A New Case of IgE Myeloma
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We report a case of IgE myeloma in a 78-year-old woman who presented with bone pain in the shoulder and hip and progressive weakness. Except for hypercalcemia, routine chemistry values were within normal limits. Hemoglobin was decreased and the leukocyte count slightly increased. Plasma cells were not observed in the peripheral blood. Serum protein electrophoresis showed a monoclonal protein in the β-globulin fraction. Immunofixation confirmed the presence of an IgE κ monoclonal protein. A bone marrow biopsy revealed an interstitial and nodular infiltration of abnormal plasma cells comprising 60% of nucleated cells present. Skeletal roentgenograms and bone scans of this patient showed osteolytic lesions and osteopenia of the thoracic and lumbar spine and osteolytic destruction of the right half of the sacrum. Flow-cytometric analysis of mononuclear cells isolated from peripheral blood showed that 15% of the lymphocytes bound IgE. Using cell-surface markers, we identified 45% of the IgE-positive cells as natural killer cells. Similar results have been found in other diseases marked by increased IgE. The clinical, radiological, and laboratory findings for this patient are compared with previously reported cases of IgE and other types of myeloma.

Additional Keyphrases: monoclonal gammopathies · bone · osteopenia · plasma cells · natural killer cells

Since the first description of IgE myeloma (1, 2), 28 cases have been reported (3–30). One case of IgE monoclonal gammopathy of undetermined significance was also described (31). Twelve of these cases were reported within the last decade. Six of all cases had plasma-cell leukemia, for an incidence of 20%, which exceeds the 5% incidence reported for myelomas of all other types (32).

We report another patient with IgE myeloma without plasma-cell leukemia. Clinical, radiological, and laboratory findings including immunofluorescent studies of peripheral blood lymphocytes are compared with those of previously reported cases of IgE and other types of myeloma.

Case History

The patient, a 78-year-old black woman, was admitted with bone pain in the shoulder and hip and progressive weakness. Past medical history included rheumatoid arthritis, hypercalcemia, and hypertension. Laboratory evaluation on admission gave the following: hemoglobin, 106 g/L; creatinine, 14 mg/L; blood urea nitrogen, 110 mg/L; calcium, 6.6 mmol/L; total protein, 76 g/L; and albumin, 36 g/L. Serum protein electrophoresis showed a beta fraction of 28 g/L containing a monoclonal protein. Immunelectrophoresis and immunofixation techniques showed an increased and abnormal reaction with IgE and κ antisera, a negative reaction with IgD, and markedly decreased reactions with IgG, IgA, and IgM antisera. Free κ and λ chains were not detected in serum or urine. Quantification of immunoglobulins gave IgG, 3.54 g/L; IgA, 82 mg/L; IgM, 170 mg/L; and IgE, 14 g/L. The concentration of β2-microglobulin in serum was within normal reference limits. Parathyroid hormone (C-terminal assay) was 5.83 pmol/L (normal, 0.73–4.98 pmol/L). The 24-h excretion of protein in urine was 195 mg (normal, <150 mg). The leukocyte count was 10.7 × 109/L, and the differential count was 0.77 segmented neutrophils, 0.04 band cells, 0.14 lymphocytes, and 0.05 monocytes. Plasma cells were not observed. The platelet count was 148 × 109/L.

Examination of a bone marrow biopsy revealed hypercellular marrow with an overall cellularity of 80%. There was a prominent interstitial and nodular infiltration of abnormal plasma cells. On Wright's-stained smears of bone marrow aspirate, plasma cells made up 80% of nucleated cells. Many of the plasma cells had an immature appearance characterized by enlarged nuclei with fine chromatin and prominent nucleoli (Figure 1). Percentages of other bone marrow cells were decreased.

Immunoperoxidase staining on paraffin sections of the aspirate clot cell block demonstrated diffuse cytoplasmic positivity for κ light chains in plasma cells; staining was completely negative for λ chains. Although IgE was found bound to T cells in the patient's peripheral blood, attempts to demonstrate cytoplasmic IgE in formalin-fixed paraffin sections of bone marrow clot were not successful.

Roentgenograms of the bones revealed osteopenia and mild compression fractures from T5 down through all of the lumbar vertebra. There was osteolytic destruction in the right half of the sacrum.

The patient was treated with fluids for the hypercalcemia and started on melphalan, 12 mg/day for 4 days, and prednisone, 100 mg/day for 5 days. This regimen was continued every 6 weeks.

The patient responded to chemotherapy and improved clinically. The calcium concentration became normal.

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and the beta fraction containing the paraprotein decreased to 7 g/L and then gradually increased to 11 g/L within 10 months after admission. The beta fraction increased further to 24 g/L and the patient died 16 months after admission. The direct cause of death is unknown. An autopsy was not performed.

**Materials and Methods**

Electrophoresis and Immunochemical Methods

Electrophoretic separation and quantification of serum and urine proteins were performed with cellulose acetate (Gelman Sciences, Ann Arbor, MI) and densitometry (Beckman, Brea, CA). Immunoelectrophoresis (Behring Diagnostics, Sommerville, NJ), high-resolution electrophoresis (Ciba-Corning, Rochester, NY), and immunofixation of immunoglobulins (Ciba-Corning) and free light chains were performed with agarose-gel media. Anti sera to immunoglobulins and free light chains were obtained from Behring Diagnostics. The specificity of the antisera for IgD, IgE, and \( \kappa \) and \( \lambda \) light chains was determined with controls obtained from Behring Diagnostics and Kallistad Diagnostics (Austin, TX) and with reference specimens of IgD and IgE obtained from inpatients. IgE, parathyroid hormone (C terminal), and \( \beta_2 \)-microglobulin in serum were quantified by radioimmunoassay.

Flow Cytometry

Mononuclear cells were isolated from peripheral blood by standard procedures (33, 34) with Ficoll/Hypaque centrifugation, washed three times, and in some experiments incubated in RPMI 1640 medium (Sigma Chemical, St. Louis, MO) for 1 h at 37 °C to remove cytophilic antibody (35). Washed cells (2 × 10⁶) were incubated with fluorescein isothiocyanate (FITC)-conjugated OKT4 (CD4; T-cell HLA class II specific, helper cells), OKT8 (CD8; T-cell HLA class I specific, cytotoxic and suppressor cells), and HLA-DR monoclonal antibodies (all from Ortho Diagnostics, Raritan, NJ); or phycoerythrin-conjugated Leu 1 (CD5; pan T cell), Leu 2 (CD8), Leu 3 (CD4), Leu 11c (CD16; IgG Fc receptor, natural killer cells), Leu 19 (CD66; adhesion molecule, N-CAM, natural killer cells) (all from Becton Dickinson, Mountain View, CA); or FITC-conjugated B2 (CD21; complement receptor II, pan B cells), and B4 (CD19; pan B cells) (both from Coulter Cytometry, Hialeah, FL). For two-color staining, FITC-F(ab')₂ anti-human Ig isotype IgM, IgA, IgG, or IgE heavy-chain-specific antibody (Kallistad Labs, Austin, TX) and the phycoerythrin-conjugated monoclonal antibody were incubated simultaneously with 2 × 10⁶ cells at 4 °C for 30 min in the dark in the presence of 30 μL of fetal calf serum. After washing them twice in phosphate-buffered saline plus 10 mL of fetal calf serum per liter, we fixed the cells in 10 g/L paraformaldehyde in phosphate-buffered saline and analyzed with an Ortho Spectrum III flow cytometer (Westwood, MA).

Immunohistochemical Preparations

Formalin-fixed bone marrow was reacted with antisera to \( \kappa \) and \( \lambda \) free chains and to IgE (Dako Corp., Carpinteria, CA). Immunocomplexes were identified by staining with peroxidase-labeled anti-IgG (Sigma Chemical).

Discussion

IgE myeloma has been reported in 17 males and 13 females (ratio, 4:3). The male/female ratio in all other types of myeloma has been reported as 1:1 (36) and 4:3 (37). The ratio in a series of 133 cases of IgD myeloma was 3:1 (36). Most diagnoses of all types of myeloma are made in the sixth and seventh decades of life.

Clinical symptoms such as weakness, fatigue, and weight loss are common in myeloma, and one-third of the patients with IgE myeloma showed these symptoms. Bone pain is frequently present at the time of diagnosis, occurring in ~68% of patients with all types of myeloma. Bone pain is usually present in patients with compressed fracture of the vertebrae and osteolytic lesions of the spine, chest, pelvis, and extremities. Nineteen patients with IgE myeloma complained of bone pain, including our patient, who had multiple compression fractures of three vertebral bodies.

Approximately 4–21% of patients with myeloma present with lymphadenopathy, hepatomegaly, splenomegaly, or a combination of these (37). The incidence of these conditions is reported to be 55% in IgD myeloma (36). Eight patients with IgE myeloma presented with hepatomegaly, splenomegaly, or both, but none with lymphadenopathy.

Renal insufficiency is common in myeloma. Eight patients with IgE myeloma had creatinine values ranging from 19 to 62 mg/L. Five patients presented in renal failure, a condition known to indicate a poor prognosis (38). The survival time of these five patients was 1–13 months. The mean survival time was 19 months for 23 patients monitored with IgE myeloma who were not in renal failure. Three patients were not monitored but survived longer than 19 months (17, 18, 24); one of these survived longer than 8.4 years (26).

Skeletal roentgenograms and bone scans of our pa...
tient showed osteolytic lesions and osteopenia of the thoracic and lumbar spine and osteolytic destruction of the right half of the sacrum. Multiple compression fractures of L1, L2, and L3 vertebral bodies were present. These types of lesions and bone loss were found in 17 patients with IgE myeloma. In some of these patients, the skull, rib, pelvis, and proximal portions of the humerus and femur were involved. Skeletal abnormalities (osteolytic lesions, osteopenia, and osteoporosis) occur in up to 79% of patients with other types of myeloma. Osteosclerosis, which is rarely seen in myeloma (39), was found in two patients with IgE myeloma (4, 11). No patient with IgE myeloma was reported to have amyloidosis, which was found in 7% of patients with other types of myeloma (37).

Twenty-eight patients with IgE myeloma presented with anemia (hemoglobin 40–129 g/L). Eight of these patients had an initial hemoglobin concentration of <80 g/L. Approximately one-half to two-thirds of patients with other types of myeloma present with anemia (36, 37). A reduced hemoglobin has not been shown to affect the prognosis for the patient.

Leukopenia (leukocytes <4 × 10⁹/L) was present in three (14, 19, 25) and leukocytosis (leukocytes >10 × 10⁹/L) in six patients (1, 4, 5, 20, 27, 30) with IgE myeloma. Thrombocytopenia (<100 × 10⁹/L) was present initially in six patients (3–5, 12, 14, 17) and thrombocytosis (>300 × 10⁹/L) in four patients (18, 21, 22, 28). Thrombocytosis and thrombocytopenia occur in ~11% and ~13%, respectively, of patients with other types of myeloma (37).

Bacterial and viral infections are relatively common in patients with myeloma who have various degrees of immunosuppression. Bacterial and viral infections were reported in 14% of untreated and treated patients with myeloma (37). Infections were the cause of death in 13% of patients with IgD myeloma (36). Six of 30 patients (20%) with IgE myeloma were reported to have respiratory-tract infections on admission or later in the course of the disease (3, 6, 16, 22, 23, 25). Our patient had no evidence of infection on admission or after therapy.

Plasma-cell leukemia was not present in our patient but was reported in six patients with IgE myeloma (1, 3, 6, 14, 20, 27). Plasma-cell counts ranged from 10% to 65%. The incidence of plasma-cell leukemia was reported to be 16% for other types of myeloma (37). Our patient had 60% plasma cells in a bone marrow aspirate (Figure 1) with 10% to >90% (mean, 48%) reported in 22 other patients with IgE myeloma. This range is similar to that found in other types of myeloma where the mean is 36% (37).

Hypercalcemia was found initially in our patient and in four other patients (6, 12, 23, 27) and hypocalcemia was found in four patients (8, 9, 19, 24). Hypercalcemia is one cause of renal insufficiency, although only two of the patients with hypercalcemia were reported to have this condition (6, 27). Of patients with other types of myeloma, 30% were reported to have hypercalcemia initially and 1% to have hypocalcemia initially (37).

Ninety percent of patients with myeloma had an erythrocyte sedimentation rate (ESR) >20 mm/h (37). Of 26 patients with IgE myeloma, 25 had an increased ESR and one had a normal ESR. A normal ESR does not exclude a diagnosis of myeloma. We did not measure ESR in our patient.

Agarose-gel electrophoresis of our patient’s serum on admission showed a relatively high concentration of IgE (14 g/L) in the beta globulin fraction (28 g/L). After 6 months of therapy, the beta globulin fraction decreased to 7 g/L but gradually increased to 24 g/L just before death. Other patients with IgE myeloma were initially found to have concentrations of IgE ranging from 0.2 to 75 g/L within the globulin fractions. The total serum protein concentration was normal in our patient and in 13 other patients with IgE myeloma (range 51–125 g/L for all 30 patients). Six patients had normal or decreased total protein concentrations and normal globulin concentrations, which emphasizes that routine screening of total serum protein and albumin concentrations cannot be used to detect immunoglobulin gammopathies in myeloma. Monoclonal IgE migrated in the gamma region (22 patients), the beta region (5 patients), and the alpha-2 region (2 patients). In a review of 648 patients with other types of myeloma, 457 (70.5%) had a detectable monoclonal protein in the gamma region, 182 (28.1%) in the beta, and 9 (1.4%) in the alpha-2 region (37). Many patients with myeloma have no monoclonal proteins detectable in serum by electrophoresis. About 20% of these patients have Bence Jones proteinuria and others (<0.4%) are nonsecretors (37). Monoclonal proteins of very low concentration that migrate in the beta or alpha-2 regions may not be apparent in the electrophoretic pattern of serum. In these instances, diagnosis of myeloma or monoclonal gammopathy of undetermined significance requires careful evaluation of the history and symptoms of the patient plus roentgenography of the bones and analysis of bone marrow aspirate.

Detection of a monoclonal protein in these patients can usually be demonstrated by immunofixation of serum and urine.

Immunofixation of the serum obtained from our patient showed an IgE k monoclonal protein (Figure 2). The k/λ ratio for 30 patients with IgE monoclonal gammopathies was 2:1, which is the same ratio reported in a study of 478 patients with other types of myeloma (37). We could not detect Bence Jones protein in our patient’s serum or urine by using immunofixation. Eight patients with IgE myeloma were reported to have k free chains (6, 9, 11, 17, 18, 22, 23, 28), and eight had λ free chains (1, 3, 16, 20, 24, 25, 28, 29) in urine. In three patients Bence Jones protein was not detected in urine. Bence Jones proteinuria was reported in 96% of patients with IgG or IgA myeloma and in 92% of patients with IgD myeloma. Those studies involved high-resolution electrophoresis and immunofixation (40) or immunoisoelectric focusing (40, 41) of highly concentrated urine. The inability to detect Bence Jones protein in some of the patients with IgE myeloma was probably due to the use of insensitive methods of electrophoresis or low-affinity and low-avidity antisera to

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Immunofluorescent studies of bone marrow showed that the plasma cells were strongly positive for cytoplasmic free $\kappa$ light chains. Immunofluorescent studies of bone marrow showed intracytoplasmic IgE (3, 7–9, 12, 17, 18, 20, 21, 23, 25, 30) and free $\kappa$ (7–9, 12, 17, 23) or free $\lambda$ (20, 21, 25) light chains. Immunofluorescent studies of peripheral blood showed increased numbers of morphologically normal lymphocytes with surface determinants for IgE (3, 6, 7, 12, 14).

Using flow-cytometric analysis of our patient's peripheral blood, we found that IgE was bound to lymphocytes (15%) and was not removed after incubation at 37°C for 1 h in complete medium. This latter procedure is known to remove cytophilic antibody bound nonspecifically to non-B cells (35). Binding of IgG, IgA, IgM, and IgD antibody to all cells was <1%. Additionally, peripheral blood lymphocytes had cell-surface markers that were reactive with CD5 (76%), CD4 (45%), CD8 (44%), CD16 (4%), CD19 (3%), and CD21 (<1%). The cells that bound the IgE were probably not B cells, because of the low reactivity of CD19 and CD21 obtained. Of the IgE-positive cells, 45% were positive for CD8, 58% for CD16, and 40% for CD56. The latter two are natural killer cell markers. This indicates that approximately half of the IgE was bound to CD8-, CD16-, and CD56-positive cells, assuming that these markers represent a single cell population.

Several studies using flow cytometry or other immunofluorescence techniques to measure T-cell subsets showed that patients with multiple myeloma may have reduced percentages of CD4 cells and increased percentages of CD8 cells (42–47). We found an increased percentage of CD8 cells on admission but the percentage of CD4 cells was normal. Five months after treatment of our patient, the T4/T8 ratio normalized. This contrasts with other reports where the ratio remained decreased (42–45, 48) or was normal at admission and after therapy (49). The increase in T-suppressor cells in patients with myeloma may play a role in the suppression of polyclonal immunoglobulin synthesis (50–52).

We found a decreased number of B cells present in peripheral blood lymphocytes on admission. Others have found low or unmeasurable percentages of B cells in peripheral blood lymphocytes of patients with myeloma (48, 49).

Fc receptors for IgE on natural killer cells from normal humans have been detected after incubation with IgE–anti-IgE immune complexes (53, 54). Purified natural killer cells (10–20%) bound the IgE-immune complexes. The presence of IgE-immune complexes bound to our patient's cells can be ruled out on the basis of the lack of significant reactivity of the cells with heavy-chain-specific anti-IgG, -IgA, or -IgM antibodies. This suggests that IgE alone is bound to the cells.

It has been proposed that natural killer cells and T cells with Fc receptors for IgE are involved in the regulation of antibody synthesis (53, 55) and are increased in diseases marked by increased IgE (55). The flow-cytometric results for our patient suggest that IgE is bound to a specific subset of natural killer cells with a high affinity for this immunoglobulin. Further studies are required to determine the functional significance of these cells.

References