Smoldering Myeloma Associated with Zonisamide Treatment

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Abstract

A 39-year-old man was found to have hyperproteinemia after being treated with zonisamide for 10 years. Laboratory examination revealed a serum M-protein which consisted of IgG (λ) and an increased number of plasma cells in the bone marrow, resulting in a diagnosis of smoldering myeloma. Considering his age, zonisamide was suspected to play an etiologic role in the occurrence of smoldering myeloma. Zonisamide was changed to sodium valproate. Subsequently the M-protein did not increase over 13 months. When zonisamide is used, the monitoring of serum levels of M-protein and patterns of gammaglobulin is warranted.

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Introduction

Multiple myeloma is a disorder caused by malignant proliferation of plasma cells in the bone marrow. The clinical manifestations of myeloma vary from smoldering myeloma to symptomatic plasma cell dyscrasia. Genetic or chromosomal abnormalities are involved in its pathophysiology (1–3). Besides, extrinsic factors such as exposure to radiation (4–7) and therapeutic agents (8, 9) have also been suggested to play an etiologic role. Use of anticonvulsants including phenytoin, phenobarbital and primidone have been associated with multiple myeloma (9–15). Zonisamide, a 1, 2-benzisoxazole-3-methanesulfonamide, a new benzisoxazole, was shown to be effective in both patients with partial and generalized seizures without serious adverse reactions (16, 17). Because of its broad spectrum of effectiveness and easy attainment of compliance, it has been widely used in Japan as well as in other countries during the past 10 years. We report here a young man with smoldering myeloma associated with zonisamide treatment. An initial clue to the diagnosis of smoldering myeloma was hyperproteinemia which was incidentally found during periodic health check when the patient had no symptoms related to the abnormal proliferation of plasma cells. We also discuss the significance of monitoring serum levels of gammaglobulin when patients are treated with this drug.

Case Report

A 39-year-old man visited Tokai University Hospital in July 2000 because of hyperproteinemia (8.6 g/dl), which was incidentally found on the occasion of a periodical health check. He had neither apparent family history nor a history of exposure to radiation or chemotherapy. He had a history of partial seizures due to an arteriovenous malformation in 1990. Since then he had been treated for generalized seizure with the anticonvulsant, zonisamide, at a daily dose of 200 mg for 5 years followed by 100 mg for 5 years. He had taken no medication other than zonisamide for 10 years. By reviewing his medical record, the level of serum total protein had gradually increased from 6.5 g/dl (normal range: 6.5-8.0 g/dl) in 1993 to 8.2 g/dl in 1998 during treatment with zonisamide (Fig. 1). He did not complain of any bone pain. Physical examination revealed no apparent abnormal findings except hemiparesis of the left lower extremity due to the past history of subarachnoid hemorrhage. Laboratory examination showed an elevated serum level of immunoglobulin G (IgG, 3,680 mg/dl) with suppressed levels of IgM (38 mg/dl) and IgA (40 mg/dl). Protein fractionation showed an M-peak (Fig. 2). Immunoelectrophoresis fractionation of the serum protein revealed M-protein composed of IgG with a single λ type of L chain. Bence-Jones protein in urine was not demonstrated. Serum levels of creatinine, calcium and β₂-microglobulin were not elevated. Peripheral blood examination showed no cytopenia. Helper T cell count (CD4) was normal. X-ray findings of the skull showed equivocal bone lesions reflecting a history of brain surgery. X-ray findings of ribs, lumbar spine and pelvis were within the normal limit. Bone marrow aspiration revealed moderately increased plasma cells in 8.1% of the nucleated cells (Fig. 3). Chromosomal analysis of bone marrow showed a normal karyotype of 46 XY. Electroencephalogram showed irregular spikes and waves, which were dominant in the right frontal-parietal area. Because zonisamide was suspected as the...
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Figure 1. Clinical course of the patient. Changes of serum total protein (○) and IgG (■) levels were shown in relation with zonisamide treatment.

Figure 2. Fraction analysis of the serum protein of the patient. Fraction analysis of the serum protein at initial presentation revealed an M-peak with other classes of immunoglobulin suppressed. Immunoelectrophoresis fractionation of the serum protein revealed an M-bow of immunoglobulin G with λ type of L chain.

Figure 3. The appearance of plasma cells in the bone marrow smear (May-Giemsa stain, ×1,000). Bone marrow aspiration revealed moderately increased numbers of plasma cells. The appearance of plasma cells is not apparently abnormal. One plasma cell is binucleate.
cause of the M-protein, it was replaced with sodium valproate for the treatment of seizure. Treatment with sodium valproate prevented convulsions and there was no significant increase in the serum concentration of IgG during the 13-month observation period.

Discussion

A 39-year-old man who had been treated with zonisamide for generalized seizure after surgical treatment of subarachnoid hemorrhage was incidentally found to have M-protein accompanied by suppressed levels of other classes of immunoglobulin. The clinical manifestations of myeloma vary from smoldering myeloma to symptomatic plasma cell dyscrasia. A lot of variables, alone or in combination, have been used as a discriminating index to malignant proliferation of B-lymphocytes or plasma cells. In this patient, the clinical features of malignant B-lymphocyte or plasma cell disorder were absent, including osteolysis, suppression of hemopoiesis, hypercalcemia and renal dysfunction. However, a moderately increased number of marrow plasma cells (>5%) and a high concentration of M-protein (>3.5 g/dl) with suppressed levels of other classes of immunoglobulin suggested a monoclonal malignant proliferation of B-lymphocyte or plasma cells. Thus, the patient was diagnosed as having smoldering myeloma (18).

Multiple myeloma is prevalent in the elderly, usually over the age of 60 years old, and can also occur in young adults, but onset before 40 years of age is quite rare (19, 20). Since our patient was much younger than the typical age for multiple myeloma, the presence of extrinsic factors as an etiologic role was suspected. Several anticonvulsants have been suggested to have a causal association with multiple myeloma, and most of these reported cases had IgG (λ) type of M-protein (15). The type of M-protein in our patient was also IgG (λ). Thus, it was strongly suggested that M-protein was induced by long-term treatment with zonisamide for generalized seizure. Use of some anticonvulsants such as phenytoin, phenobarbital and primidone have been associated with multiple myeloma (9, 10, 12–15).

How a monoclonal proliferation of B-lymphocytes or plasma cells is stimulated by use of anticonvulsants is not precisely understood. In experimental studies, some of these drugs have been demonstrated to cause abnormal proliferation of B cells or suppress the production of immunoglobulin (16, 21–23). The chemical structure of zonisamide does not have an ureid structure which is common among the conventional drugs that have been associated with multiple myeloma. The basic structure, which is essential for anticonvulsive action and is present in zonisamide may cause the abnormal proliferation of B-lymphocytes or plasma cells leading to myeloma. Compared with phenytoin, phenobarbital and zonisamide, valproate has quite a different chemical structure devoid of an aromatic ring structure and has not been associated with myeloma. Therefore, prescription of zonisamide was replaced with sodium valproate for the treatment of seizure. Although an observation period of 13 months is too short to determine the long-term effect, there was no increase in the serum level of total protein nor IgG. Our experience with this patient suggested that the occurrence of multiple myeloma must be taken into consideration when patients are treated with zonisamide, regardless of the patient’s age.

A few patients with IgA and/or IgG deficiency have been reported in association with zonisamide (24, 25). One of the patients with immunoglobulin deficiency recovered after cessation of zonisamide (25). The present patient was incidentally found to have hyperproteinemia during a periodical health check and was subsequently diagnosed as having smoldering myeloma in the early stage of the disease. The percentage of plasma cells in bone marrow nucleated cells was as low as 8%, which is much lower than those that have been reported in patients with multiple myeloma associated with anticonvulsants. Since a considerable proportion of patients with smoldering myeloma definitely progress to symptomatic plasma cell myeloma, the reversibility of the disease progression by removal of zonisamide in this early stage of the disease should be investigated. We recommend a periodical examination of serum levels and patterns of gammaglobulin when patients are receiving zonisamide as well as other anticonvulsants, which will be useful in early detection of M-protein as well as a deficiency in immunoglobulin. Thus, many more patients with M-protein induced by anticonvulsants would be found in the earlier stages of multiple myeloma or monoclonal gammopathy of undetermined significance (MGUS), where reversibility of the disease progression by the removal of these drugs must be investigated. This is the first report of a case with smoldering myeloma associated with zonisamide treatment.

References

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