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【 CASE REPORT 】

IgG4-type Multiple Myeloma with Diffuse Enlargement of the Thyroid Requiring Differentiation from IgG4-related Disease

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Abstract:
We herein report a 65-year-old man with elevated serum IgG4 levels, enlarged thyroid, and renal dysfunction, mimicking IgG4-related disease (IgG4-RD). The definitive diagnosis of IgG4-RD was not established because a tissue biopsy revealed no IgG4-positive cell infiltration or fibrosis. The presence of an M peak in the β fraction, Bence Jones protein in urine, and progressive anemia suggested multiple myeloma (MM). The κ/λ ratio was >100, tumor plasma cells were present at >20% in bone marrow, and immunostaining revealed IgG4-positive plasma cells; therefore, he was diagnosed with IgG4-type MM. Patients with elevated IgG4 levels with no significant mass lesions should undergo systemic examinations to exclude malignancy.

Key words: IgG4-related disease, IgG4-type multiple myeloma, elevated serum IgG4 level

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Introduction

IgG4-related disease (IgG4-RD) is a chronic inflammatory disease characterized by organ enlargement due to the infiltration of IgG4-positive plasma cells and elevated serum IgG4 levels (1). In Japan, comprehensive diagnostic criteria for IgG4-RD were proposed in 2011 (2), which led to increased opportunities for the measurement of serum IgG4 levels. However, elevated serum IgG4 levels are also found in a variety of diseases, including rheumatoid arthritis, scleroderma, polymyositis, eosinophilic granulomatosis with polyangiitis, and Castleman's disease (3).

We herein report a case of IgG4-type multiple myeloma (MM) with diffuse enlargement of the thyroid and elevated serum IgG4 levels requiring differentiation from IgG4-RD.

Case Report

In X-7, a 65-year-old man was diagnosed with hypertension and started on antihypertensive medication. He had chronic kidney disease due to nephrosclerosis. His creatinine level was 1.90 mg/dL in January X, and it increased to 2.74 mg/dL in August X despite his blood pressure being under control. He therefore visited the Department of Nephrology in our hospital in October. His creatinine levels were 3.70 mg/dL on the first examination, showing an increasing trend. A physical examination showed diffuse enlargement of the thyroid without tenderness or induration. IgG4-RD was considered as the differential diagnosis. His serum IgG4 level was as high as 1,550 mg/dL, and he was admitted to our department for a definitive diagnosis and determination of a treatment plan.

Regarding his laboratory findings upon admission (Table), his creatinine level was 3.89 mg/dL, showing a further increase; a urinalysis showed proteinuria of 3.20 g/day and an elevated urinary β2-microglobulin level of 12,913 mg/dL. A thyroid function test showed that thyroid-stimulating hormone (TSH) was 247 μIU/mL, and FT4 was 0.30 ng/dL, indicating primary hypothyroidism. The serum IgG4 level remained high at 1,700 mg/dL. Thyroid ultrasonography showed diffuse enlargement with a rough internal echo pattern. Computed tomography (CT) showed mild enlargement of the bilateral submandibular glands. Given these findings,

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Table. **Laboratory Findings.**

<CBC>		<Serological examination>	
White blood cells	3,600 /μL	CRP	0.07 mg/dL
Red blood cells	2.79×10^6 /μL	ESR	107 mm/h
Eosinophil	2.0 %	IgG	2,368 mg/dL
Hemoglobin	9.1 g/dL	IgG4	1,700 mg/dL
Reticulocyte	14 ‰	IgA	127 mg/dL
MCV	98.7	IgM	33 mg/dL
Platelet	36.7×10^4 /μL	β2-microglobulin	6.8 mg/dL
<Biochemistry>		CH50	54.0 U/mL
Total protein	7.5 g/dL	Antinuclear antibody	<40
Albumin	3.3 g/dL	SS-A antibody	<1.0 U/mL
AST	23 IU/L	MPO-ANCA	<1.0 U/mL
ALT	6 IU/L	PR3-ANCA	<1.0 U/mL
BUN	40 mg/dL	Anti-TG antibody	12 U/mL
Creatinine	3.89 mg/dL	Anti-TPO antibody	15 U/mL
Na	137 mEq/L	<Urine examination>	
K	4.1 mEq/L	pH	7.0
Cl	100 mEq//L	Urine specific gravity	1,017
Ca(correction)	9.8 mg/dL	Qualitative urine protein	3+
IP	3.6 mg/dL	Uric blood	-
Fe	93 μg/dL	Urine glucose	-
Ferritin	132 ng/dL	Urinary cast	-
TSH	247 μIU/mL	Quantitative urine protein	3.2 g/day
FT4	0.30 ng/dL	β2-microglobulin (urine)	12,913 μg/L
Erythropoietin	16.7 mIU/mL		

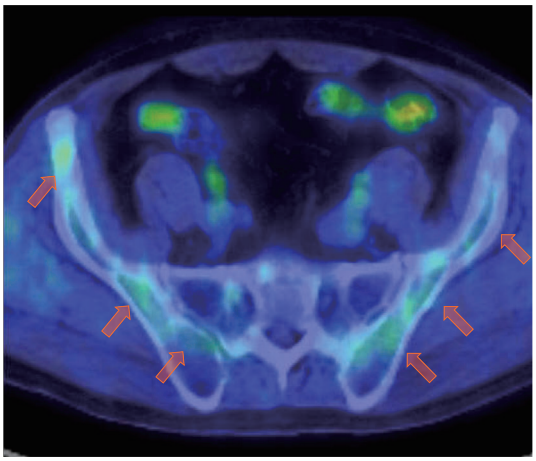

Figure 1. **PET-CT. A mildly enhanced uptake was observed in the bilateral iliac bones (arrows).**

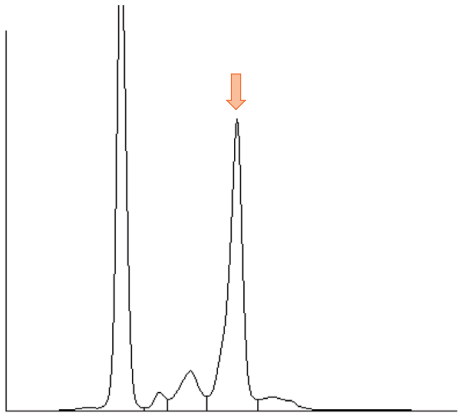

Figure 2. **Protein electrophoresis. The M-peak in the β fraction (2.7 g/dL) (arrow).**

the patient was suspected of having IgG4-RD associated with interstitial nephritis, thyroiditis, and submaxilaritis, so he underwent a tissue biopsy.

However, a thyroid biopsy showed no IgG4-positive plasma cell infiltrate or storiform fibrosis. A renal biopsy was not performed because of renal atrophy, and a submandibular gland biopsy was not performed because the patient wanted us to observe his condition without a biopsy; however, a lip biopsy showed that the small salivary gland remained intact.

Only two of the comprehensive diagnostic criteria for IgG 4-RD [diffuse organ enlargement and serum IgG4 elevation (>135 mg/dL)], were met, so a definitive diagnosis was not established. In addition, there were no eosinophilia or hypocomplementemia, which are typical characteristics of IgG4-RD. The autoantibodies related to connective tissue disease were negative. However, the patient had progressive normocytic anemia (Hb 9.1 g/dL), renal dysfunction, and total protein albumin dissociation.

Whole-body positron emission tomography (PET)-CT performed to look for potential malignancy revealed a diffuse and mildly enhanced uptake in the bilateral iliac bones (Fig. 1). Based on these results, MM was suspected, and serum protein electrophoresis showed an M-peak (2.7 g/dL) in

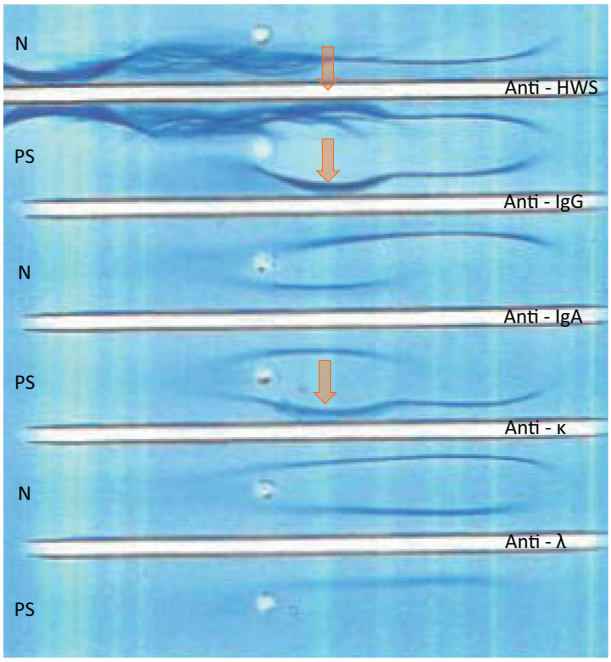

Figure 3. Immunoelectrophoresis. IgG-κ-type monoclonal protein (arrow).

the β fraction (Fig. 2). In addition, IgG-κ-type monoclonal protein was detected by serum immunoelectrophoresis (Fig. 3). An additional examination showed that the Bence Jones protein urine test was positive and that the κ/λ ratio was 227; therefore, a bone marrow biopsy was performed for a definitive diagnosis.

Hematoxylin and Eosin staining showed densely stained and enlarged nuclei and proliferation of tumor cells with an uneven distribution in the bone marrow. CD138 staining was positive, and the percentage of tumor plasma cells was ≥ 20% (Fig. 4). The patient met the diagnostic criteria for MM by the International Myeloma Working Group: the percentage of clonal tumor plasma cells in his bone marrow was ≥10%, there were characteristic findings (myeloma-defining events) such as renal failure and anemia, and the ratio of κ/λ was >100. Furthermore, most of the tumor cells were IgG4-positive, and Kappa staining was positive as well. The patient was ultimately diagnosed with IgG4-κ-type MM.

An examination of the enlarged thyroid gland showed that anti-TG antibodies and anti-thyroid peroxidase (TPO) antibodies were negative, and a tissue biopsy showed no lymphocytes, plasma cell infiltrates, or malignant findings; therefore, the lesion was diagnosed as sporadic primary hypothyroidism (suspected Hashimoto's thyroiditis) unrelated to IgG4-RD and MM.

Discussion

The key contributions of this case are two-fold. The present findings suggest that patients with IgG4-type MM can

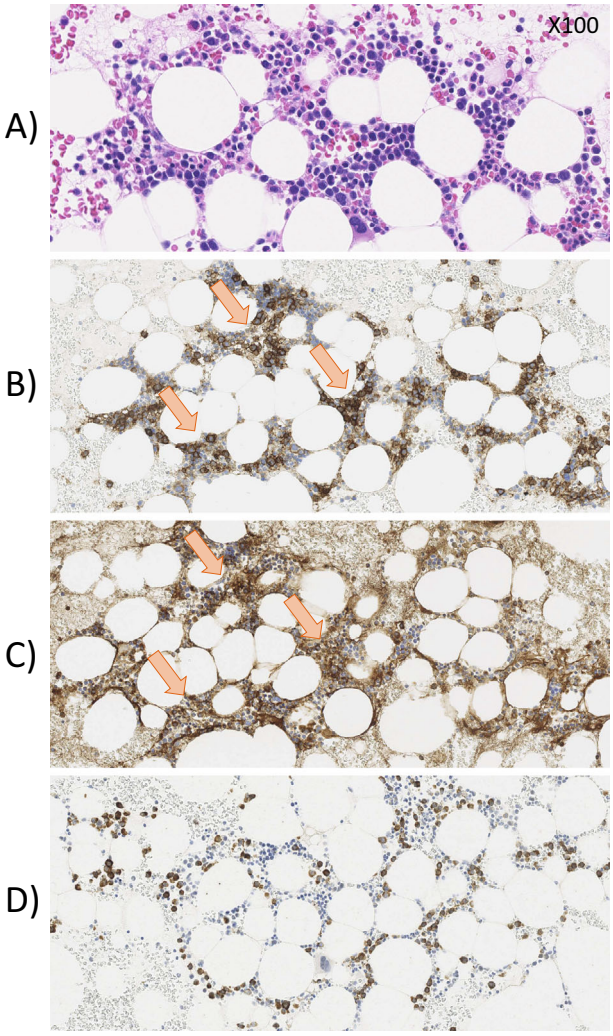

Figure 4. Bone marrow histological findings. (A) Hematoxylin and Eosin staining showed densely stained and enlarged nuclei and proliferation of tumor cells with an uneven distribution of tumor cells in the bone marrow. CD138 staining (B) showed densely stained tumor cells (arrows), most of which were positive for IgG4 staining (C) (arrows). D) Kappa staining.

have clinical manifestations similar to those with IgG4-RD due to the presence of mass lesions. Furthermore, patients who have elevated serum IgG4 levels but do not have significant findings on a biopsy of the mass lesion should undergo a systemic examination to search for potential malignancy.

Patients with IgG4-type MM can have clinical manifestations similar to those with IgG4-RD due to the presence of mass lesions. Patients with MM present with monoclonal gammopathy due to the proliferation of tumor plasma cells and have an M peak upon serum protein electrophoresis. Therefore, patients with IgG4-type MM have elevated serum IgG4 levels similar to those with IgG4-RD due to proliferation of IgG4-secreting tumor cells and a monoclonal increase in IgG4. According to a previous study, among the 158 patients diagnosed with IgG-type MM based on a bone marrow biopsy, only 6 patients (4%) had the IgG4-secreting

type. The mean serum IgG4 level was reported to be 2,700 mg/dL, which was higher than that in IgG4-RD, but it is difficult to make a differential diagnosis because there are no reports on the correlation between organ damage and the severity or characteristic findings compared with other secreting types. Most of the patients were diagnosed with MM based on characteristic organ damage findings, such as elevated serum monoclonal IgG4 levels and osteolytic lesions, but two cases were reported to have mass lesions (chronic sinusitis, lymphadenopathy, and pancreatic head enlargement) and thus required differentiation from IgG4-RD. Both cases showed organ infiltration due to MM or organ enlargement without clinical significance; therefore, the possibility of organ damage due to IgG4-RD was excluded (4, 5). As in these two patients, the present case is a rare cases of IgG4-type MM associated with mass lesions, and differentiation from IgG4-RD was especially difficult because the patient also had a mass lesion due to sporadic primary hypothyroidism and organ damage, such as renal dysfunction, commonly observed in patients with MM and IgG4-RD. Acute kidney exacerbation was caused by renal tubular damage from MM on nephrosclerosis. Similarly, progressive anemia was also induced by bone marrow suppression by MM with renal anemia in the background. Regarding submandibular gland swelling, the lack of dry mouth and the progressive enlargement over time suggested that the enlargement was a physiological change. The high TSH titer was induced by the long treatment-free interval.

Patients who have elevated serum IgG4 levels but do not have significant findings on the biopsy of the mass lesions should undergo systemic examination to look for potential malignancies. Elevated serum IgG4 levels are observed not only in patients with IgG4-RD but also in those with rheumatic and connective tissue diseases such as rheumatoid arthritis, allergic disease, and malignant tumors. An analysis of patients who showed elevated serum IgG4 levels (>135 mg/dL) but were not ultimately diagnosed with IgG4-RD, showed that 125 (19.6%) of the 635 patients with non-IgG4-RD also had malignant tumors (6). In general, when a mass lesion is detected in the diagnostic process of IgG4-RD, it is essential to rule out malignant etiologies. In particular, approximately 10% of patients with pancreatic cancer and biliary cancer have elevated serum IgG4 levels, so a tissue biopsy is necessary to rule out other diseases (7, 8). However, patients with IgG4-type MM can have elevated serum IgG4 levels without developing mass lesions. In the present case, a mass lesion was observed without any significant findings, and malignancy was suspected based on the elevated serum IgG4 level, for which a systemic examination had been performed, leading to the diagnosis of IgG4-type MM.

Patients with IgG4-type MM can have clinical manifestations similar to those with IgG4-RD due to the presence of mass lesions. Patients who have elevated serum IgG4 levels but do not have significant findings on the biopsies of the mass lesions should undergo a systemic examination in order to search for potential malignancy. When patients with elevated serum IgG4 levels do not meet the diagnostic criteria for IgG4-RD, they may have malignant diseases, such as MM, without the formation of mass lesions, or alternatively solid cancer that was not detected in the initial detailed examination of IgG4-RD. Thus, a systemic examination should be performed whenever possible. The evaluation of potential hematological malignancy and a comprehensive physical examination using PET-CT should also be considered.

Author's disclosure of potential Conflicts of Interest (COI).
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