Multiple Myeloma in a Patient With Familial Mediterranean Fever

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of painful inflammation in the abdomen, chest, or joints. The coexistence of multiple myeloma (MM) and FMF is an extremely rare event. Here, we report a case of FMF with concurrent MM. A 63-year-old woman was diagnosed with FMF since 15 years earlier. She was admitted with a complaint of low back pain. Regarding the presence of back pain, anemia, hypercalcemia, and kidney failure, a diagnosis of MM was suspected. A skeletal survey showed punched-out lesions in the skull. Serum protein electrophoresis demonstrated an immunoglobulin G kappa monoclonal gammopathy, and bone marrow aspiration revealed 30% involvement by abnormally appearing plasma cells, suggestive of MM. Although the association between FMF and MM may be a mere coincidence, further studies are necessary to understand their concurrent development.

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of painful inflammation in the abdomen, chest, or joints.1,2 The FMF gene, also named as Mediterranean fever (MEFV) gene, is located on the short arm of chromosome 16.3 Multiple myeloma (MM) is a neoplastic plasma-cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction.4 Multiple myeloma in patients with FMF is very rare and its association with FMF is very exceptional. We report a case of FMF presenting with nephrotic syndrome and chronic kidney failure which were found to be due to MM.

CASE REPORT

A 63-year-old Iranian woman was diagnosed with FMF 15 years earlier. The clinical presentations of the FMF were characterized with recurrent short episodes of fever and severe abdominal pain accompanied by unilateral pleuritis. Although the clinical presentations of the patient was suggestive of FMF, we performed a molecular analysis of her DNA looking for mutations in the MEFV alleles and 2 mutations were identified as V726A and A744S. Oral administration of colchicine, 1 mg daily, was started, and the response was dramatic: the febrile attacks disappeared and the patient had an increased feeling of well-being and rising levels of physical activity for many years.

At the time of FMF diagnosis, laboratory values were as follows: serum creatinine, 1.4 mg/dL (reference, 0.5 mg/dL to 1.1 mg/dL); blood urea nitrogen, 48 mg/dL (reference, 6 mg/dL to 20 mg/dL); and urine protein excretion in 24-hour urine collection, 3800 mg (reference, < 150 mg). Amyloidosis was clinically suspected, and an abdominal fat-pad biopsy was performed, which was positive for Congo red stain for amyloid. The patient was treated with colchicine, calcitriol, losartan, and captopril. Several months after the
start of treatment, kidney function was improved and proteinuria declined to less than 500 mg/d. The patient was visited at the outpatient clinic 4 times per year.

Six month prior to the most recent clinic visit, the patient was admitted to the neurosurgery department with a complaint of severe low back pain. Back pain had been intensified with activity and prevented the patient from everyday activities. However, the diagnosis was severe osteoporosis of the lumbar spine, and the patient underwent an external fixation of lumbar spine.

Five months after discharge from the neurosurgery service, the patient was admitted to our department with complaints of peripheral edema and no improvement in back pain. On physical examination, the patient was hemodynamically stable. There was no palpable lymphadenopathy, hepatomegaly, or splenomegaly. Her complete blood count showed a hemoglobin level of 10.6 g/dL (reference, 12 g/dL to 16 g/dL), a platelet count of 350 × 10^9/L (reference, 150 × 10^9/L to 450 × 10^9/L), and a leukocytes count of 8.6 × 10^9/L (reference, 4.5 × 10^9/L to 10 × 10^9/L). Other laboratory tests on the serum showed a urea nitrogen level of 54 mg/dL, a creatinine level of 1.7 mg/dL, an albumin level of 4.2 g/dL (reference, 3.5 g/dL to 5.5 g/dL), an erythrocyte sedimentation rate of 85 mm/h (reference, ≤ 29 mm/h), a sodium level of 136 mEq/L (reference, 135 mEq/L to 145 mEq/L), a potassium level of 4.8 mEq/L (reference, 3.5 mEq/L to 5.0 mEq/L), and a calcium level of 11.5 mg/dL (reference, 8.5 mg/dL to 10.2 mg/dL). The results of 24-hour urine collection showed a nephrotic-range proteinuria (7000 mg/d).

Regarding the presence of back pain, anemia, elevated erythrocyte sedimentation rate, hypercalcemia, and kidney failure, a diagnosis of MM was suspected. A skeletal survey showed multiple well-defined lytic lesions (punched-out lesions) with variable sizes in the skull (Figure 1). Serum protein electrophoresis and immunofixation electrophoresis were performed that demonstrated immunoglobulin G kappa monoclonal gammapathy (Figure 2), and bone marrow aspiration and biopsy showed 30% involvement by abnormally appearing plasma cells with eccentric nuclei and a perinuclear halo of clearer cytoplasm, suggestive of MM (Figure 3). The patient was then treated with chemotherapy (bortezomib, cyclophosphamide, and dexamethasone). However, clinical follow-up showed no improvement in back pain and kidney failure.

**DISCUSSION**

Although the exact etiologic factors of MM are not known or well established, there are some factors which may increase the risk of developing the disease. An elevated risk of MM has been associated with older age, male sex, black race, positive family history, radiation, immunosuppression, infections, medication use, occupational exposures, and lower levels of education, income, and socioeconomic status. The role of medication use in MM risk remains unclear. However, there is very little information on medication use and subsequent risks of MM. In a population-based case-control study among
Colchicine is a neutral and liposoluble alkaloid that interferes with microtubule growth and mitosis. Colchicine blocks mitosis and has been associated in rare cases with hematological complications and leukemia. Until additional reports of drug toxicity become available, patients with gout receiving colchicine should undergo careful hematological evaluation. Thus, the occurrence of MM in patients with gout might be accepted as a manifestation of colchicine toxicity.

There are reports that show a co-occurrence of a group of malignancies with FMF, which leads to the conclusion that some of the connections between the FMF and carcinogenesis have been established. It is hypothesized that the MEFV gene is a cancer susceptibility gene. High frequencies of the MEFV gene mutations have been identified in patients with myeloid neoplasm. In patients with the MEFV gene, pyrin serves a key role in regulating the intensity of the inflammatory response. Pyrin, the protein product of the MEFV gene, functions in the modulation of interleukin-1β and nuclear factor kappa B. Therefore, any variant of the MEFV gene prevents the formation of normal pyrin protein.

<table>
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<tr>
<th>Study</th>
<th>Year</th>
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<th>Sex</th>
<th>Symptoms of FMF</th>
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<tr>
<td>Esquinas Blanco et al</td>
<td>1992</td>
<td>Spain</td>
<td>55</td>
<td>Male</td>
<td>Articular involvement</td>
<td>Not reported</td>
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<tr>
<td>Salem et al</td>
<td>2013</td>
<td>Tunisia</td>
<td>53</td>
<td>Male</td>
<td>Abdominal pain, Febrile paroxysms, Inflammatory arthritis</td>
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<td>Present report</td>
<td>2015</td>
<td>Iran</td>
<td>63</td>
<td>Female</td>
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<td>V726A/A744S mutation</td>
<td>Bone pain</td>
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and it may lead to postponed apoptosis and inflammation due to the reduced ability of pyrin to control nuclear factor kappa B and interleukin-1β activation.14

The above data suggest that factors such as older age, colchicine, and the MEFV gene may have a role in the occurrence of MM in FMF. The combination of FMF in MM is reported only twice in the world literature.15,16 Demographic and clinical data of the presented cases compared to previously reported cases are shown in the Table.

Although the association between FMF and MM may be a mere coincidence, further studies are necessary regarding this matter.

CONFLICT OF INTEREST
None declared.

REFERENCES

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