Insulin Autoimmune Syndrome Accompanied by Multiple Myeloma

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Abstract

In 1981, a 48-year old man was diagnosed with insulin autoimmune syndrome. In 2005, he experienced a substantial increase in his monoclonal insulin antibody levels; in 2006 and 2007, serum monoclonal gammopathy and an 11% marrow plasmacyte ratio were confirmed. In 2012, asymptomatic multiple myeloma was diagnosed based on an increased γ-globulin fraction and serum M-protein (IgG) levels. The insulin antibody binding rate was 75.4% in 2005 and 78.8% in 2012. In 2012, he was hospitalized for ileus and died. Autopsy identified multiple myeloma and no endocrinological tumors in the pancreas.

Key words: insulin autoimmune syndrome, multiple myeloma, hypoglycemia, MGUS

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Introduction

In 2009, we first reported a rare case of insulin autoimmune syndrome (IAS) induced by insulin monoclonal antibodies (1). Since then, we have observed the subsequent process of the repeated development of hypoglycemia accompanied by multiple myeloma in this patient. M-protein seen in multiple myeloma is an abnormal globulin that is not involved in the immune response. Currently, few reports exist on cases of multiple myeloma complicated by IAS or on the significance of M-protein in such cases. We herein report on the follow-up of our case, with additional histopathological findings obtained based on the findings of an autopsy of this patient.

Case Report

Case: An 80-year-old man presented to our hospital with chief complaints of weakness, shiver, and sweating at night, early mornings, and before meals.

Medical history: He had experienced cervical spondylotic myelopathy and lumbar spinal canal stenosis at 69 years of age and bladder cancer at 78 years of age.

Family history: Unremarkable

Weight history: He weighed 45 kg at 20 years of age, with a maximum weight of 72 kg at 40 years of age.

Drinking/smoking: None

History of present illness: In 1981, at 48 years of age, the patient was transported to a local hospital owing to sudden hypoglycemia. IAS was diagnosed at this hospital, as he had no history of insulin or antithyroid agent use. Subsequently, hypoglycemic symptoms with mild episodes of impaired consciousness occurred every few days late at night, early morning, and/or before meals, although the symptoms could normally be managed by supplementary food, etc. At 61 years of age, he started receiving 0.9 mg/day of voglibose; however, there was no pre- to post-dose change in the symptoms. Subsequently, hypoglycemia frequently occurred, ranging from mild symptoms to delirium and severe symptoms requiring emergency hospitalization. He was transferred to our hospital in 2004, and thereafter underwent intensive examinations as an inpatient in 2005.

Physical findings: His height was 154 cm; weight, 46 kg; body mass index, 19.4 kg/m²; blood pressure, 108/60 mmHg; and pulse rate, 54/min. He was conscious, with no conjunctival anemia, no jaundice, a normal vesicular sound upon breathing, a clear heart sound without any noise, a flat abdomen with no abnormality on palpation, and no edema in the legs.

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Examination results: 1) General examination and immunoendocrinological examination (Table 1) at the time of admission - While the fasting blood glucose level was 76 mg/dL and the glycated hemoglobin (HbA1c) was 5.9% (40.9 mmol/mol), high values were observed for the immunoreactive total insulin (t-IRI) level (114.6 μU/mL), blood C peptide level (2.7 ng/mL), insulin-antibody binding rate (78.3%), and proinsulin level (1,000 pmol/L). The glutamic acid decarboxylase antibody and anti-insulin receptor antibody tests were negative. A human leukocyte antigen examination did not identify DRB1*0406, which is frequently found in IAS. 2) A Scatchard analysis (antigen : human insulin) (Fig. 1): According to the Scatchard analysis, the insulin antibody was monoclonal; the affinity constant (k₁) was as low as 0.00071×10⁻⁸ M⁻¹ and the number of binding sites (b₁) was as high as 420×10⁻⁸ M⁻¹, indicating that the insulin antibody had a low affinity and a high binding capacity. Unlike the insulin antibodies (k₁ ≈ 1.0×10⁻⁸ M⁻¹) observed after insulin administration, the patient’s antibodies showed a low affinity and a high binding capacity, which are characteristic of IAS. 3) Other examinations, including abdominal contrast-enhanced computed tomography and abdominal echography, did not reveal any abnormalities in the pancreas.

Progression during and after the hospital stay: IAS was also diagnosed at our hospital because of the presence of an insulin antibody despite no previous history of insulin use, the abnormally high levels of blood t-IRI, and the occurrence of hypoglycemia. Even during the hospital stay, hypoglycemia would usually develop between midnight and early morning and before supper every day; therefore, 300 mg/day of acarbose and 30 mg/day of prednisolone (PSL) were initiated. As the hypoglycemia consequently disappeared, the PSL dose was reduced to 20 mg/day and the patient was discharged from the hospital. PSL was gradually reduced to 10 mg for suppression of hypoglycemia and continuously used for 1 year from 2005. As a result, the incidence of hypoglycemia decreased, except for the early morning events. According to the results of the Scatchard analysis in 2006, the number of binding sites was reduced, and the production

Table 1. Laboratory Data on Admission.

| TP         | 6.7g/dL | T-Chol      | 204mg/dL | GAD Ab   | <1.3U/mL |
|------------|---------|-------------|----------|----------|----------|
| Albumin    | 59.1%   | TG          | 211mg/dL | insulin receptor Ab | (-)     |
| α₁-globulin| 2.7%    | CRP         | 0.07mg/dL| (-)      | Urinalysis|
| α₂-globulin| 9.7%    | HBs-Ag      | (-)      | (-)      | sugar    |
| β-globulin | 8.3%    | HCV-Ab      | (-)      | (-)      | protein  |
| γ-globulin | 20.2%   | WBC         | 6,260μL  | (+)      | Microsome test |
| T-Bil      | 1.1mg/dL| RBC         | 440×10⁶μL| ketone bodies | (-)     |
| AST        | 38IU/L  | Hb          | 13.7g/dL | (+)      | DRB1*0901 |
| ALT        | 13IU/L  | Ht          | 41.9%    | TSH      | 0.6μU/mL |
| LDH        | 185IU/L | MCV         | 95μl     | FT4      | 1.7ng/mL |
| ALP        | 174IU/L | MCH         | 31.1μg   | Thyroid test | <100 |
| γ-GTP      | 15IU/L  | MCHC        | 32.7%    | Micronuclear Ab | (-) |
| ChE        | 4230IU/L| Ph          | 22.5×10⁶μL| (-)      |
| BUN        | 17.8mg/dL|            |          |          |          |
| Cr         | 0.62mg/dL|            |          |          | DRB1*1101|
| IgM        | 63mg/dL | HbA1C       | 5.9%(40.9mmol/mol) | DRB1*0901 |
| IgG        | 1,144mg/dL| IRI       | 114.6μg/mL| DQA1*0302 |
| IgA        | 109mg/dL| CPR         | 2.7μg/mL | DQA1*0505 |
| Na         | 144mEq/L| insulin antibody | 75.4μe | DQB1*0301 |
| K          | 4.5mEq/L| proinsulin  | 1000.0pmol/L| DQB1*0303 |
| CL         | 106mEq/L| urinary CPR | 55.2μg/day| (-)      |
of insulin antibody was suppressed by PSL (Fig. 1). In 2006, the blood IgG was within the normal range; however, IgG-κ-type M-protein was present. In 2007, the marrow plasma ratio was 11%. Thereafter, early-morning hypoglycemia continuously occurred, and supplementary food, voglibose, and PSL were administered for continuous treatment. The marrow plasmacyte ratio gradually increased from 11% in 2007 to 12.8% in 2012 and to 20.6% in 2013. The blood IgG exceeded the normal level in 2011 and became higher than 3 g/dL in 2012 (Table 2). At this time, bone marrow aspirates were analyzed by flow cytometry regarding the plasma cells identified by CD38. The plasma cells comprised CD138+, CD19-, CD45-, CD49e-, and MPC-1+/− which were compatible with the myeloma cells of immature and intermediate types (Table 3). Within the detectable range, no abnormalities were found in terms of the chromosomes, whole-body bone surveillance, blood calcium, or β2-microglobulin. Based on the diagnostic standards of the International Myeloma Working Group (1), asymptomatic myeloma was diagnosed. The insulin antibody binding rate remained high at 78.8% in 2012. At this time, according to the Scatchard analysis, the patient’s insulin antibody was continuously found to be a low-affinity monoclonal antibody with 92,200×10⁻⁸ M binding sites, which was increased 280-fold compared to the level in 2006 (Fig. 2). The classes of immunoglobulins of the insulin antibody were not deter-

Table 2. Developmental Table.

| Year | 2005 | 2006 | 2007 | 2008 | 2011 | 2012 | 2013 |
|------|------|------|------|------|------|------|------|
| Marrow plasmacytic % | 11.0 | 12.8 | 20.6 |
| IgG mg/dL | 1,144 | 1,012 | 1,380 | 1,214 | 2,444 | 3,879 | 3,760 |
| Insulin antibody combination rate % | 75.4 | 83.2 | 74.2 | 78.8 |
| Blood sugar level pre test mg/dL | 75 | 75 | 55 | 51 | 41 |
| 30 min | 182 | 157 | 141 | 163 | 82 |
| 60 min | 224 | 207 | 219 | 238 | 138 |
| 120 min | 305 | 303 | 307 | 243 | 242 |
| IRI pre test μU/mL | 98.8 | 77.7 | 102.1 | 137.1 | 863.0 |
| 30 min | 194.9 | 173.1 | 225.9 | 221.7 | 772.0 |
| 60 min | 264.4 | 236.4 | 896.0 | 693.0 | 790.0 |
| 120 min | 974.0 | 938.0 | 1,387.0 | 1,359.0 | 955.0 |
| CPR pre test mg/dL | 4.4 | 2.4 | 2.0 | 3.3 | 4.3 |
| 30 min | 6.0 | 5.0 | 5.4 | 5.9 | 4.1 |
| 60 min | 9.3 | 5.8 | 9.1 | 8.3 | 4.9 |
| 120 min | 10.4 | 11.1 | 11.3 | 12.9 | 7.1 |

Table 3. Flow Cytometry of the Bone Marrow Aspirates.

| 38 (CD56×19) | 1.4% |
| 56−/19− | 0.1% |
| 56−/19− | 95.1% |
| 56−/19− | 3.3% |
| CD38 positive | 10.0% |
| preB Cell | 0.1% |
| Mature B Cell | 0.1% |
| 38 (MPC1×45) | 59.0% |
| MPC1−/45− | 2.3% |
| MPC1−/45− | 38.2% |
| MPC1−/45− | 0.4% |
| 38 (CD49e×45) | 2.6% |
| 49e−/45− | 1.1% |
| 49e−/45− | 93.9% |
| 49e−/45− | 2.4% |
| 38 (CD138) | 97.8% |
| 38 (CD13) | 2.7% |
| 38 (CD20) | 62.9% |

Figure 2. A Scatchard analysis of the insulinautoantibodies in 2012.
mired. Regarding the evolution of the HbA1c and fasting blood t-IRI, the HbA1c level increased from 6.0% in 2005 to 8.0% in 2012 (Fig. 3), and the blood t-IRI substantially increased from 98.8 μU/mL to 863.0 μU/mL (Table 2). In September 2012, fever, vomiting, and constipation developed and the patient was hospitalized for suspected ileus. The treatment of ileus was successful, however, he nevertheless died of aspiration pneumonia in February 2013.

Autopsy findings: In the bone marrow, a cluster of differentiation-79a-positive atypical plasmacytes was found to be diffusely proliferated, and this condition was determined to be myeloma (Fig. 4A, B). In the pancreas, the islets of Langerhans were well maintained, and no amyloid deposits were found (Fig. 4C). No findings indicative of endocrinological tumors, including insulinoma, hyperplasia of the pancreatic islets, or nesidioblastosis were obtained. In the kidneys, coagulation necrosis of the tubules was observed, probably due to an end-stage circulation disorder, and an acidophilic substance (cylinder) was observed in the tubules, potentially suggesting the presence of myeloma kidney (Fig. 4D, E). A white lesion with a partially ill-defined border was found at the pancreatic head, and, histologically, the infiltration and proliferation of atypical small epithelial cells that formed a cord-like pattern and small ducts were

![Figure 3. The course of hemoglobin A1c.](image1)

![Figure 4. Pathological findings: marrow, islets of Langerhans and renal tubules.](image2)
observed. These observations indicated a diagnosis of poorly differentiated adenocarcinoma. Non-curative resection was performed for bladder cancer of the patient in 2011. At that time, poorly differentiated cancer cells were found in a biopsy specimen of the bladder cancer. While two primary cancers or metastases of bladder cancer to the pancreas or of a primary pancreatic cancer to the bladder were all considered possibilities, a definite diagnosis could not be made. No marked changes were observed either macroscopically or histologically in the small or large intestine. Therefore, ileus, which had been the cause of hospitalization, may have been only a functional disorder.

Discussion

This case was diagnosed with IAS because of the presence of insulin antibodies despite the absence of any history of insulin injection, an abnormally high level of blood IRI, and the occurrence of hypoglycemia. As mentioned above, a Scatchard analysis showed that the patient’s insulin antibody was a low-affinity monoclonal type with a low k1 (<1.0×10^4 M^-1), which is a characteristic of IAS, unlike the insulin antibody level observed after insulin injection (>1.0×10^4 M^-1). Uchigata and Hirata reported that IAS characterized by a monoclonal antibody is rare in Japan, as such a case was found in only 1 of 51 IAS cases in their case series (2).

The cause of IAS is still unknown, although it has been speculated to involve drugs with α-lipoic acid or a thiol group, autoimmunity, and/or virus infections. In the present case, no drugs with a thiol group had been used in oral or injection form. Moreover, the patient had experienced no obvious virus infection prior to development of the disease. Based on the repeated occurrence of hypoglycemia over a 20-year period and the presence of a monoclonal antibody, asymptomatic myeloma was diagnosed after careful follow-up investigations of the progression of the disease. Along with the increase in the M-protein level, the t-IRI level continuously increased and the insulin antibody binding rate remained high. Accordingly, we speculated that IAS had therefore likely been continuously present from the beginning of the disease course, as the M-protein is capable of binding to insulin during the process of chronic monoclonal gammopathy of undetermined significance (MGUS) developing into multiple myeloma. According to Kyle et al., the time to diagnosis of multiple myeloma from the time of MGUS onset ranges widely between 1 to 32 years (mean, 10.4 years), with only 21% of MGUS patients aged 70 years or older successfully diagnosed with MGUS at routine health checkups (3).

Regarding the Scatchard analysis, k1 in 2012 was a hundredth of that in 2006. The evolution from MGUS to myeloma may have some relationship with the change in the affinity of the insulin autoantibodies.

Very few reports are available concerning IAS-associated multiple myeloma or MGUS. In fact, only 1 previous case has been reported in Japan (4), along with 7 cases from other countries (5-11). The period from the onset to diagnosis is generally 2 to 6 years, which differs greatly from the period of less than 3 months required for a spontaneous resolution in 80% of regular IAS cases (12). Hence, when IAS persists for a long time, the M-protein level should be analyzed, and any potential associations with MGUS or multiple myeloma should be investigated. Meanwhile, there are 3 previous reports of 9 cases of monoclonal antibody-induced IAS (2, 13, 14); however, it is unknown whether MGUS or multiple myeloma was subsequently observed in these cases.

In the present case, according to the findings of the pancreatic tissues, no hypertrophy or the growth of the Langerhans islets was observed upon hematoxylin-eosin staining, and the ratios of cells were 20%, 70%, and 10% for A-, B-, and D-cells, respectively, which were all within the normal ranges. The islets of Langerhans were not uniform in size, ranging from 150 to 300 μm. To date, the findings of pancreatic tissues have been reported for 7 IAS cases (15-21). While no change was observed in the islets of Langerhans in 1 of these 7 cases, hypertrophy was noted in 1 case and an enhanced growth was observed in the remaining 5 cases. In 3 of these 5 cases, hypertrophy of the islets of was also observed. In contrast, neither hypertrophy nor growth of the islets of Langerhans was observed in the present case, likely owing to the long duration of the disease, as the patient had probably already passed the phase where the number of cells would increase to compensate for the weakened reactivity, and the cells were exhausted and found to be shrinking at the time of the analysis. Furthermore, the findings of the pancreatic tissues ruled out the possibility of endocrinological tumors, including insulinoma, hyperplasia of the pancreatic islets, and nesidioblastosis. Instead, we hypothesize that the hypoglycemia observed in this case may have been induced by the multiple myeloma. However, the further accumulation of similar cases will be necessary in the future in order to confirm our findings.

An autopsy of an IAS case with multiple myeloma has rarely been conducted. In this report, we describe the histopathological findings together with our clinical observations of such a case.

The authors state that they have no Conflict of Interest (COI).

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