Acquired Hemophilia A Associated with Dipeptidyl Peptidase-4 Inhibitors for the Treatment of Type 2 Diabetes Mellitus: A Single-Center Case Series in Japan

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ABSTRACT

Herein we describe four patients with acquired hemophilia A (AHA) caused by factor VIII (FVIII) inhibitor and histories of dipeptidyl peptidase-4 inhibitor (DPP4-I) treatment for diabetes mellitus (DM). Drug exposure can cause a breakdown of immune tolerance to FVIII associated with CD4 T cells, resulting in the induction of autoantibodies against FVIII. In patient 1 in the present series, FVIII inhibitor disappeared after DPP4-I treatment. The DPP4-I treatment was stopped faster in patient 1 than it was in patient 2, whose FVIII inhibitor titer was higher than patient 1’s. Two patients died: patient 3 due to brain infarction after recurrence associated with the development of sigmoid colon rupture, and patient 4 due to multiple organ failure associated with Clostridium difficile colitis. DPP4-I treatment may create an ideal environment for the induction of new antibodies and AHA onset associated with tumor necrosis factor-α reduction. These are the first reported cases of the potential development and/or prolonging of AHA after DPP4-I treatment for DM, and they suggest possible disease associations.

Keywords: Acquired hemophilia A; Diabetes mellitus; Dipeptidyl peptidase-4 inhibitors; Tumor necrosis factor-α

INTRODUCTION

Acquired hemophilia A (AHA) is caused by autoantibodies that inhibit factor VIII (FVIII) activity and lead to life-threatening hemorrhage [1]. It can be associated with autoimmune conditions, underlying malignancies, or drug allergies, but no specific cause is identified in an estimated 50% of patients [2, 3]. Diabetes mellitus (DM) is a highly prevalent condition diagnosed via well-established criteria, but the main causes of DM have not been well characterized. Genetics, environmental factors, poor diet, obesity, medications, infections, and a sedentary lifestyle are variably associated with DM in some cases [4]. Dipeptidyl peptidase-4 inhibitors (DPP4-Is) are relatively new oral antidiabetic drugs that have various effects on...
the immune system, including plasma tumor necrosis factor (TNF)-α reduction [5] and the inhibition of pathogenic T cells [6]. In patients with type 2 DM, DDP4-I has reportedly reduced the risk of rheumatoid arthritis [7] but increased the risk of inflammatory bowel disease [8]. Currently, there are no reports on associations between AHA and DDP4-I administration in type 2 DM patients.

CASES

Herein we describe four patients with AHA and histories of DDP4-I treatment for DM (Table 1). Two were male and two were female, and their ages ranged from 61 to 84 years. Activated partial thromboplastin times (APTTs) ranged from 71.1 to 115.5 s (normal range = 21–33 s), which is markedly prolonged (see figures in the Electronic supplementary material, ESM). Anemia progressed to 5.2–6.0 g/dL of hemoglobin (normal range = 13.5–17.0 g/dL), necessitating red blood cell transfusions of 16–24 units. FVIII activity levels were <1% in all cases (normal range = 60–150%), and FVIII inhibitor titers ranged from 14 to 100 Bethesda units/mL (normal titer = 0 Bethesda units/mL). Serum glycoprotein levels ranged from 15 to 20% (normal range = 12.4–16.3%) and all patients received a DDP4-I (sitagliptin phosphate hydrate in three cases and alogliptin benzonate in one case). Due to limitations on the use of FVIII imposed by the Japanese health insurance system, AHA patients can receive recombinant activated factor VII but not FVIII. Therefore, recombinant activated factor VII was administered to all four patients (three at diagnosis, one at recurrence) to control bleeding after bleeding diathesis, an isolated prolonged APTT, detection of low coagulation factor activity in mixing studies, or failure to exhibit APTT normalization after mixing of the patient’s serum with a nonhemophiliac donor’s serum. Mixing studies are performed to determine the presence of factor deficiency or factor inhibitors, or the presence of nonspecific inhibitors such as lupus anticoagulants, if APTT is prolonged in the specimen. With regard to immunological treatments for the eradication of inhibitors, prednisolone was administered to all four patients, cyclophosphamide was administered to patient 1, and rituximab was administered to patient 4. In patient 1, FVIII inhibitor disappeared after DPP4-I treatment. The DPP4-I treatment was stopped faster in patient 1 than it was in patient 2, whose FVIII inhibitor titer was higher than patient 1’s. In patient 2, FVIII inhibitor decreased from 27 Bethesda units/mL to 1 Bethesda unit/mL with the use of recombinant activated factor VII and the administration of prednisolone (daily dose of 1 mg/kg/day), and hemostasis was achieved. Prednisolone was tapered off and the FVIII inhibitor titer was negative after approximately 18 months. Two patients died: patient 3 due to brain infarction after recurrence associated with the development of sigmoid colon rupture, and patient 4 due to multiple organ failure associated with Clostridium difficile colitis. The present case series was retrospective and did not involve any experimental intervention. Accordingly, no institutional ethical approval was required or sought. Informed consent was obtained from all individual participants included in the study.

DISCUSSION

AHA is characterized by the presence of an autoimmune mechanism that either alone or accompanied by autoimmune disease, aging, or drug exposure causes a breakdown in immune tolerance to FVIII autoantibodies involving CD4 T cells and results in the development of autoantibodies against FVIII. DPP4-I may be responsible for the impaired proliferative response of CD4 T cells to antigens and mitogens observed in hemophiliacs [9]. Although immunosuppressive treatment should eradicate inhibitors as soon as a diagnosis of AHA is confirmed, immunosuppression is associated with significant side effects including sepsis and colitis in older DM patients. TNF-α inhibitors may activate autoimmune reactions and the production of autoantibodies, and in 2/4 of the present cases AHA may have been induced by TNF-α inhibitors, as has previously been reported [10, 11]. DPP4-I treatment may create an ideal environment for new antibody formation.
### Table 1 Patient characteristics and treatment outcomes

| Case | Age | Sex | Underlying conditions (duration of diseases) | Site of bleeding | Minimal Hb (g/dL) | RBC transfusions (total amount in units) | Glycoprotein (%) | FVIII inhibitor titer (BU/mL) |
|------|-----|-----|---------------------------------------------|-----------------|-----------------|------------------------------------------|-----------------|------------------------|
|      |     |     |                                             |                 |                 | At diagnosis | At recurrence | At diagnosis | At recurrence |
| 1    | 61  | M   | DM (5 years), HT (5 years), OMI (5 years)   | Subcutaneous    | 5.2             | 16           | 15            | –           | 35          | –           |
| 2    | 70  | M   | DM (2 months)                               | Subcutaneous, intramuscular | 6               | 16           | 16            | –           | 27          | –           |
| 3    | 71  | F   | DM (1 years 6 months), CKD (1.5 years)      | Subcutaneous    | 5.4             | 16           | 18            | 14          | 14          | 3           |
| 4    | 84  | F   | DM (5 years)                                | Subcutaneous    | 6               | 24           | 20            | 24          | 100         | 20          |

| Case | Total dose of rFVIIa administered (mg) | Immunological treatments (dose) | Duration of PSL | Anti-DM treatment At diagnosis (dose, duration of treatment) | Anti-DM treatment After diagnosis | Outcome | OS (days) | Cause of death |
|------|-------------------------------------|-------------------------------|-----------------|-------------------------------------------------------------|-------------------------------|---------|-----------|----------------|
| 1    | 160                                 | PSL (1 mg/kg) + CPA (50 mg/days) | 4 months        | Sitagliptin phosphate hydrate (50 mg/days, 5 years)         | Insulin → none               | Surviving without recurrence | 3225    | None      |
| 2    | 90                                  | PSL (1 mg/kg)                 | 19 months       | Sitagliptin phosphate hydrate (50 mg/days, 2 months)        | Sitagliptin phosphate hydrate | Surviving without recurrence | 687     | None      |
| 3    | 120                                 | PSL (1 mg/kg)                 | Until death (21 months) | Alogliptin benzonate (6.25 mg/days, 1 year 6 months)       | Alogliptin benzonate + insulin → liraglutide | Death after recurrence | 158     | Brain infarction |
| 4    | 400                                 | PSL (1 mg/kg) + RIT (375 mg/m² × 3) | Until death (1 months) | Sitagliptin (25 mg, 5 years) phosphate hydrate              | Sitagliptin phosphate hydrate + insulin | Death after recurrence | 30      | Multiple organ failure |

Hb hemoglobin, RBC red blood cell, FVIII factor VIII, BU Bethesda units, M male, F female, DM diabetes mellitus, HT hypertension, OMI old myocardial infarction, CKD chronic kidney disease, PSL prednisolone, CPA cyclophosphamide, rFVIIa activated recombinant factor VII, d days, RIT rituximab, OS overall survival
and AHA onset associated with TNF-α reduction.

Cases of the onset of AHA associated with hypersensitivity to drugs such as antibiotics (penicillin, sulfonamides, and chloramphenicol), anticonvulsants (phenytoin), antihypertensive agents (methyldopa), and vaccination have been reported [12]. As increasing titers of FVIII inhibitors due to drug hypersensitivity disappear after termination of the responsible drug [13], immunological treatments to eradicate FVIII autoantibodies may not be required in patients who experience drug hypersensitivity.

While the observations in the present case series are suggestive of associations, there are substantial limitations to the conclusions that can be drawn from it. The study was a retrospective case series that only included four patients, and low patient numbers can hinder the recognition of small differences in outcomes. Notwithstanding this, the results are concordant with an association between AHA and DPP4-I. Current AHA therapeutic strategies in DM patients who have undergone DDP4-I administration may not improve outcomes in patients who are resistant to immunological treatments to eradicate FVIII autoantibodies. Because the analysis of various comorbidities in DM patients was beyond the scope of the current study, and the best immunological treatments to use in DM patients with AHA remain uncertain, carefully designed prospective trials are essential to determine the contribution of immunological treatments to the successful eradication of FVIII autoantibodies. Another consideration that limits the interpretation of the present study is a lack of knowledge pertaining to predisposing factors for AHA. Lastly, a longer follow-up period may be needed to better evaluate eligibility criteria for DDP4-I administration in DM patients with AHA.

In conclusion, data derived from the present case series suggest that DDP4-I treatment for DM may induce and/or prolong AHA. Prospective observations and studies with larger numbers of patients are needed to improve the safety and efficacy of DDP4-I treatment in DM patients with AHA.

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Compliance with Ethics Guidelines. The present case series was retrospective and did not involve any experimental intervention. Accordingly, no institutional ethical approval was required or sought. Informed consent was obtained from all individual participants included in the study.

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