Multiple Myeloma with Myeloma Nephropathy in a Patient with Hashimoto's Thyroiditis

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Abstract: Hashimoto's thyroiditis is associated with myeloproliferative and lymphoproliferative neoplasms. The risk of carcinoma of the thyroid gland is increased in these patients. Furthermore, multiple myeloma can present together with some autoimmune diseases. We report the case of a 57-year-old woman with Hashimoto's thyroiditis who developed multiple myeloma with myeloma nephropathy. Her renal function deteriorated to end stage and she required maintenance hemodialysis. Although autoimmune disorder might play an important role in lymphomagenesis in patients with Hashimoto's thyroiditis, it is not known whether the chronic inflammation that takes place in Hashimoto's thyroiditis stimulates the development of multiple myeloma. The pathogenetic mechanisms responsible for the development of multiple myeloma in patients with Hashimoto's thyroiditis remain unclear.

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Key words:
Hashimoto's thyroiditis
autoimmune thyroiditis
multiple myeloma
myeloma nephropathy

Hashimoto's thyroiditis is a chronic and organ-specific autoimmune disease associated with the production of autoantibodies and characterized by progressive lymphocytic infiltration of the thyroid gland [1, 2]. It is associated with myeloproliferative and lymphoproliferative neoplasms (eg, malignant lymphoma) and increased risk of carcinoma of the thyroid gland [2]. However, to our knowledge, the association of Hashimoto's thyroiditis with multiple myeloma has not been reported. Multiple myeloma can occur together with autoimmune diseases including rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus (SLE), and primary biliary cirrhosis [3–6]. We report the case of a patient with Hashimoto's thyroiditis who developed multiple myeloma with renal failure.

Case Report

A 57-year-old Taiwanese woman had a 30-year history of anterior neck swelling and hypertension without good control for the past 3 to 4 years. Her brother and sister had a history of Graves' disease. In 1998, she visited our hospital for further evaluation of the neck mass. Sonography of the thyroid gland showed diffuse goiter and fine needle aspirates from both lobes of the thyroid demonstrated many Hürthle cells with lymphocyte infiltration. Elevated antimicrosomal antibody (700 μU/mL; normal < 100 μU/mL) was also found and Hashimoto's thyroiditis was diagnosed.

In June 2001, she visited our hospital again because of progressive enlargement of the anterior neck mass. Thyroid function tests showed serum concentrations of free thyroxine of 1.02 ng/dL (normal, 0.71–1.85 ng/dL), thyroid-stimulating hormone of 2.27 μU/mL (normal, 0.49–4.67 μU/mL), and human thyroglobulin of 172 ng/mL (normal, < 55 ng/mL). Fine needle aspiration cytology revealed moderate amounts of Hürthle cells with a lymphocyte background and infiltration, but no evidence of malignancy. Antimicrosomal antibody was positive and antithyroglobulin antibody was negative. She was admitted to the surgery ward on June 28, 2001, for management of diffuse nodular goiter. Surgical intervention was cancelled later due to renal function impairment (blood urea nitrogen, 43 mg/dL; serum creatinine, 8.6 mg/dL). On July 4, 2001, she was admitted to the nephrology ward with complaints of general weakness and mild dyspnea. Physical

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examination revealed an enlarged thyroid gland on the anterior neck. It was fixed, non-tender, and slightly firm in consistency, and there was no associated lymphadenopathy. Cardiopulmonary and abdominal examinations were normal and neurologic examination demonstrated no special signs. There were no skin lesions. Laboratory investigations showed mild normocytic, normochromic anemia (hemoglobin, 10.6 g/dL) with normal white blood cell count (8.5 x 10^9/L), its differentials, and platelet count (306 x 10^9/L). Impaired renal function (blood urea nitrogen, 75 mg/dL; serum creatinine, 10.2 mg/dL) was noted. Her serum albumin concentration was 3.2 g/dL (normal, 3.7–5.3 g/dL) and total protein was 5.5 g/dL (normal, 6.4–8.4 g/dL). Other serum biochemistry including sodium, potassium, calcium, phosphorus, alkaline phosphatase, glucose, and liver enzymes were within normal ranges. Skeletal roentgenogram survey showed no evidence of osteolytic lesions. Needle biopsy of the kidney, to determine the cause of acute renal failure, showed many intraluminal casts surrounded by macrophages, consistent with myeloma cast nephropathy (Fig. 1). Immunoglobulin G (IgG) was normal (754 mg/dL), while IgA (60 mg/dl) and IgM (24 mg/dL) were diminished. Free kappa monoclonal gammopathy was detected on serum protein electrophoresis and a kappa monoclonal band was identified by immunofixation in urine. Bone marrow examination of iliac-crest bone biopsy revealed a picture of hypercellular bone marrow replaced largely by immature plasma cells (Fig. 2). The diagnosis of multiple myeloma with renal failure was made on the basis of immunologic, biochemical, and pathologic findings. Chemotherapy including vincristine sulfate and epirubicin was started. Her symptoms improved after two courses of chemotherapy. However, renal function progressively deteriorated. The patient was followed at our hematology department and was receiving maintenance hemodialysis at our nephrology unit 10 months after the diagnosis of multiple myeloma.

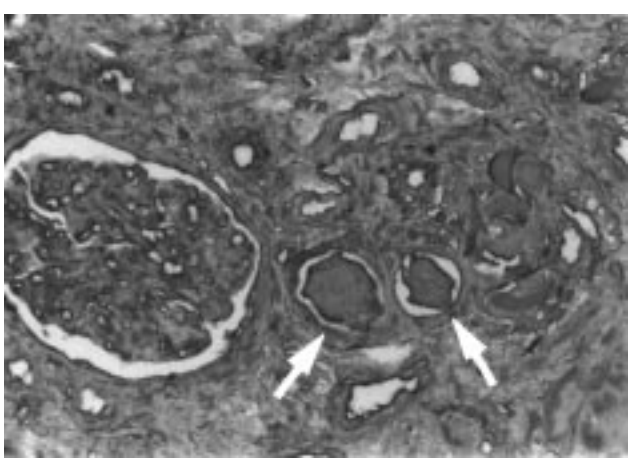

Fig. 1. *Kidney biopsy shows formation of many intraluminal casts (arrow) consistent with myeloma nephropathy (immunohistochemical stain for kappa light chain, x 400)*

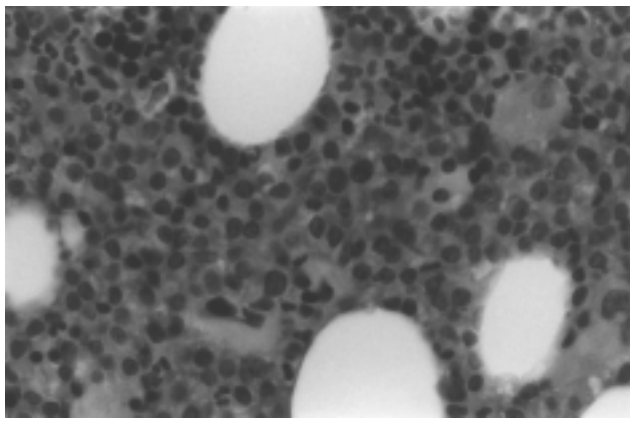

Fig. 2. *Bone marrow aspiration from iliac-crest bone demonstrates a hypercellular picture of immature plasma cells with an increased nuclear:cytoplasmic ratio (hematoxylin & eosin stain, x 400)*

Discussion

Hashimoto's thyroiditis is an autoimmune inflammatory disease of the thyroid frequently affecting women of middle age [1]. It appears to be increasing in prevalence and is now more easily detected by sensitive molecular techniques and more invasive procedures such as fine needle aspiration [2]. The presence in the serum of increased concentrations of various antithyroid autoantibodies allows the use of laboratory assays to confirm the clinical diagnosis. These autoantibodies include antithyroglobulin antibody, detected by tanned red cell agglutination test, and antithyroid peroxidase (or microsomal) antibody, detected by immunofluorescence or the more sensitive enzyme-linked immunosorbent assay [2, 7]. Pathologic features of Hashimoto's thyroiditis include diffuse infiltration of lymphocytes usually with formation of lymphoid follicles, varying degrees of fibrosis, oxyphilic change, or squamous metaplasia in the epithelial cells. Hürthle cells may be found in non-malignant thyroidal diseases such as Hashimoto's thyroiditis [1, 8]. The usual presentation is generally only diffuse and elastic hard goiters detected by palpation. In some patients, hypothyroidism develops with progression of the disease, and destructive thyroiditis accompanied by a thyrotoxic state may develop during the course of the disease. In our patient, the diagnosis of Hashimoto's thyroiditis was confirmed by its clinical manifestations, immunologic test results, and histologic features.

Patients with chronic lymphocytic thyroiditis have an increased risk of myeloproliferative and lymphoproliferative neoplasms [9]. The relationship between Hashimoto's thyroiditis and malignant lymphoma is

now well documented [2, 9]. The association of Hashimoto's thyroiditis and carcinoma of the thyroid gland has also been reported [9].

Multiple myeloma, the disseminated form of plasma cell disorder, is a proliferation of malignant plasma cells that may appear as myelomatosis, solitary myeloma of bone, or extraosseous plasmacytoma [10]. The average age at diagnosis is between 60 and 65 years and fewer than 2% of cases are under the age of 40 [10, 11]. Multiple myeloma was initially diagnosed in our patient based on the identification of a monoclonal immunoglobulin fragment (kappa light-chain) on serum and urine electrophoresis and histologic features of the kidney consistent with myeloma nephropathy. Renal failure is usually present at the diagnosis of myeloma and may be the presenting feature, as in our patient. Renal involvement accounts for approximately 25% of cases of multiple myeloma [10, 11]. Chemotherapy is the mainstay of treatment for multiple myeloma.

Previous reports have stressed the association between multiple myeloma and some autoimmune diseases. These autoimmune diseases include primary biliary cirrhosis, rheumatoid arthritis, Sjögren's syndrome, and SLE [3–6]. A previous study, which isolated genomic DNA from patients with non-Hodgkin's lymphomas (NHL), found that somatic *Fas* (APO-1/CD95) mutation may play a role in the pathogenesis of some lymphomas. It also suggested a link between *Fas* mutation, cancer, and autoimmunity. *Fas* mutations have been found in multiple myeloma, and a high incidence of autoreactive phenomena, such as SLE, Sjögren's syndrome, and Hashimoto's thyroiditis, are present in NHL patients with *Fas* mutations [12]. Monoclonal gammopathy (M-component) may be found in some patients with Hashimoto's thyroiditis [13]. It has also been reported that about 1% of sera from Hashimoto's thyroiditis patients shows a myeloma-like protein on electrophoretogram [14]. Some immunologic and immunohistologic studies have shown that all thyroid lymphomas associated with Hashimoto's thyroiditis were of the B-cell type [1, 2]. It has been suggested that immune deficiency is a predisposing factor for B-cell lymphoma [1]. The impaired normal immunoglobulin production found in multiple myeloma may be due to the presence of monocytes or macrophages that suppress the maturation of normal B-cell lymphocytes into antibody-secreting plasma cells. On the other hand, solitary plasmacytomas occur most commonly in patients with Hashimoto's thyroiditis, which must be considered to indicate involvement of the thyroid in multiple myeloma [15]. Thus, multiple myeloma can develop in autoimmune disorders such as Hashimoto's thyroiditis. In our patient, multiple myeloma developed about 30 to 40 years after the onset of Hashimoto's thyroiditis. One possible explanation for this observation is that continuous immunologic stimulation, perhaps by an autoantigen, may lead to malignant transformation of immunocompetent cells in plasma cell series [16]. An alternative possibility is that the patient had an underlying primary disorder of plasma cells and that the presence of Hashimoto's thyroiditis and multiple myeloma may, therefore, have been a coincidence. Furthermore, our patient had a family history of autoimmune disease (her brother and sister had Graves' disease). The familial tendency for autoimmune disease may cause disturbances of cell function in both plasma cell and monocyte series, and contribute to the likelihood of plasma cells disorders [16, 17].

In conclusion, the pathogenetic mechanism responsible for the association of Hashimoto's thyroiditis and multiple myeloma has not been elucidated. Although active immune disorder might play an important role in lymphomagenesis in patients with Hashimoto's thyroiditis, it is not clear whether the chronic inflammation that takes place in Hashimoto's thyroiditis stimulates the development of multiple myeloma. The identification of factors that influence the development of multiple myeloma in patients with Hashimoto's thyroiditis deserves further investigation.

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