

Acromegaly Associated with Monoclonal Gammopathy of Undetermined Significance (MGUS)

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Abstract. Here we report the case of a 65-year-old woman with acromegaly complicated with monoclonal gammopathy of undetermined significance (MGUS). The patient visited Shimane University Hospital for treatment of spinal canal stenosis, and was diagnosed as acromegaly with GH 43.1 ng/ml, insulin-like growth factor (IGF)-I 510 ng/ml and the detection of a pituitary adenoma by MRI. She was also diagnosed as MGUS with IgG 2208 mg/dl, the existence of IgG- κ type monoclonal protein, and 5.6% plasma cells in bone marrow. After a pituitary adenoma was operatively removed by transsphenoidal approach, IgG levels, as well as GH and IGF-I levels, decreased spontaneously and simultaneously. We suspect a pathogenetic link between acromegaly and MGUS in this case, because both GH and IGF-I are known to directly promote immunoglobulin production from plasma cells, thus inducing the proliferation of the cells *in vitro*.

Key words: Acromegaly, MGUS, Multiple myeloma, Growth hormone, Insulin-like growth factor-I

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ACROMEGALY is characterized by elevated levels of growth hormone (GH) and IGF-I with resultant soft tissue and organ growth, and a variety of other signs of hyperanabolism. Progression of the disorder results in a two-fold increase in age-related mortality; a majority of patients die of cardiorespiratory disease, while 18% of them die of malignancies from various origins [1]. Here we report a case of acromegaly complicated with monoclonal gammopathy of undetermined significance (MGUS). It is known that GH and IGF-I can activate B cell lymphocytes [2], and that IGF-I receptor is universally expressed in multiple myeloma (MM) cells [3]. However, the complication of acromegaly with multiple myeloma or MGUS in patients has rarely been reported until now [4, 5]. We describe such a case here

and discuss the link between elevated GH and IGF-I levels versus the production of IgG from B cell lymphocytes/plasma cells.

Case Report

The patient was a 65-year-old Japanese woman. She was diagnosed as diabetes mellitus in 1994, and had been treated by insulin since 1997. She noticed lumbago in 2003, and was referred to the Shimane University Hospital in 2004. She was diagnosed as spinal canal stenosis, and underwent operation. The surgeon consulted our department after the operation for the treatment of diabetes mellitus.

On admission, she had no headache or impairment of visual field. Physical findings were height, 154.5 cm; body weight, 53.8 kg; body mass index, 22.5 kg/m²; blood pressure, 120/80 mmHg; pulse rate, 85 beats/min; and body temperature, 36.8°C. She presented the frontal skull bossing and fleshy lips, suggestive of acromegaly (Fig. 1). Goiter and lymph nodes were not

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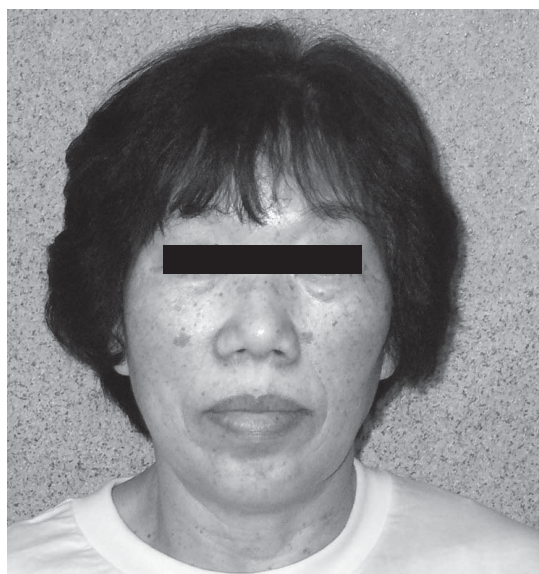


Fig. 1. Facial appearance of the patient presented projection of eyebrows and thickening of lips.

palpable. There were no abnormal findings in lung, heart or abdomen. No edema was found in pretibia or foot. Neurological examination showed that patella tendon reflex and Achilles tendon reflex were attenuated. Tinel and Phalen tests were positive on the right hand, showing the complication of carpal tunnel syndrome.

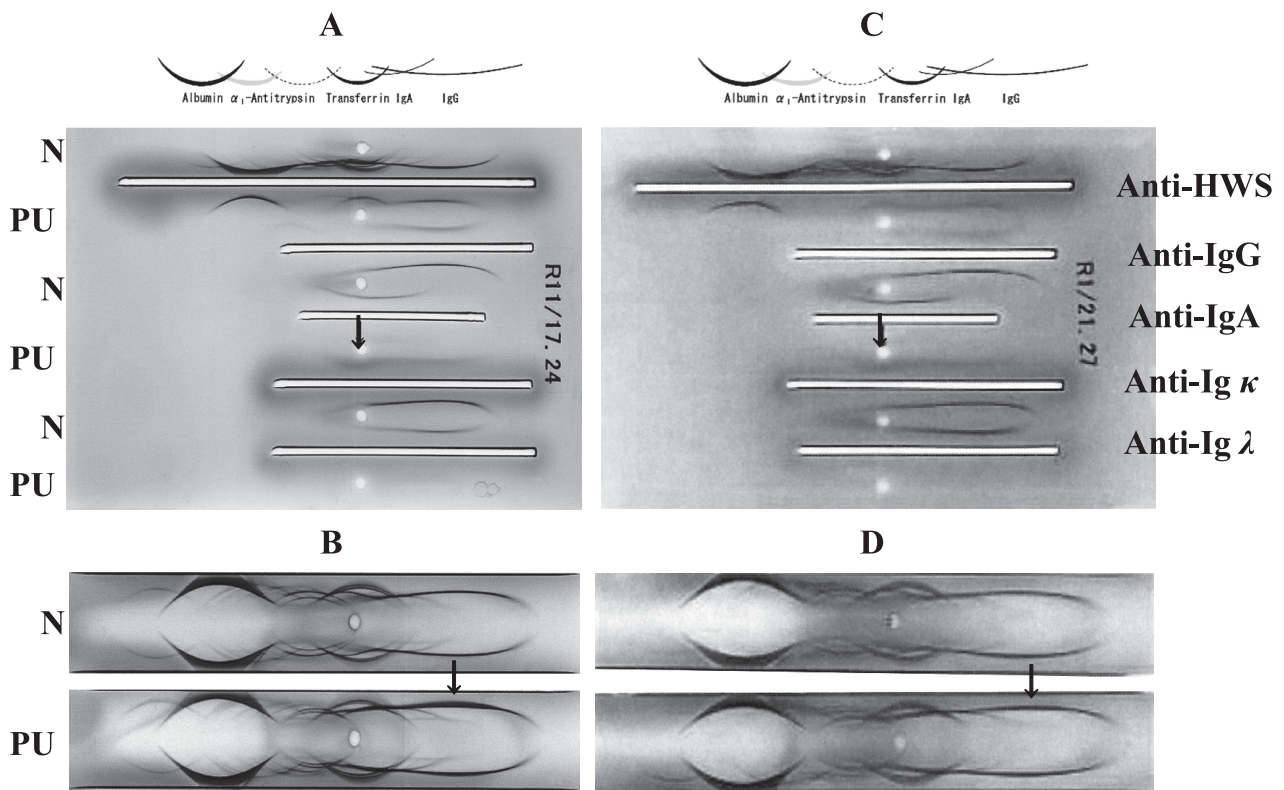
Laboratory data on admission are shown in Table 1. There was a slight anemia due to blood loss during the operation. Diabetes mellitus was noticed, with FPG 141 mg/dl and HbA1c 7.4%. Serum GH and IGH-I levels were markedly elevated (43.1 ng/ml and 510 ng/ml, respectively). The elevation of IgG (2208 mg/dl) was also noticed, while the rest of the immunoglobulin were within normal values. IgG- κ type monoclonal (M) protein was detected by immunoelectrophoresis in serum and urine (Fig. 2).

Magnetic resonance imaging (MRI) revealed a pituitary tumor (9×7 mm), occupying the sellar region adjacent to the right inner carotid artery (Fig. 3). Bone marrow aspiration biopsy revealed that nucleated cell count was $29.9 \times 10^4/\mu\text{l}$ and a plasma cell percentage was 5.6% without any dysplasia. Thus, she was diagnosed as having acromegaly due to pituitary adenoma complicated with MGUS, diabetes mellitus, spinal canal stenosis, and carpal tunnel syndrome. MGUS was diagnosed according to the criteria of Southwest Oncology Group [6].

Table 1. Laboratory data on admission

CBC	
WBC	7150/ μl
Neutro	67.7%
Eos	0.8%
Baso	0.4%
Mono	5.5%
Lymph	25.6%
RBC	$322 \times 10^4/\mu\text{l}$
Hb	9.7 g/dl
Ht	31.0%
PLT	$24.3 \times 10^4/\mu\text{l}$
Urinalysis	
Glu	—
Pro	—
Hyaline cast	5–9/WF
Biochemistry	
TP	7.5 g/dl
Alb	3.9 g/dl
AST	27 IU/l
ALT	32 IU/l
γ -GTP	57 IU/l
T-cho	159 mg/dl
TG	115 mg/dl
HDL-C	37 mg/dl
BUN	10.0 mg/dl
Crea	0.39 mg/dl
Na	141 mEq/l
K	4.0 mEq/l
Cl	102 mEq/l
Ca	9.0 mg/dl
IP	4.0 mg/dl
FPG	141 mg/dl
HbA1c	7.4%
CRP	0.2 mg/dl
IgG	2208 mg/dl
IgA	355 mg/dl
IgM	78 mg/dl
IgE	19.3 IU/ml
IgD	2.2 mg/dl
Endocrinology	
GH	43.1 ng/ml
IGF-I	510 ng/ml
ACTH	10 pg/ml
Cortisol	6.9 $\mu\text{g/dl}$
TSH	0.16 $\mu\text{U/ml}$
fT4	1.3 ng/ml
LH	19.8 mIU/ml
FSH	41.0 mIU/ml
E2	10 ng/dl
PRL	10.6 ng/ml

After the resection of pituitary adenoma by the trans-sphenoidal approach, IgG levels, as well as GH and IGF-I levels decreased spontaneously and simultaneously, although no specific therapy for MGUS was



N: Normal serum, PU: Patient's urine, PS: Patient's serum

Fig. 2. Serum and urine immunoelectrophoretic analysis shows the presence of IgG- κ type M protein (arrows). A and B are before the resection of pituitary adenoma, while C and D are after operation.

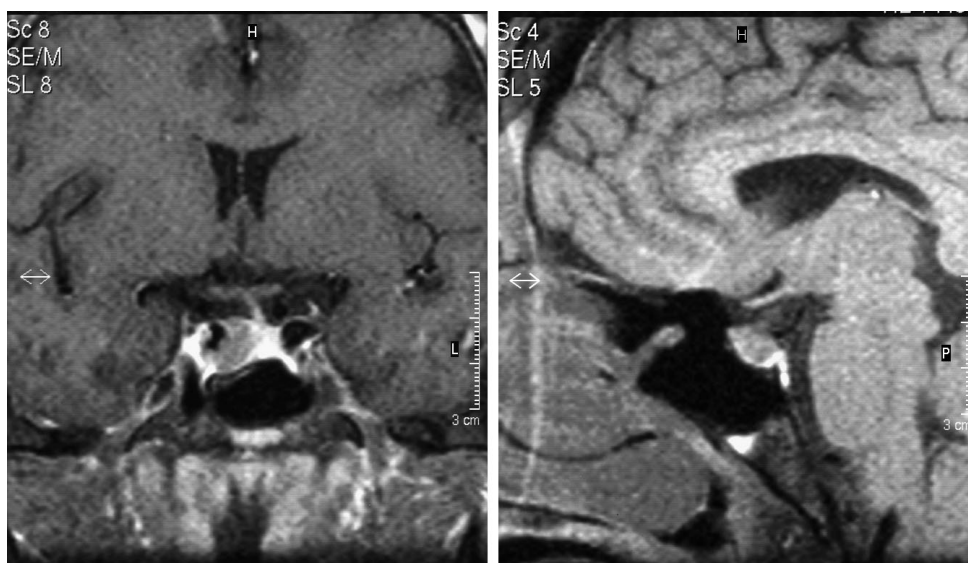


Fig. 3. Cranial (left) and sagittal (right) enhanced MRI in the patient. The pituitary tumor (9 × 7 mm) occupied the sellar region adjacent to the right inner carotid artery.

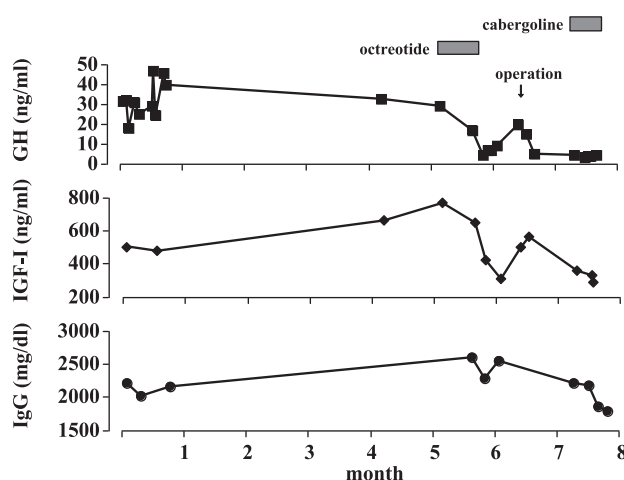


Fig. 4. Clinical course showing chronological changes in serum levels of GH, IGF-I and IgG. After transsphenoidal removal of pituitary adenoma, serum GH and IGF-I levels decreased. In addition, serum IgG levels also decreased in parallel to serum GH and IGF-I levels.

implemented (Fig. 4). Immunoelectrophoresis showed that IgG- κ type M protein also decreased (Fig. 2 C and D), and bone marrow aspiration revealed that a plasma cell percentage reduced to 1.8%. Cabergoline was administered because the pituitary adenoma partly remained after operation, IgG levels have remained within normal limits over two years since the resection of the pituitary adenoma.

Discussion

Patients with acromegaly are known to suffer from high incidence of cancer with observed/expected ratio ranging from 0.76 to 3.4 [3]. In 1982, an association of colonic polyposis with acromegaly was reported, and its occurrence has been shown to be related to the duration of the activity of acromegaly [7]. Several retrospective epidemiologic studies suggest that elevated IGF-I levels may be associated with the higher risk of cancer in patients with acromegaly. Although it is unclear whether the tumor is actually triggered by high circulating IGF-I levels in acromegaly, it has been suggested that acromegaly should be aggressively treated if a neoplasm is complicated, because elevated IGF-I levels could stimulate the growth of neoplastic tissue [8].

In the general population, MGUS affects up to 2 percent of persons older than 50 years of age, and about 3

percent of those older than 70 years. The risk of progression of MGUS to multiple myeloma (MM) or related disorders is thought to be about 1 percent per year [9]. Thus, MGUS is considered to be a pre-myeloma state and to possess neoplastic nature.

Georgii-Hemming *et al.* showed that IGF-I and its receptor mRNA were expressed in human MM cell lines, and that IGF-I stimulated the proliferation of the cells [3]. Ge and Rudikoff have recently shown that insulin receptor substrate 1, a down stream component of IGF-I receptor, was phosphorylated, in seven of eight MM cell lines, leading to the activation of phosphatidylinositol-3'-kinase (PI-3K) [10]. PI-3K, in turn, was shown to regulate two distinct pathways; the first pathway is mediated by Akt and Bad, leading to the inhibition of apoptosis; the second one is mediated by the mitogen-activated protein kinase (MAPK), resulting in proliferation. In addition, *in vivo* administration of IGF-I in SCID mice inoculated with the OPM-2 myeloma cell line led to approximately twice the growth rate of the tumor cells compared to controls [10]. Thus, IGF-I seems to contribute significantly to the expansion of myeloma cells *in vivo*. Recently, Mitsiades *et al.* showed that specific IGF-I receptor inhibition with neutralizing antibodies, antagonistic peptides, or the selective kinase inhibitor NVP-ADW742 caused the suppression of multiple myeloma, even if the myeloma was resistant to conventional therapies [11]. In this context, MGUS could be complicated with acromegaly through the effect of high circulating IGF-I, and should be considered to be one type of neoplasm associated with acromegaly.

Hagg *et al.* reported three cases of multiple myeloma associated with acromegaly [4]. However, serum GH, IGF-I levels were not documented in their cases and thus a correlation between the two disorders is unclear. Tucci *et al.* have recently reported a case of transformation of MGUS to overt multiple myeloma in a patient complicated with acromegaly. They suspected a pathogenetic link between acromegaly and transformation of gammopathy to overt myeloma [5]. The clinical course of our patient showed parallel changes between GH/IGF-I and IgG levels, suggesting that high levels of GH and IGF-I might promote the expansion of the plasma cell clone, and that a reduction in serum GH and IGF-I levels may be of therapeutic benefit to MGUS. Maintaining GH and IGF-I levels within normal ranges by intensive treatment might be needed if acromegaly is associated with myeloma or MGUS.

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