative
dsDNA	Negative	Negative
SSA	Negative	Negative
SSB	Negative	Negative
ANCA	Negative	Negative
LA	Negative	Negative
aCL	Negative	Negative

GAD — decarboxylase antibody; IAA — insulin autoantibody; ALT — alanine aminotransferase; AST — aspartate aminotransferase; TSH — thyroid stimulating hormone; HIV — human immunodeficiency virus; ANA — antinuclear antibody; dsDNA — anti double-stranded DNA; SSA — antiSSA antibody; SSB — antiSSB antibody; ANCA — antineutrophil cytoplasmic antibody; LA — lupus anticoagulant; aCL — anticardiolipin antibodies



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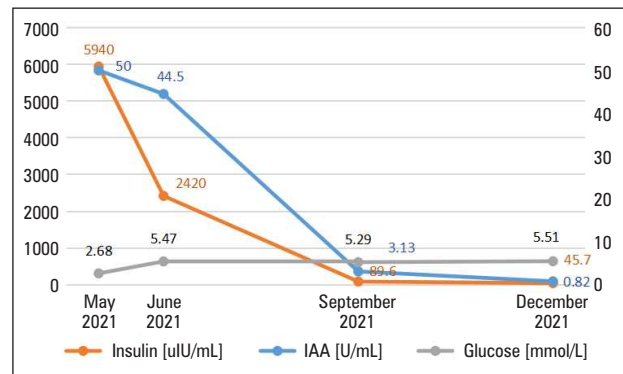
Table 2. Results of oral 75 g glucose tolerance test

	0 min	60 min	120 min	Normal range
Serum glucose [mmol/L]	2.50	10.3	7.6	3.9–6.1
C-peptide [ng/mL]	2.93	8.98	9.83	1.1–4.4
Insulin [uIU/mL]	> 1000	> 1000	>1000	1.9–23.0

of blood routine, liver and renal function, cortisol, thyroid hormones, antinuclear antibody (ANA), anti-double-stranded DNA (dsDNA), rheumatoid factor, and antineutrophil cytoplasmic antibody were normal (Tab. 1). Pancreatic magnetic resonance (MR) scans ruled out insulinoma, which is a common cause of hyperinsulinaemic hypoglycaemia. Based on these findings, the patient was diagnosed with IAS. Esomeprazole was discontinued on the first day after admission, and the patient was advised to have small frequent meals with complex carbohydrates to reduce postprandial hypoglycaemia. After 15 days of treatment, the frequency of hypoglycaemia decreased and the patient was discharged. One month after discharge, the hypoglycaemic episodes dropped to 8 times a week, the IAA level was 44.5 U/mL, and the insulin level was 2420.0 uIU/mL. Three months after discharge, he had no symptomatic hypoglycaemia, with an IAA level of 3.13 U/mL and an insulin level of 89.6 uIU/mL. At the 6-month follow-up, the patient had a significantly lower IAA level (0.82 U/mL) and insulin level (45.7 uIU/mL, Fig. 1).

We report a rare case of esomeprazole-induced IAS. Esomeprazole does not have a sulfhydryl group, but its active metabolite can react covalently with the sulfhydryl group on cysteine residues in the extracellular domain of hydrogen potassium ATPase (H⁺/K⁺-ATPase) [3]. As haptens, sulfhydryl group drugs interact with disulphide bonds in insulin and increase its immunogenicity, changing the structure of endogenous insulin [4]. This triggers an immune response that produces IAA and activates endogenous insulin specific T-helper cells to enhance their immunogenicity. After oral glucose load, more insulin secretion occurs as high postprandial glucose continues to stimulate insulin production by pancreatic β -cells, but IAA binds to these insulin molecules, making them unable to exert their effects [5].

Studies have found that IAS is closely related to human leukocyte antigen (HLA) haplotype. In Asian populations, a strong association between the HLA-DRB1*0406 allele and sulfhydryl group medication side effects has been found. Furthermore, the HLA-DRB1*0403 allele may be involved in genetic susceptibility in Caucasian populations [1]. These alleles

**Figure 1.** Patient blood glucose data during follow-up. IAA — insulin autoantibody

are 10–30 times more prevalent in Asian patients than in Caucasian patients.

In conclusion, IAS should be suspected in patients presenting with hyperinsulinaemic hypoglycaemia, unusually high insulin levels, and moderately raised IAA levels, even when no drugs have been known to be used. Clinical suspicion of IAS can avoid expensive imaging and unnecessary surgery in affected patients.

Authors' contribution

Y.L. — conceptualisation, writing; X.S., Y.W., D.S. — data collection; Z.Z. — investigation; Y.L., Y.L. — formal analysis; Y.L. and Y.L. contributed equally to this work.

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None declared.

Conflict of interest

No conflict of interest.

Ethical statements

The research protocol was approved by Northern Jiangsu People's Hospital (No. 2021ky305). Written informed consent was obtained from the patient.

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