IgD (Kappa) “Nonsecretory” Multiple Myeloma: Report of a Case

By Carlo Bartoloni, Giovanna Flamini, Carlo Logroscino, Luisa Guidi, Flavia Scuderi, Gino Gambassi, and Tullio Terranova

A case of IgD “nonsecretory” multiple myeloma in a 48-yr-old woman is reported. Despite the presence of disseminated osteolytic lesions, both serum protein electrophoresis and serum and urine immunoelectrophoresis were normal. In addition, bone scintigraphic study was normal. Bone marrow biopsy and aspirate obtained from the left femur lytic lesion showed only myelomatous proplasmocytes; when examined by immunofluorescence with monospecific antisera, the cytoplasm showed only the presence of delta and kappa chains, suggesting that the neoplastic plasma cells might belong to a single clone. Lymphocyte studies indicated the presence of a normal amount of both B and T cells.

Careful studies such as immunoelectrophoresis (IEP) of serum and concentrated urine, bone marrow aspirate examination, and quantitation of immunoglobulins (Ig) allow an easy diagnostic laboratory approach to plasma cell dyscrasias. Nevertheless, about 1% of the patients with multiple myeloma do not show any detectable monoclonal protein in the serum. This condition was called “nonsecretory” myeloma.1

Among those cases presenting the clinical and laboratory features of the classical “secreting” Kahler’s disease, only 1.2% belong to the IgD class.2 The delta class heavy chain, in contrast to other myelomas, is most frequently found to be associated (90%) to lambda type light chain.3

The nonexcretory type of multiple myeloma was first described by Serre4 more than 20 yr ago. Subsequently, about 30 cases have been reported displaying the clinical features of plasma cell dyscrasias without any monoclonal immunoglobulin in the serum; they included IgG, IgA, IgM, and κ-light chain classes.

In the bone marrow of most of these subjects, atypical plasma cells were found showing the same intracytoplasmic homogeneous immunoglobulin. A few cases were classified as “nonproducers” because in the cytoplasm of the neoplastic plasmocytes none of the usual immunoglobulins were detectable. The latter cases of multiple myeloma were considered to be related to a decreased cellular differentiation.4,5 Other authors, however, by means of ultrastructural studies, have suggested that the plasma cells display no impaired capacity for protein synthesis, but produce an antigenically unrecognizable substance.5

Myeloma cell immunofluorescence provides an effective technique in order to detect those B-derived cells capable of producing the characteristic monoclonal protein which, in the nonsecretory form, represents a cytoplasmic storage marker.

Immunofluorescence studies employing monospecific antisera directed against the known heavy chain classes of immunoglobulins (including IgE and IgD) were only performed in a minority of the more recently reported cases. Nonexcretory plasma cell myelomas belonging to the IgG, IgA, IgM, and κ-light chain classes have only been described until now.5

In this article we report the finding of a case presenting a nonsecretory IgD-kappa multiple myeloma.

CASE REPORT

A 46-yr-old woman was admitted to our hospital complaining of progressive headache since August 1979. One month later, severe pain and stiffness occurred at the back of the neck. Cervical spine roentgenogram showed a large osteolysis at the second cervical vertebra level. Myelography was negative. Radiologic skeletal survey revealed disseminated lytic lesions (especially right humerus and right femur, left lesser trochanter), although careful scintigraphic study was normal. Chest x-ray was normal.

Total protein, serum protein electrophoresis, and serum and urine immunoelectrophoresis were normal. Quantitation of immunoglobulins was as follows: IgG 8.9 g/liter, IgA 1.53 g/liter, IgM 1.9 g/liter, and an undetectable amount of IgD and IgE (less than 14 IU/ml and 920 IU/ml, respectively). Blood urea nitrogen (BUN) and serum creatinine were normal; cryoglobulins were absent. Other laboratory findings were: erythrocyte sedimentation rate (ESR) 20 mm in 1 hr; Hb 9.2 g/dl; WBC 4.2 × 10⁹/liter with a normal differential count; RBC 3.46 × 10¹²/liter; urinary calcium 1.76 mmole/liter (normal value less than 5 mmole/liter).

Routine sternum and hip-bone marrow aspirates showed reduced cellularity; lymphocyte/erythrocyte (L/E) ratio was 2:1; both plasma cells and lymphocytes were slightly increased but displaying no atypical features. On the contrary, bone marrow biopsy and aspirate obtained from the left femur lytic lesion showed only myelomatous proplasmocytes; when examined at immunofluorescence, they exclusively contained an IgD-kappa monoclonal protein. Lymphocyte studies were within the normal range, as described under Results.

The patient died 3 mo later. At autopsy, the diagnosis was confirmed by the pathologist.
MATERIALS AND METHODS

Protein Studies
Agarose gel immunoelectrophoresis on serum and concentrated urine (100x) was performed using monospecific rabbit anti-human immunoglobulin class sera (gamma, alpha, mi, kappa, lambda, epsilon, delta) according to the micromethod of Scheidegger. Immunoglobulin quantitation was performed by radial immunodiffusion according to Mancini.

All these reagents were purchased from the Behring Institute.

Bone Marrow Studies
For light microscopy, films from bone marrow aspirates were fixed and then stained with May-Grunewald-Giemsa.

For immunofluorescence study the slides were fixed in acetone and then FITC-conjugated rabbit anti-human immunoglobulin class (gamma, alpha, mi, kappa, lambda, epsilon, delta) monospecific sera were applied. Slides previously treated with the homologous nonfluoresceinated antisera and with phosphate-buffered saline (PBS) alone were respectively used as controls. After washing the slides were examined at Leitz Ortoplan microscope equipped with Osram HBO 100 W/2 u.v. light.

Lymphocyte Studies
Peripheral blood lymphocytes (PBL) were separated by standard procedure (Lymphoprep, Nyeggard). Monocytes were labeled with latex particles 1.1 μm in diameter (Dow Diagnostics).

The E-rosette assay was performed according to R. J. Winchester and G. Ross. E-active rosettes were measured according to J. Wybran and H. H. Fudenberg. EA rosettes were detected using chicken erythrocytes coated with rabbit IgG. "Mixed" rosettes were detected using both sheep red blood cells and EA chicken reagents.

Surface immunoglobulins (SIg) were studied by immunofluorescence with rabbit FITC-conjugated monospecific antisera against IgG, IgA, IgM, IgD, kappa, and lambda chains (Behring Institute).

Antisera
The antisera had been rendered monospecific by the purchaser (Behring Institute, Marburg, F.R.G.) by immunizing the rabbits with highly purified antigens and then by means of affinity chromatography and repeated absorptions employing the suitable immunoglobulin fragments.

The specificity of both the FITC-conjugated and the nonfluoresceinated monospecific antisera (as well as those employed for immunoelectrophoresis) was controlled by means of IEP against either a pool of normal human sera or an IgD-rich fraction.

In addition, the anti-delta heavy chain serum did not stain plasma cells from other types of myeloma except IgD.

RESULTS

Studies on Serum and Urine
No monoclonal protein was discovered by routine serum electrophoresis on cellulose acetate (Fig. 1). The marked increase of alpha-2 globulin in the patient's serum could be explained in relation to "acute phase reactant" presence, as a possible nonspecific reaction against the neoplasm.

No abnormalities could be observed on serum and concentrated urine immunoelectrophoresis employing rabbit anti-human immunoglobulin class monospecific sera.

Fig. 1. Patient's serum electrophoresis (A) compared with normal human serum (B). No M-component is detectable.

Fig. 2. Immunoelectrophoretic pattern of patient's serum (P) compared with normal human serum (N). Gamma, alpha, mi, kappa, lambda precipitation arcs are normal. No precipitation arc can be detected against anti-delta and anti-epsilon monospecific sera.
sera (gamma, alpha, mi, epsilon, delta, kappa, lambda); the serum immunoelctrophoretic pattern is shown in Fig. 2. Anti-delta and anti-epsilon heavy chain sera did not demonstrate any precipitation arc. Proteinuria was absent.

The results of the quantitative determination of serum immunoglobulins were consistent with the immunoelctrophoresis data; although IgG was slightly reduced, all the major immunoglobulin classes were within the normal range (IgG 8.0–18.0 g/liter; IgA 0.9–4.5 g/liter; IgM 0.6–2.5 g/liter). IgD and IgE were found to be below the minimum amount detectable by the radial immunodiffusion technique (less than 14 IU/ml and 920 IU/ml, respectively), and these classes could be considered virtually absent in the patient's serum.

Studies on Bone Marrow

In the bone marrow aspirates obtained from two distinct (sternum and hip-bone) nonosteolytic areas, there was only a slightly increased amount of lymphocytes and plasma cells without any morphological abnormality.

Careful light microscopy and immunofluorescence studies on the cells obtained from one of the involved bones (left femur) demonstrated the presence of a large infiltration of myelomatous plasmocytes that stained only with anti-delta heavy chain and anti-kappa-type light chain sera. They were producing, therefore, a complete IgD-kappa. The bone marrow aspirated from the osteoblastic area did not contain any cells that stained for other classes of immunoglobulins (Fig. 3 and 4). In addition, histologic examination of a bone marrow specimen obtained from the same area demonstrated no signs of metastatic involvement.

Lymphocyte Studies

Immunofluorescence studies for surface immunoglobulins on B lymphocytes revealed these proportions of lymphocytes bearing Slg: IgG 1%; IgA 1%; IgM 10.7%; IgD 9%; κ-type L chain 9.3%; λ-type L chain 3%.

The following values expressed as percent of PBL were found in the rosette assays for T lymphocytes: E-active 16%; E 66%; “mixed” 6%.

Thirteen percent of PBL were Ea-rosette-forming cells.

All the above data are to be considered within the normal range.
IgD-K "NONSECRETORY" MULTIPLE MYELOMA

DISCUSSION

The case described here displays the characteristics of an immunoproliferative neoplastic condition as demonstrated by means of a bone marrow aspirate light microscopy study from the osteolytic areas detected while performing a complete radiologic skeletal survey.

The failure to demonstrate either a serum or a urinary monoclonal component on electrophoresis and immunoelectrophoresis suggested it to be a "nonsecretory" multiple myeloma. The intracellular immunoglobulin in the cytoplasm of the malignant plasma cells seemed to have normal antigenic properties and to be, probably, structurally intact.

The location of the intracellular defect leading to the nonexcretory plasma cell dyscrasia is not clear. The presence of a normal amount of peripheral blood lymphocytes suggests that the defect in the immunoglobulin secretion might be in the plasmocytes themselves. From a clinical point of view, the negative bone scintigraphic study, even when performed at the level of the osteolytic area, is to be emphasized, whereas Wille and associates found increased uptake of the radioisotope in the involved bones. Bone marrow aspirates obtained from the routine sites (sternum and hip-bone) showed a picture consistent with a generalized medullary reaction against a chronic infection or a metastatic neoplasm. A careful study aimed at one of the osteolytic areas revealed the myelomatous tissue, which was characterized as a homogeneous proliferation of neoplastic plasma cells bearing a unique storage-complete immunoglobulin (IgD-kappa). These cells, therefore, seemed to belong to a single clone.

Nonsecretory multiple myeloma might be difficult to distinguish from malignant infiltration of the bone. The former occurrence, however, should be considered in those patients presenting skeletal destruction, hypercalcemia, hypochromic anemia, normal or reduced immunoglobulin classes, and undetectable primary neoplasm. Immunofluorescent techniques applied to a bone marrow specimen, preferably obtained from an osteolytic area, might be of help to the conventional diagnostic approach.

In the case described here, the failure to demonstrate the presence of either a serum or urinary M-component on electrophoresis and the results obtained in immunofluorescence studies with monospecific anti-delta and anti-kappa sera meet all the criteria characterizing a nonsecretory IgD-kappa plasma cell dyscrasia.

ACKNOWLEDGMENT

We are grateful to Dr. G. Mango for his cooperation in performing the light microscopy study.

REFERENCES

IgD (kappa) "nonsecretory" multiple myeloma: report of a case

C Bartoloni, G Flamini, C Logroscino, L Guidi, F Scuderi, G Gambassi and T Terranova