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LETTER TO THE EDITOR

Human serum albumin: Possible cause of insulin autoimmune syndrome

Insulin autoimmune syndrome (IAS), which was first reported by Hirata *et al.*[1], is known to be induced by the use of various kinds of drugs containing the sulfhydryl (SH) group, such as methimazole, or the use of α-lipoic acid[2,3].

Here we report the case of an 80-year-old-woman with IAS that was induced by intravenously dripped albumin preparation accompanied by very severe and unpredictable hypoglycemia. She had been receiving hemodialysis for 6 years as a result of chronic renal failure, and had no past history of diabetes. One day, she vomited substantial amounts of blood, and was urgently hospitalized in the Department of Gastroenterology at Kawasaki Medical School Hospital, Kurashiki, Japan. After emergent endoscopic examination, she was diagnosed as duodenal ulcer perforation. Fortunately, bleeding was well treated with an endoscopic hemostasis. Because of the life-threatening complications, central venous hyperalimentation, blood transfusion, and intravenous injection of antibiotics and albumin preparation were carried out. During such treatment, substantial amounts of non-recombinant albumin (137.5 g in total) were intravenously injected. Fortunately, her physical condition was markedly improved and central venous hyperalimentation was stopped. However, anemia was still observed, probably as a result of chronic renal failure. Nevertheless, almost 30 days after albumin transfusion, severe hypoglycemia was observed. The patient became unconscious, unpredictably accompanied by palpitation and sweating. Her glucose level was as low as 20 mg/dL, and she was referred to the Division of Diabetes, Endocrinology and Metabolism. There were several abnormalities including hypoglycemia, hyperinsulinemia, severe anemia, hypoalbuminemia, renal dysfunction, and increased C-reactive protein and brain natriuretic peptide levels (Table 1). After intravenous glucose injection, the patient became conscious, but she experienced severe hypoglycemia many times. We ruled out the possibility of exogenous administration of insulin or other antidiabetic drugs, insulinoma and adrenal insufficiency, but her anti-insulin antibody level was ≥5,000 nU/mL and her insulin binding ratio was ≥90.0%. The total and free insulin level was 38.0 μIU/mL and 0.14 μIU/mL, respectively. Scatchard analysis showed a low affinity and a high binding capacity ($K_1 = 0.337 \times 10^8$ mol/L, $R_1 = 2.54 \times 10^{-8}$ mol/L, $K_2 = 0.004 \times 10^8$ mol/L, $R_2 = 50.8 \times 10^{-8}$ mol/L). In human leukocyte antigen deoxyribonucleic acid typing, HLA-DRB1*0406 was confirmed, which is known as IAS-susceptibility

Table 1 | Laboratory findings on admission to the Division of Diabetes, Endocrinology and Metabolism

RBC	168 × 10^4/μL	TP	4.5 g/dL	TSH	2.02 μU/mL
Hb	5.7 g/dL	Alb	1.9 g/dL	FT3	2.75 pg/mL
Ht	17.1%	AST	14 U/L	FT4	0.84 ng/dL
WBC	8,610/μL	ALT	7 U/L	ACTH	7.2 pg/mL
Neut	92.0%	γ-GTP	10 U/L	Cortisol	11.3 μg/dL
Lymph	3.0%	T-bil	0.4 mg/dL	DHEA-S	16 μg/dL
Eosi	2.0%	LDH	200 U/L	PRA	0.1 ng/mL/h
Mono	2.0%	ChE	77 U/L	PAC	13.8 pg/mL
Plt	13.6 × 10^4/μL	Cre	5.85 mg/dL	Dopamine	41 pg/mL
		BUN	34 mg/dL	PRL	21.9 ng/mL
Na	132 mEq/L	UA	6.3 mg/dL	GH	1.96 ng/mL
K	3.1 mEq/L			IGF-I	117.3 ng/mL
Cl	99 mEq/L	HbA1c	5.1%		
Ca	7.0 mg/dL	GA	18%	IgG	1,174 mg/dL
IP	4.1 mg/dL	FPG	54 mg/dL	IgA	151.6 mg/dL
		IRI	84.5 μIU/mL	IgM	24.9 mg/dL
CRP	5.81 mg/dL	sCPR	6.3 ng/mL	C3	48.3 mg/dL
				C4	20.3 mg/dL
BNP	803.0 pg/mL	T-chol	86 mg/dL	CH50	34.4 U/mL
				ANA	12.6

ACTH, adrenocorticotropic hormone; Alb, albumin; ALT, alanine transaminase; ANA, antinuclear antibody; AST, aspartate transaminase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; C3, complement 3; C4, complement 4; CH50, complement 50; CRP, C-reactive protein; ChE, cholinesterase; DHEA-S, dehydroepiandrosterone sulfate; Eosi, eosinophil; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; γ-GTP, gamma-glutamyl transferase; GA, glycoalbumin; GH, growth hormone; Hb, hemoglobin, HbA1c, glycated hemoglobin; Ht, hematocrit; IgA, immunoglobulin A; IGF-I, insulin-like growth factor-1; IgG, immunoglobulin G; IgM, immunoglobulin M; IRI, immunoreactive insulin; LDH, lactate dehydrogenase; Lymph, lymphocyte; Mono, monocyte; Neut, neutrophil; PAC, plasma aldosterone concentration; Plt, platelet; PRA, plasma renin activity; PRL, prolactin; RBC, red blood cells; sCPR, serum C-peptide immunoreactivity; T-bil, total bilirubin; T-chol, total cholesterol; TP, total protein; TSH, thyroid-stimulating hormone;UA, uric acid; WBC, white blood cells.

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gene[4]. Based on these findings, we diagnosed this patient as IAS. Next, to examine the reason for the severe anemia, we carried out bone marrow puncture and diagnosed this patient as myelodysplastic syndrome (MDS).

It is well known that insulin autoantibody is produced by the use of drugs containing the SH group[1–3]. In addition, it has recently been shown that albumin has cysteine residue (Cys34), of which the reducing capacity is strong, and that albumin has anti-oxidant effects, as observed with α–lipoic acid[5]. In the present case, there was no other medication that could cause IAS, especially containing the SH group. Furthermore, the patient had never experienced such severe and unpredictable hypoglycemia before the use of albumin preparation. Therefore, we believe that the IAS in this patient was induced by intravenously dripped albumin. Furthermore, as myelodysplastic syndrome is often complicated with various autoimmune diseases, we believe that this patient was vulnerable to immunological abnormality. We did not give any treatment for IAS, such as steroid therapy, but the frequency of hypoglycemia was gradually decreased without using an albumin preparation. This point is also compatible with drug-induced IAS. At the time of transfer, the patient experienced severe midnight hypoglycemia every day, but severe hypoglycemic attack was observed two or three times per week within 3 weeks. After then, overt hypoglycemic attack was not observed.

As albumin preparation is often used in medical practice, especially for the treatment of severe hypoalbuminemia, we should keep in mind that albumin has SH groups with strong reducing capacity and thereby albumin has anti-oxidant effects. Furthermore, we should be aware of the possibility that albumin preparation induces IAS, especially in patients who are receiving hemodialysis and/or who are vulnerable to immunological abnormality.

DISCLOSURE

The authors declare no conflict of interest.

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