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An Observation of Plasma Cell Dyscrasia Developing to Multiple Myeloma With a Rare Association of Pituitary Adenoma and Pituitary Apoplexy

Takashi Isobe¹, Yasuhiko Okimura², Hiromi Abe³, Hidesuke Kaji⁴, Hajime Yamada⁵, Riko Kitazaka³, Sohei Kitazawa³, Sakan Maeda³, Takuo Fujita¹, Tomohiko Taminato⁴, Hiroo Imura⁵, and Kazuo Chihara²

A 67-year-old male showed clinical manifestations of two different disorders in his clinical course for more than 20 years. In fact, he started his complaint of headache at the age of 27, when he was hypertensive. Acromegaly was noted at the age of 33 and glucosuria at the age of 42. Clinical manifestations at the age of 45 included general fatigue, thirst, polydipsia–polyuria, and impotence. A clinical examination made a diagnosis of pituitary adenoma. At the age of 47, an episode of severe headache with fever for 10 days made him normotensive and panhypopituitarism, indicating pituitary apoplexy. In his clinical course, however, there was another manifestation of serum monoclonal immunoglobulin of IgG(k) type. On the basis of low plasma cell proliferation, and low concentration of M-protein, benign monoclonal gammopathy was a diagnosis at that time. After the following 14 years, changes from benign monoclonal gammopathy to multiple myeloma were noted. The patient died of exacerbated malignant state of myeloma, hypercalcemia, anemia, associated DIC and generalized infections. Two different course of two different disorders were discussed, in connection with clinical and pathological findings.

Key Words
Monoclonal immunoglobulin,
Pituitary apoplexy,
Pituitary adenoma,
Multiple myeloma.

Introduction
Monoclonal immunoglobulin is generally considered to be a prototype tumor marker, among cases with monoclonal gammopathy, multiple myeloma, macroglobulinemia, heavy chain disease, AL amyloidosis and benign monoclonal gammopathy. Although immunoglobulins represent biological antibody and antibody activity, it is usually very rare to demonstrate antibody activities among monoclonal immunoglobulins. In this paper, we describe an unusual association of benign monoclonal gammopathy with pituitary adenoma. Moreover, there are interesting developments of these two clinical entities, respectively. The first is benign monoclonal gammopathy into obvious multiple myeloma, and the second is pituitary adenoma producing acromegaly.
falling into panhypopituitarism after an abrupt attack of pituitary apoplexy. The relationship of these rare events in a patient is discussed in the present paper.

Case Presentation

Wak., 67 year-old male, visited the hospital with a chief complaint of headache on February of 1976 at his age of 31. His family history showed hypertensive of his mother. His past history disclosed that he had started to have headache at the age of 27, when he was hypertensive. He noticed an abnormal enlargement of size of shoes-gloves for daily use at the age of 33. Glucosuria was found at 42. A series of clinical manifestations started to appear at 45 of his age, including general fatigue, thirst, polydipsia-polyuria, and impotence. A clinical diagnosis was tentatively made as diabetes mellitus. A clinical investigation for a possible diagnosis of acromegaly prompted him to have a schedule of endocrine tests in the other hospital.

Accidentally and suddenly, during clinical examinations he had an episodic attack of severe headache around the frontal portion, and high-grade fever, followed by transient loss of consciousness. His hypertension normalized after the following day of an severe headache. The episodes of headache associated with fever continued for 10 days. He was transferred to our clinic, the Third Department of Medicine in the Kobe University Hospital for further examinations.

On admission his height was 160 cm, 60 kg in weight and he was well-developed and moderately nourished. There were no abnormal findings on the eyeballs, fundus, pupils or visual field. There was also no evidence of goiter, lymphadenopathy, hepatomegaly, splenomegaly or neurological abnormality. However, unbalanced enlargement of the nose and mandible were noted. Figure 1 showed gradual changes of facial appearances of acromegaly over a 15 year period, with supraorbital ridges and nose, with thickening of lips from the age of 31 to 45.

Laboratory examinations on admission included a red blood cell count of $404 \times 10^4/\mu l$, hemoglobin 13.3 gm/dl, hematocrit 39.0%, white blood cell 8,400/ml (band-form 12%, segmented 21%, eosinophil 4%, basophil 2%, monocyte 3% and lymphocyte 58%), platelet 19.3$\times 10^4/\mu l$.

Figure 1. Changes in facial appearance of the patient with acromegaly over a 20 year period. The development of an acromegalic appearance is seen with an enlargement of supraorbital ridges and nose, with thickening of lips. Photos were taken at the age of 31, 40, 45 and 51, respectively from the left to right.
CRP negative, GOT 18 IU/l, GPT 19 IU/l, γ-GTP 4 IU/l, alkaline phosphatase 67 IU/l, choline esterase 5,851 IU/l, serum bilirubin 0.3 mg/dl, serum total protein 7.4 g/dl, including albumin 3.8 g/dl and gammaglobulin 2.4 g/dl of abnormal shape. The serum protein electrophoresis showing a definite monoclonal (M-type) protein on the first admission at the age of 31. The monoclonal peak was of IgG(k) type in gamma mobility in association with residual background immunoglobulin. Serum immunoglobulin levels were estimated IgG 3,480 mg/dl, IgA 39 mg/dl and IgM 80 mg/dl, and thus there were already lowered IgA at the time of first examination on the patient. There were normal renal functions of a blood urea nitrogen 15 mg/dl, and creatinine clearance 110 l/day. A electrolyte data showed Na 142 mEg/l, K 4.3 mEg/l, CI 108 mEg/l, Ca 8.9 mg/dl, and P 3.6 mg/l. Immunological estimations showed all negative data with rheumatoid factor, DNA test; Coombs test, LE test, and thyroid microsome test. An urinalysis showed no proteinuria, positive glucosuria and normal urobilinogen. An erythrocyte sedimentation reta was 16 mm per an hour and 66 mm per 2 hours.

X ray survey showed a definite abnormality on the lateral view of the skull, with a widening of the sella turcica of integral portion of the sphenoid bone, as shown in Figure 2. Figure 3 and Figure 4 demonstrated a series of endocrine examination, after an episodic attack of headache with fever. As shown in Figure 3, a basal level of plasma growth hormone (GH) was lower than 5 ng/ml. With an intravenous loading of TRH 500 mg, plasma GH levels unresponsive. Plasma prolactin (PRL) levels slightly increased in response to TRH. Definite increase of plasma GH levels after an oral load of L-DOPA 0.5 g was not seen at this time of examination. Another test of intravenous loading regular–insulin 0.1 u/kg showed only a small increase of GH, suggesting decreased amount of GH pool in the pituitary at this time of test in the present case. Oral administration of glucose 50 gm did not suppress plasma GH levels suggesting residual GH–producing adenoma cells (Figure 3).

As for pituitary–thyroid stimulating system, Triosorb test, Tetrasorb test and radio–labeled iodine uptake indicated hypothyroidism. Furthermore, low TSH levels and no TSH response to an intravenous TRH 500 mg showed secondary hypothyroidism due to TSH deficiency. Regarding pituitary–gonadotropin hormone, an intravenous administration of LH–RH 100 mg showed a good response. Pituitary–adrenal system was examined by cheek–up of circadian rhythm of plasma cortisol level, with a result of decreased cortisol 4.9 mg/dl in the morning, and further decrease at night. An oral load of metopirone 1.5 g showed a similar pattern as normal adults. There was also no abnormality with urine 17 OHCS as well as 17 KS, and also plasma cortisol level after intravenous regular insulin 0.1 u/kg (Figure 4).

In short summary of endocrine tests, there was no evidence of active acromegaly at this time of examination after an episode of headache and fever. However, small number of adenoma cells might have been remaining. With having gonadal or adrenal functions of pituitary stimulating system, there was a definite non–functioning of GH, PRL and TSH. It is therefore assumed that once the patient had pituitary adenoma, and an accidental episode of pituitary apoplexy with a clinical episode of severe headache and fever for 10 days resulted in
hypopituitarism in the course of this initially acromegalic patient.

Since there was no direct evidence of mutual relationship between pituitary adenoma followed by pituitary apoplexy and serum monoclonal immunoglobulin in the present case, another line of documentation was drawn in Figure 5 as to immunoglobulin and its related abnormality. Figure 5 included (1) the changes of electrophoretic patterns of serum protein, (2) serum concentrations of albumin and monoclonal protein, (3) presence or absence of residual immunoglobulins (indi-
Pituitary Adenoma and Multiple Myeloma

1. GH and Prolactin

TRH 500\(\mu\)g i.v.

\[
\begin{array}{|c|c|c|}
\hline
\text{GH (ng/mL)} & 0 & 60 & 120 \\hline
\hline
\text{Prolactin (ng/mL)} & 0 & 10 & 20 \\hline
\end{array}
\]

1-DOPA 0.5g p.o.

\[
\begin{array}{|c|c|c|}
\hline
\text{GH (ng/mL)} & 0 & 60 & 120 \\hline
\hline
\text{Prolactin (ng/mL)} & 0 & 10 & 20 \\hline
\end{array}
\]

Regular Insulin 0.1 u/kg i.v.

\[
\begin{array}{|c|c|c|}
\hline
\text{GH (ng/mL)} & 0 & 60 & 120 \\hline
\hline
\text{Blood sugar (mg/dL)} & 0 & 50 & 100 \\hline
\end{array}
\]

50g glucose p.o.

\[
\begin{array}{|c|c|c|}
\hline
\text{GH (ng/mL)} & 0 & 60 & 120 \\hline
\hline
\text{Blood sugar (mg/dL)} & 0 & 50 & 100 \\hline
\end{array}
\]

Figure 3. Endocrine examination (part 1). GH and prolactin. See in the text.

cated as arrow in the figure), (4) serum total protein, (5) presence or absence of urinary Bence Jones protein, (6) plasma cell percent out of nucleated cells on aspirated bone marrow smears, (7) serum calcium levels, (8) serum levels of beta-2 microglobulin, and (9) hemoglobin concentrations.

An obvious observation was shown in this Figure 5, ie, small sized serum M-protein with residual background gammaglobulin developed to large sized myeloma protein. Along with this observation, there were several signals of clinical myeloma indicating lowered serum albumin, increased serum total protein, appearance of Bence Jones protein, proliferation of marrow plasma cells, hypercalcemia, high titer of beta-2 microglobulin, and increasing anemia, as demonstrated in Figure 5.

For more than 20 years of clinical observations, the patient had a relapse of myeloma after 3 years’ remission. Rapid progression of malignant state of multiple myeloma made inductions of disseminated intravascular coagulation with generalized bleeding tendency as well as systemic infections. He died on December 30, 1998, at his age of 67. Autopsy finding were listed as follows; (1) multiple myeloma of IgG(k) type with metastasis to bones (skull, ribs, thoracic and lumbar spines) as shown in Figure 6, and myeloma kidneys (calcification, renal tubular damage and plasma cell infiltrations), (2) DIC, bleeding to retroperitoneal cavity and erosive mucous mem-

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2. Pituitary-Thyroid

- TRH 500 μg i.v.
- LH-RH 100 μg i.v.

3. Pituitary-Gonad

- LH
- FSH

4. Pituitary-Adrenal

- Circadian Rhythm
  - Cortisol
    - 9:00: 4.9 (μg/dl)
    - 16:00: 3.0
    - 23:00: 0.5
  - Metopirone Test (1.5 g p.o.)
    - ACTH Before: 9:00 N.D. (pg/ml)
    - After: 8:00 95
    - 10:00 43
  - Urine 17 OHCS: 6.4 mg/day
  - 17 KS: 2.9 mg/day

Figure 4. Endocrine examination (part 2). Thyroid, Gonad, Adrenal and others. See in the text.

- Triosorb 22.6 %
- Tetrasorb 3.4 μg/dl
- ¹³¹ I-uptake 2.9 %

Serum Testosterone 5.1 ng/ml
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<tr>
<th>Year</th>
<th>MP (g/dl)</th>
<th>ALB (g/dl)</th>
<th>TP (mg/dl)</th>
<th>BJP (%)</th>
<th>PC (mg/dl)</th>
<th>Ca (mg/dl)</th>
<th>β2M (mg/l)</th>
<th>Hb (g/dl)</th>
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<td>3.9</td>
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<td>1996.12</td>
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<td>1.5</td>
<td>10.1</td>
<td>(+)</td>
<td>92.0</td>
<td>12.4</td>
<td>39.0</td>
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(M10mg + P80mg/d) × 4d × 2

Figure 5. Serum protein electrophoresis and associated major laboratory data in the clinical course.
was found at the age of 42. Gradual progression of acromegaly suggested a clinical diagnosis of growth-hormone producing pituitary adenoma. At his age of 47, a severe attack of headache with fever suggested pituitary apoplexy, since endocrinological data showed panhypopituitarism afterwards. Possibly unrelated to acromegaly–pituitary apoplexy, the patient had serum monoclonal protein of IgG(k) type. Progression from benign monoclonal gammopathy to multiple myeloma was confirmed by exacerbations of plasma cell proliferations, increased immunoglobulins in the serum, hypercalcemia, and anemia.

Discussion

The pituitary is located in a saddle-shaped cavity, the sella turcica, which is integral portion of the sphenoid bone. The average dimensions of the pituitary are 10 mm (anterior–posterior) by 13 mm (transverse) by 6 mm (height). Pituitary weight varies from 0.5 to 0.7 gram, being slightly greater in women. The anterior blood supply of the pituitary origi-
As to immunoglobulin abnormality of monoclonal gammopathy of multiple myeloma, there was no evidence of multiple myeloma at the age of 47. Benign monoclonal gammopathy (BMG) was diagnosed at the time of initial admission of the present case. An association of pituitary adenoma is rare among BMG, as described in detail in the literature. In spite of rare association, there could be any significant relationship between pituitary monochlonal M-protein. Possible speculations were considered as followings at the time pituitary apoplexy and simultaneous IgM-protein. There could be (1) some tissue components pathologically produced from the pituitary after pituitary apoplexy which, as antigen, produced IgM-protein as an antibody, (2) on the contrary, IgM-protein in the present case could have been autoantibody, (3) on the contrary, IgM-protein in the present case could have been autoantibody.
be a trigger to pituitary apoplexy, and
(3) IgM-protein could be a primary cause of acromegaly. It is worthy of pursuit to provide a direct proof of these speculations, although application of immunologic technique to investigate in vivo phenomenon of antigen–antibody reaction is fur from exact documentation. A real progression from BGM to myeloma would provides significant profile of one of natural course of plasma cell dyscrasia in clinical medicine.

References