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LETTER TO THE EDITOR

Onset of type 1 diabetes mellitus and heparin-induced thrombocytopenia in a patient with Basedow's disease and idiopathic thrombocytopenic purpura: Novel combination as autoimmune polyglandular syndrome

Type 1 diabetes mellitus is often complicated with some other autoimmune disorders, and the complication of various autoimmune disorders is known as autoimmune polyglandular syndrome (APS)[1,2]. We experienced a patient who developed type 1 diabetes mellitus and heparin-induced thrombocytopenia (HIT) in addition to Basedow's disease and idiopathic thrombocytopenic purpura (ITP). To our best knowledge, this is the first report showing that HIT is observed in APS patients.

When the patient was aged 65 years, she had Basedow's disease. She was treated with thiamazole (30 mg) or propylthiouracil (300 mg), but agranulocytosis was induced after starting the treatment with propylthiouracil. Therefore, she had radioactive iodine treatment (^{131}I 6 mCi). After the treatment, she had secondary hypothyroidism and started taking levothyroxine (50 μg/day). During the treatment, her platelets were decreased to $40 \times 10^3/\mu L$ and platelet-associated immunoglobulin G was positive. She was diagnosed with ITP, which was well treated with prednisolone. After starting the treatment with prednisolone, the platelet-associated immunoglobulin G level was decreased and after several months it was finally normalized.

When she was aged 77 years, she felt thirst, general fatigue, nausea and appetite loss. As such symptoms persisted for several months, she was hospitalized at Kawasaki Medical School Hospital, Kurashiki, Japan. Her height and bodyweight were 150.0 cm and 37.2 kg, respectively. Blood pressure and heart rate were 153/96 mmHg and 140 b.p.m, respectively. Body temperature was 37.2°C, blood glucose level was 737 mg/dL, glycated hemoglobin was 10.3% and glycoalbumin was 48.4%. Insulin secretion was markedly suppressed: immunoreactive insulin was <1.0 μIU/mL and serum C-reactive protein was 0.3 ng/mL. Ketone bodies were markedly increased: 3-hydroxybutyric acid was 11,310 μmol/L and acetoacetic acid was 3,850 μmol/L. In an arterial blood gas test, the pH was 7.21. The value of anti-glutamic acid decarboxylase antibody in this patient was ≤1.3U/mL. However, considered from the onset speed of diabetes and depletion of insulin secretion, we diagnosed this patient with acute-onset type 1 diabetes mellitus and diabetic ketoacidosis. In addition, as various auto-antibodies (anti-glutamic acid decarboxylase antibody, anti-islet antigen-2 antibody, islet cell autoantibody and zinc transporter 8) were negative, we diagnosed this patients with type 1B diabetes mellitus. Renal dysfunction, probably as a result of dehydration, was observed: creatinine was 1.68 mg/dL and blood urea nitrogen was 73 mg/dL. Liver function and other endocrine hormone levels were within the normal range. As she had various autoimmune disorders, such as Basedow's disease, ITP and type 1 diabetes mellitus, we diagnosed her with APS type 3. Human leukocyte antigen typing was as follows: DRB1, *04:05, *08:03; DQB1 04:01, 06:01, which were also compatible with type 1 diabetes mellitus and APS type 3[3]. Hyperglycemia and ketoacidosis gradually recovered with fluid replacement and insulin therapy.

As the patient had atrial fibrillation, we gave her unfractionated heparin (5,000 U/day for 3 days). After that, her platelets markedly decreased from $90 \times 10^3/\mu L$ to $40 \times 10^3/\mu L$ within several days. In addition, anti-HIT antibody was positive. After starting the treatment with heparin, purpura was observed in both legs. Therefore, we stopped heparin, and after then the purpura disappeared. Furthermore, this patient had a past history of stroke. Although the patient had completely recovered from stroke without any sequela, it seemed that this stroke was also related to HIT. In addition, the 4Ts score in this patient was 4 points (thrombocytopenia 2 points, timing of platelet count fall 0 points, thrombosis or other sequela 1 point, other causes for thrombocytopenia 1 point). We finally diagnosed the patient with HIT based on its diagnosis criteria. HIT is a serious side-effect of heparin, and is observed in a small percentage of patients treated with heparin. HIT leads to the development of thromboembolism and is a life-threating disease without appropriate therapy, such as stopping heparin. Anti-HIT antibody is an antibody against the complex of platelet factor 4 and heparin, which is thought to lead to the onset of

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HIT. Very recently, the HLA-DRB3 *01:01 allele was identified as a potential risk factor for HIT in people of European ancestry[4]. Although we did not check this allele, this allele might have been associated with the onset of HIT in this patient. To the best of our knowledge, this is the first report showing a case of HIT together with APS. As it is difficult to diagnose HIT without using heparin, it is likely that the presence of HIT has been missed in patients with APS. ITP is an autoimmune thrombocytopenia that is caused by an antibody reaction with platelet-associated antigen glycoprotein IIb/IIIa or Ib/IX complex on the surface of the platelet membrane. HIT is also an immune-associated disorder. Anti-HIT antibody is an antibody against the complex of platelet factor 4 and heparin. Although there is a difference in the kind of antigen in such immune responses between both diseases, it is common in the etiology, especially from the view of autoimmune reaction.

Taken together, we should keep in mind the possibility that various and unknown autoimmune disorders are induced in patients with APS. In addition, we should be careful of the development of HIT when we use heparin in patients with APS.

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