IgE Myeloma With Osteoblastic Lesions

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A 69-yr-old man with persistent anemia had multiple myeloma with an IgE-type kappa M component and Bence Jones proteinuria. Bone x-rays revealed occasional lytic lesions associated with a diffuse sclerotic reaction throughout the skeleton. Special bone histologic studies utilizing tetracycline labeling, undercalciﬁed sections, and microradiography conﬁrmed active osteoblastic activity. This case was compared with the four previously reported cases of IgE myeloma, one of which also had osteosclerosis.

A NEW CLASS OF HUMAN IMMUNOGLOBULINS, IgE, identical with the reaginic antibody responsible for isologous skin-sensitizing activity, was described in 1966 by Ishizaka et al.1 Subsequently, four cases of IgE multiple myeloma have been described.2 5 The purpose of this paper is to present a fifth case, contrasting it to the previous four. The unusual presence of osteoblastic lesions has been conﬁrmed by special histologic methods.

CASE REPORT

A 69-yr-old man was referred for evaluation of a progressive anemia of 2 yr duration. He complained of recent anorexia with mild nausea and vomiting and a 10-lb weight loss. The patient’s past history included three episodes of nephrolithiasis 12 yr prior to admission. For the past 7 yr, he had been treated with digoxin and spironolactone for congestive heart failure and hypertension. He denied any history of allergies or asthma. The family history was unremarkable.

Physical examination revealed a pale but healthy appearing 69-yr-old white male. The fundi showed arteriovenous nicking. He had an S3 gallop and a grade III/VI systolic murmur. No hepatic or splenic enlargement was detected. The prostate was mildly enlarged, with a soft 0.5-cm nodule on the right lobe.

The hemoglobin was 8.1 g/dl with a 23% hematocrit, a 6500/cu mm white blood count, a 299,000/cu mm platelet count, and 2.3% reticulocytes. The peripheral smear demonstrated marked rouleaux and a rare plasma cell. The erythrocyte sedimentation rate was 153 mm/hr. The urine was positive for protein by the sulfosalicylic acid method. The blood urea nitrogen was 30 mg/dl, creatinine 2.6 mg/dl, and uric acid 9.2 mg/dl. The creatinine clearance was 28 ml/min, and 24-hr urinary protein excretion was 2.91 g. Serum calcium, phosphorus, acid phosphatase, and prostatic acid phosphatase were normal. The serum alkaline phosphatase was 126 units/liter (normal 30-100 units/liter). Serum prostaglandin (PgE) level was 450 (normal 25-100) pg/ml. The total serum protein was 10.7 g/dl with 4.9 mg/dl albumin. Serum protein electrophoresis showed an “M” spike of 4.17 g/dl in the midgamma region. Immunoelectrophoresis disclosed an IgE type kappa protein in the serum and a Bence Jones type kappa protein in the urine. IgG, IgA, and IgM were reduced markedly. Serum viscosity was normal. Bone marrow aspirate revealed sheets of abnormal plasma cells, many having nucleoli and others being multinucleated. Bone marrow biopsy

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Submitted March 25, 1976; accepted September 17, 1976.

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Blood, Vol. 49, No. 2 (February), 1977 295
was hypercellular, with greater than 50% plasma cells. A bone survey revealed a diffuse sclerotic reaction involving the spine, pelvis, and ribs and long bones without thickening of cortical margins (Fig. 1). Scattered osteolytic lesions were also seen in these areas. Numerous classical "punched out" osteolytic lesions were present in the calvarium.

The patient was transfused with packed red cells and begun on a loading dose of melphalan (Alkeran), 10 mg, and prednisone, 40 mg daily. Treatment with allopurinol was also initiated, but had to be discontinued because of the development of a drug rash. The patient's course was characterized by the rapid progression of his disease, with the development of bone marrow and renal failure (Fig. 2). Bone pain was never present, and his calcium and phosphorus remained normal, while his alkaline phosphatase gradually rose to twice normal levels. Six months after diagnosis, he developed a right hemiparesis thought to be secondary to an occlusion of the left middle cerebral artery, and he died quietly at home.

MATERIALS AND METHODS

Special bone histologic studies were performed utilizing a biopsy specimen obtained with a No. 11 Jamshidi needle from the iliac crest 24 hr after completion of a 4-day course of tetracycline, 250 mg four times a day. The specimen was fixed in phosphate-buffered (pH 7.4) for-
maldehyde, dehydrated, embedded in epoxy, and cut at 10 μm on a sledge microtome and at 50 μm on a Buehler Isomet saw. The thinner sections were stained with hematoxylin and eosin. Thicker sections were viewed and photographed with an epifluorescent microscope, HBO 50 mercury bulb, BP 405/5 exciter filter, and LP 418 barrier filter. The same sections were used for microradiography using the method of Dunn et al. Serum PGE levels were performed by the method of Demers et al.7

RESULTS

All spicules of bone were lined by long rows of large plump osteoblasts interspersed with clusters of osteoclasts in Howship’s lacunae (Fig. 3A). Cement lines were numerous and slightly irregular. The marrow spaces were cellular and were filled with slightly pleomorphic plasma cells. A thin line of osteoid covered virtually all of the bone surface (Fig. 3B). Spicules varied from 100 to 300 μm wide, and every spicule contained a large amount of fluorescent material (Fig. 3C). The fluorescence appeared in bands that averaged 40 μm thick, with an additional nonfluorescent band on the surface that was 10 μm thick.
Microradiography showed that the fluorescent areas had a decreased density of calcification (Fig. 3D). Numerous resorption centers corresponding to the clusters of osteoclasts were evident on the microradiographs.

DISCUSSION

The first two reported cases of IgE myeloma were characterized by the presence of plasma cell leukemia, lambda myeloma protein with corresponding lambda Bence Jones proteinuria, and the absence of skeletal lesions. The third case, reported by Fishkin et al., resembled the present case in that the patient had a kappa type M component and widespread osteosclerotic lesions. Surgical biopsy showed mild-to-moderate thinning and decrease in the number of cancellous bone trabeculae on initial presentation when the skeletal survey revealed minimal patchy demineralization. It was suggested that "the lack of 18 F uptake by the skeleton on two occasions . . . correspond[ed] with low osteoblastic activity," but a bone biopsy after the appearance of progressive osteosclerosis was not done. The fourth case had a kappa type-M component with diffuse osteolytic and no osteoblastic lesions.

Osteoblastic lesions are unusual in myeloma, occurring in only 3% of the reported cases. Magolik and Veliath described three patterns of osteosclerosis: isolated foci, diffuse or multiple forms, and sclerotic rings around a central lytic lesion. Similar patterns have been described by others. Histologic descriptions of osteosclerotic lesions in myeloma are few in number and vary from marked osteoblastic activity to areas of osteosclerosis with no evidence of active bone formation. Whether sclerosis results from decreased bony resorption or increased bony reaction has not yet been determined.

In the present case, the immense number of osteoblasts, numerous resorption centers, the numerous slightly irregular cement lines, and the incorporation of tetracycline within large areas of every spicule examined, indicated very active bone turnover. The histology and microradiography confirmed the radiologic findings of diffuse sclerosis or "osteoblastic lesions" in that production in this area exceeded resorption. This change was apparently secondary to an increase in the number of spicules rather than an increase in thickness. Although the amount of bone present in the needle biopsy was too small to allow quantitative analysis, tetracycline deposited in calcifying osteoid formed bands that averaged 10 \( \mu \text{m} \)/day. Such accretion rates would lead to incredibly wide spicules in a very short time if osteoclastic activity were not also increased.

Cultures of bone marrow cells from patients with myeloma have been shown to produce a bone resorbing or osteoclast-stimulating factor, and it has been suggested by Mundy et al. that osteolytic bone lesions in myeloma are due to the secretion of a soluble factor by myeloma cells that, in turn, stimulates osteoclastic activity in adjacent bone.

It has also been postulated that a pluripotential osteoprogenitor cell gives rise to both osteoclasts and osteoblasts. Because an osteoclastic phase always precedes but never follows an osteoblastic phase of activity, the sequence of events in bone formation is thought to occur as follows: osteoprogenitor cell \( \rightarrow \) pro-osteoclast \( \rightarrow \) osteoclast \( \rightarrow \) proosteoblast \( \rightarrow \) osteoblast \( \rightarrow \) osteocyte.

Prostaglandin E (PGE) can stimulate osteoclastic bone resorption. This patient had elevated PGE values and significant osteoclastic activity. The
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cause of the more dramatic osteoblastic activity remains an enigma, but it would be of great interest to know if this IgE protein or some other substance produced by the IgE myeloma cell was capable of stimulating the modulation of osteoprogenitor cells to osteoblasts. Since two of the five reported patients with IgE myeloma have had osteosclerosis, this association may be more than coincidental.

Note added in proof: Since this manuscript was submitted for publication, two additional cases of IgE myeloma have been reported, and another has been cited in Russian literature (Millo et al: Clin Exp Immunol 23:228, 1976; Weiner E, DiCamelli R, Showel J, Osmand AP, Sasseti RJ, Gewerz H: IgE myeloma presenting with classical myeloma features. J Allergy Clin Immunol 58:373, 1976; Stefani DV, Mokeeva RA: Two occurrences of the rare form of myeloma illness (type D and E). Probl Haematol 12:44, 1972).

ACKNOWLEDGMENT

We wish to thank Dr. Howard Dickler for his generous gift of IgE antisera, and for confirmation of the specificity of this protein. We also wish to thank Dr. Lawrence Demers for the performance of the IgE levels, and Dr. Thomas Meloy of Huntingdon, Pa. for the referral of this patient.

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