IgE Multiple Myeloma: A Report of the Third Case

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The third known case of IgE multiple myeloma is described. The patient was a 65-yr-old woman who died 11 mo after a diagnosis of multiple myeloma was made by a surgical biopsy of the left iliac crest. Her serum contained approximately 2.7 g/100 ml of a paraprotein of mid-γ mobility. The isolated anomalous protein gave a reaction of identity with the IgE myeloma protein of the second reported case when reacted with a specific IgE antiserum.

ISHIZAKA ET AL. HAVE DESCRIBED¹ a new class of human immunoglobulins, called IgE, that is identical with the well-established reaginic antibody, which mediates a variety of allergic sensitivities such as hay fever, atopic dermatitis, etc.² In normal serum the low concentration of IgE, of about 50 μg/100 ml, makes its study very arduous. In 1967, Johansson and Ben nich² reported a patient (N.D.) with multiple myeloma whose serum contained 4.5 g/100 ml of a paraprotein antigenically identical to the normal IgE immunoglobulin described by Ishizaka.³ Subsequently, considerable information about IgE immunoglobulins has been accumulated. However, IgE multiple myeloma is extremely rare, as only a single additional case (Sha) has since been reported by Ogawa et al. in 1969.⁴ The clinical features of both cases had some striking similarities: plasma cell leukemia, absence of skeletal lesions, and considerable A-type Bence Jones proteinuria. This report is concerned with the third IgE myeloma patient, whose clinical manifestations differed from the two prior cases.
A 65-yr-old woman (Hea) was admitted to St. John’s Hospital on March 5, 1970 for investigation of a severe anemia. She had consulted her physician (LES) because of progressive weakness, fatigue, dyspnea on exertion, and tachycardia. Her hemoglobin was found to be 5.0 g/100 ml.

The patient had been well until 6 mo prior to admission when she became aware of some weakness. Two months before admission she had generalized pruritis that subsided several weeks later and 3 wk before admission she had lost a cup of blood from a spontaneous nose bleed.

Her past history disclosed an episode of serum-induced hepatitis in 1951, an attack of gout in 1953 and subsequent persistent hyperuricemia, the onset of easy bruisingability in 1963, a duodenal ulcer in 1964, and an oophorectomy and segmental colectomy for a Brenner tumor and grade I polyploid adenocarcinoma, respectively in 1966. At this time, the hematocrit was 37%, the urine negative for protein, and the uric acid 8.6 mg/100 ml.

Physical examination revealed a comfortable pale woman. The liver was palpable two fingerbreadths below the right costal margin. The spleen edge was also felt. Ecchymoses were present on the arms and abdomen. Fundoscopic examination was unremarkable. The laboratory data were: hemoglobin, 5.0 g/100 ml; hematocrit, 18%; platelets, 62,000/cu mm; white cell count, 12,700/cu mm with 1% blast, 3% myelocytes, 4% metamyelocytes, 3% stabs, 75% neutrophils, 10% lymphocytes, 2% eosinophils, and 2% basophils; 50 nucleated red cells/100 white blood cells; and rouleaux formations. The sedimentation rate was 80 mm/hr (Wintrobe). The urine was negative for protein as determined by Labstix and 20% sulfosalicylic acid tests. The stool gave a 3+ guaiac test. The prothrombin time was 11.8 sec (control 12 sec). The creatinine was 1.2 mg, calcium 9.5 mg, phosphorus 2.7 mg, and uric acid 11.9 mg/100 ml. The serum alkaline phosphatase was 12 King-Armstrong (KA) units. Serum electrophoresis disclosed a total protein of 8.4 g, albumin 3.8 g, alpha1 globulin 0.3 g, alpha2 globulin 0.7 g, beta globulin 0.9 g, and gamma globulin 2.7 g/100 ml. A mid-γ mobility spike was present. Relative serum viscosity or plasma volume studies were not performed. X-ray films of the skull, thorax, spine, pelvis, and long bones demonstrated minimal patchy demineralization of the bony thorax and long bones but were not considered significant.

Three attempts at bone marrow aspirations from different sites were unsuccessful. A surgical left iliac crest biopsy revealed a mild to moderate thinning and decrease in the number of cancellous bone trabeculae. The marrow was heavily infiltrated with aggregates of poorly differentiated plasma cells, although foci of well-differentiated plasma cells were present. Four units of packed red cells raised the hemoglobin to 11.5 g/100 ml. Melphalan (0.1 mg/kg per day × 4; 0.067 mg/kg per day × 20) and allopurinol therapy were instituted, and the patient was discharged from the hospital on March 14.

On April 3, melphalan was discontinued after a total dose of 108 mg because of leukopenia. A week later, patient Hea was readmitted to the hospital because of weakness, tachycardia, widespread petechiae and ecchymoses, and gastrointestinal bleeding. She was pancytopenic. Four units of packed red cells and 12 platelet packs were transfused. The hemoglobin ranged from 5.5 to 12.0 g/100 ml, platelets from 4000 to 89,000/cu mm, white cells from 700 to 1300, and absolute neutrophils from 226 to 600/cu mm. The alkaline phosphatase had increased to 38 KA units, whereas the total serum protein and globulin had decreased to 6.9 and 3.1 g/100 ml, respectively. The patient was discharged on April 20.

Melphalan (0.067 mg/kg per day) therapy was reinstated on May 6 for a total dose of 40 mg. Because of a pancytopenic state she was readmitted to the hospital on May 20. She now complained of dull aching pains in the pelvic and upper femoral areas. The hemoglobin ranged from 5.5 to 12.0 g/100 ml, platelets from 4000 to 89,000/cu mm, white cells from 700 to 1300, and absolute neutrophils from 226 to 600/cu mm. The alkaline phosphatase had increased to 38 KA units, whereas the total serum protein and globulin had decreased to 6.9 and 3.1 g/100 ml, respectively. The patient was discharged on April 20.

Melphalan (0.067 mg/kg per day) therapy was reinstated on May 6 for a total dose of 40 mg. Because of a pancytopenic state she was readmitted to the hospital on May 20. She now complained of dull aching pains in the pelvic and upper femoral areas. The serum alkaline phosphatase was 47 KA units. A skeletal X-ray survey disclosed coarse trabeculae in a setting of a mottled decrease in density of the upper femoral regions, which had not been present on the earlier examination. Four units of packed red cells were given, and the patient was discharged with a hemoglobin of 13.0 g/100 ml on May 27.

From June 5 to June 20, a total dose of 1100 mg of cyclophosphamide (1.66 mg/kg per day × 7; 0.83 mg/kg per day × 8) was administered with an attendant decrease in the
MULTIPLE MYELOMA

Fig. 1. Evolution of widespread diffuse osteosclerotic lesions. Admission X-ray film of pelvis (3/6/70) shows no significant alterations.

bone pain. On July 1 she was again admitted to the hospital because of anemia. The liver edge was felt, but the spleen was no longer palpable. The serum alkaline phosphatase was 55 KA units. X-ray studies demonstrated a mottled sclerosis with a rare lucency in the pelvic bones and the upper femurs. After 4 U of packed red cells, the hemoglobin was 12.9 g/100 ml, and the patient was discharged on July 7.

Another course of cyclophosphamide (1.66 mg/kg per day × 3; 0.83 mg/kg per day × 10) for a total dose of 800 mg was administered from July 17 through July 29. Hospitalization was required on July 31 because of pancytopenia and lower extremity symptoms. An intense pain that started in the knees and moved to the ankles and feet was incapacitating. It was associated with erythema and a nondependent edema of the feet and ankles. Narcotics were required for relief. The serum uric acid was 7.3 mg/100 ml, and the alkaline phosphatase 50 KA units of hepatic type according to isoenzyme fractionation. A serum electrophoretogram did not reveal a paraprotein. An 131I Rose Bengal liver scan demonstrated a 63% uptake that was compatible with mild hepatocellular dysfunction. X-rays showed osteosclerosis involving virtually the entire skeleton (Fig. 1). A sodium radiofluoride (18F) bone scan revealed an increased concentration in both knee joints. Five units of packed red cells were transfused. On August 14, the day of discharge, the hemoglobin was 14.1 g/100 ml, platelets 47,000/cu mm, white cell count 2700/cu mm with 65% neutrophils.

For several months the patient was comfortable, but a recurrence of migratory bone pain involving the shoulders, thoracic cage, pelvis, and upper femurs and agonizing thigh muscle cramps prompted a hospital admission on December 16. Skeletal X-rays demonstrated a progression of the sclerosis. Subcutaneous nodules palpable on the inner thighs were biopsied and disclosed myeloma invading the quadriceps femoris muscle. Serum electrophoresis demonstrated a return of the mid-γ mobility spike. Serum and urine samples were submitted to one of us (BGF) on February 12, 1971. The anomalous protein was identified as IgEk, and the urine contained 10 mg/100 ml of k chains. Elevated uric acid levels were reduced with allopurinol. Prednisone (20-40 mg/day from January 4 to January 22) and 3 U of blood were administered. The blood count was normal except for an occasional nucleated red blood cell and an immature plasma cell at the time of discharge to a convalescent home on February 20, 1971 where she expired on February 22. An autopsy was not performed.

MATERIALS AND METHODS

Serum or concentrated urine were analyzed by microimmunoelectrophoresis and by agar double gel diffusion according to the method of Ouchterlony. A sheep antiserum to the
CELLULOSE ACETATE

NHS
Hea 2/3/1971

UREA STARCH GEL pH 3.5

IgE
Ra IgE
BJP

STARCH GEL pH 8.8

NHS
Hea

Fig. 2. Analysis by cellulose acetate and starch gel electrophoresis of normal human serum (NHS), serum (Hea), isolated IgE, reduced and alkylated IgE (Ra IgE), and isolated urinary Bence Jones protein (BJP) of patient Hea.

IgE myeloma protein N.D. and a rabbit antiserum to the IgE myeloma protein Sha were kindly provided by the National Institutes of Health Immunoglobulin Reference Center and by Dr. H. Grey, respectively. Antisera specific for IgG, IgA, IgM, and IgD, as well as k and \( \lambda \) light chains were obtained from rabbits or goats injected with the respective myeloma proteins or Bence Jones protein incorporated into complete Freund's adjuvant. IgG, IgA, IgM, and IgD serum concentrations were determined by radial diffusion as described by Mancini et al. Light chains in the urine were also quantitated by a modification of the Mancini technique. The IgE myeloma protein of the patient was isolated by DEAE-cellulose chromatography. The serum was dialyzed against 0.005 M phosphate buffer pH 8.0 and applied to a DEAE-cellulose column equilibrated with the same buffer. Most of the IgG was eluted from the column with this buffer and the IgE myeloma protein was subsequently eluted using 0.015 M phosphate buffer pH 8.0. The isolated IgE myeloma protein contained about 3%-5% of IgG. Since only a small amount of serum was available for study, no attempt to purify the IgE myeloma protein further was made. A Beckman microzone electrophoresis apparatus was used to carry out cellulose acetate electrophoresis. Vertical starch gel electrophoresis employing either a 0.05 M glycine buffer pH 8.1 or a 0.05 M formate 8 M urea buffer was also used to examine the isolated myeloma protein. The IgE myeloma protein was reduced in 0.5 M tris buffer pH 8.2 for 1 hr at room temperature at a concentration of 0.02 M dithiothreitol and alkylated at a concentration of 0.05 M twice recrystalized iodoacetamide for 1 hr in the cold.

RESULTS

Cellulose acetate and starch gel electrophoretic patterns of the serum obtained on February 3, 1971 are shown in Fig. 2. The former demonstrated a
monoclonal band of medium \( \gamma \) mobility representing 25% of the total serum protein, or approximately 2.0 g/100 ml. Starch gel electrophoresis of the isolated Bence Jones protein revealed a monoclonal band that had a mobility identical to the light chain of the reduced and alkylated IgE myeloma protein. Quantitatively the serum contained 160 mg of IgG, 40 mg of IgA, and 20 mg of IgM per 100 ml, and IgD was not detectable. Serum electrophoresis, employing specific antisera for the different classes of immunoglobulins, revealed a broad diffuse precipitin arc with the anti-IgE serum and only faint precipitin arcs with anti-IgG, IgA, and IgM antisera indicative of IgE antigen excess. To compare the isolated IgE myeloma protein from our patient with the anomalous IgE protein of the previous cases both were submitted to Ouchterlony analysis. As can be seen in Fig. 3, Hea formed a line of identity with the IgE immunoglobulin of the second patient (Sha) using an antiserum prepared against the myeloma protein of the first patient (N.D.). Both the isolated myeloma protein and the concentrated urine reacted with the antisera specific for \( \kappa \) light chains but not with anti-\( \lambda \) antisera. Radial immunodiffusion quantitation of light chains in the urine revealed 10 mg/100 ml of \( \kappa \) chains and no \( \lambda \) chains. Screen tests (urine layered over concentrated HC1; p-toluene sulfonic acid; heating of acetate buffered urine in a water bath) for Bence Jones protein were negative.

DISCUSSION

Laboratory and bone marrow studies conclusively established the diagnosis of IgE multiple myeloma in patient Hea. Her serum contained a monoclonal

Fig. 3. (A) Double diffusion analysis in agar of isolated IgE myeloma protein Hea (Hea) as compared to IgE myeloma protein Sha (Sha) and myeloma proteins of classes \( \gamma G \), \( \gamma A \), \( \gamma M \) and \( \gamma D \), using an antiserum to IgE myeloma protein N.D. (aE). Each well contains purified proteins at concentration of 1 mg/ml. (B) Double diffusion analysis of isolated IgE myeloma protein (H. \( \gamma E \)) and urine chain antisera. Two human \( \gamma G \) myeloma proteins of \( k \) and \( \lambda \) light chain type are used as reference proteins (k\( \gamma G \), \( \lambda \gamma G \)).
protein that reacted specifically with an anti-IgE antiserum and was antigenically identical to the IgE myeloma protein of the second reported case (Sha) of IgE multiple myeloma. A histologic examination of an iliac crest biopsy was required to make the diagnosis of multiple myeloma that was further substantiated by the demonstration of invasive myeloma in the quadriceps femoris muscles. Prior to the biopsy evidence of myeloma, the clinical combination of leukoerythroblastic anemia, hepatosplenomegaly, and three unsuccessful efforts at bone marrow aspirations suggested a diagnosis of idiopathic myelofibrosis or metastatic carcinoma.

The myeloma protein present in the serum of patient Hea represents the first recognized IgE myeloma of \( \kappa \) light-chain type, as both previously reported IgE myeloma proteins were of \( \lambda \) type.

The clinical data of the case under discussion differed in a number of respects from the two previously reported cases (Table 1). Patient Hea had a relatively low serum concentration of IgE paraprotein, absence of overt Bence Jones proteinuria, a leukoerythroblastic peripheral blood, the evolution of diffuse osteosclerotic lesions, and was of the female sex. By contrast, patients N.D. and Sha had a high serum concentration of IgE paraprotein, heavy Bence Jones proteinuria, plasma cell leukemia, absence of visible skeletal abnormalities, and were of the male sex. However, all three cases had some uncommon manifestations of multiple myeloma—either plasma cell leukemia\(^5\) or osteosclerotic lesions.\(^{12,13}\)

Sclerotic lesions of the skeleton unrelated to therapy or fractures are uncommon in multiple myeloma.\(^{12,13}\) The sclerosis may be circumscribed\(^{14}\) or diffuse\(^{13}\) and local\(^{15}\) or widespread.\(^{13}\) Lucencies may form the core of the sclerotic foci or be independent of them.\(^{12}\) A Guillain-Barré-like syndrome\(^{14-16}\) has occasionally been observed in patients with circumscribed sclerotic foci. Hea had diffuse widespread osteosclerotic lesions as reported by Clarisse\(^7\) and Langley et al.\(^{13}\) These changes were most likely induced by the underlying disease process rather than therapy. Recalcification is not evident until approximately 5–6 mo after the institution of urethane\(^8\) or melphalan\(^9\) therapy. In Hea, however, local sclerosis became apparent 80 days after the first dose of melphalan and then progressed rapidly to involve the skeleton extensively. Moreover, the sclerosis became progressively more intense despite the absence of therapy for a period of 6 mo which suggests that the sclerosis was most likely related to the underlying disease.

<table>
<thead>
<tr>
<th>Patients Identification</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>M-Spike (g/100 ml)</th>
<th>Light Chain Type</th>
<th>Bence Jones Proteinuria</th>
<th>Plasma Cell Leukemia</th>
<th>Skeletal Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.D.</td>
<td>M</td>
<td>50</td>
<td>4.5</td>
<td>( \lambda )</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Sha</td>
<td>M</td>
<td>60</td>
<td>7.5</td>
<td>( \lambda )</td>
<td>+</td>
<td>+</td>
<td>−†</td>
</tr>
<tr>
<td>Hea</td>
<td>F</td>
<td>65</td>
<td>2.7</td>
<td>( \kappa )</td>
<td>−</td>
<td>−</td>
<td>+‡</td>
</tr>
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*Negative screen tests; positive immunochemical detection.
†Lytic bone lesions found at autopsy.
‡Osteosclerosis.
Serum alkaline phosphatase is usually not elevated in multiple myeloma as osteoblastic activity of the skeleton is low. Histologic examination of osteosclerotic lesions from myeloma patients ordinarily demonstrates thickened trabecular bone without osteoblastic activity. The lack of $^{18}F$ uptake by the skeleton on two occasions in patient Hea correspond with low osteoblastic activity despite the widespread diffuse sclerosis. Furthermore, isoenzyme fractionation of the serum alkaline phosphatase pointed toward hepatic rather than bone origin.

The three reported cases of IgE myeloma have clinical features that are uncommon to the other forms of myeloma. However, information from additional cases should be available before definitive statements with regard to the pathophysiology of IgE myeloma can be made.

REFERENCES

16. Fishkin, B. G.: Personal observation at Veterans Administration Hospital (Wadsworth), Los Angeles, Calif.