Plasma Cell Myeloma Showing Progressive Bone Destruction during Long-term Clinical Remission

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A case of plasma cell myeloma initially producing Bence Jones protein of lambda type was presented. BJ protein disappeared within two months of cyclophosphamide and betamethasone administration. A complete remission continued for the following 2 years and 8 months with no medication, although the patient insidiously developed osteolytic lesions. The discrepancy of long-term negative BJP and clinical remission without medication and progressive bone destruction was reported.

Key Words: Plasma cell myeloma, Bence Jones protein (BJP), Bone destruction, Osteolytic lesion, Plasma cell, Endoplasmic reticulum, Complete remission

Plasma cell myeloma characteristically displays the features of an autonomous neoplasm of plasma cells with widespread skeletal destruction, production of monoclonal immunoglobulins (Ig) or Ig fragments and increased numbers of plasma cells in the marrow. In this paper, we present a case of myeloma initially producing Bence Jones protein (BJP) of lambda type and subsequently developing widespread osteolytic lesions without BJP for 2 years and 8 months. Characteristics of the case are discussed.

MATERIALS AND METHODS

Cellulose acetate electrophoresis, agarose immunoelectrophoresis, and Ouchterlony immuno-diffusion analyses were done as described previously. All analyses were performed on freshly obtained serum and urine samples. Urine samples were concentrated by dialysis against 50% polyethylene glycol (#6000) prior to analysis. Antisera against γ, α, β, δ, ε, κ, and λ chains were commercially obtained (Hoechst Co.).

Immunoperoxidase staining studies were performed with six micron sections from paraffin blocks. For the sandwich technique using peroxidase-labelled antibody, sections were first treated with the specific rabbit antisera described above, and then with peroxidase-conjugated goat antibody directed against rabbit IgG, followed by staining with the diaminobenzidine (DAB) reaction with eosin counterstaining.

Immunofluorescence studies were performed with bone marrow smears using fluorescein-conjugated antisera. Localization of specific immunoglobulin heavy or light chain type was determined by ultraviolet microscopy.

CASE REPORT

M. Mae; This 42 y.o. housewife had been healthy until the age of 37, when she developed pains in the scapulae and lumbar spine. She was found to be anemic with sciatic pain in June 1975. Routine laboratory data included 320 × 10⁴/mm³ red cells, white cells 6,100/mm³, 18.2 × 10⁴/mm³ platelets, serum calcium 10.3 mg/dl and serum phosphorus 2.1 mg/dl. X-ray survey revealed multiple osteolytic lesions. The total serum protein was 6.8 g/dl including 0.9 g/dl gamma globulin without a detectable monoclonal spike. Serum IgA was 145 mg/dl, IgG 1,000 mg/dl and...
IgM 74 mg/dl. Urine protein electrophoresis revealed a monoclonal band as shown in Figure 1 in 1975. After repeated aspiration biopsies were unsuccessful, a bone marrow biopsy performed on the iliac bone revealed abnormal plasma cells consistent with myeloma.

On the basis of the clinical diagnosis of myeloma, 100 mg cyclophosphamide and 2 mg betamethasone were administered daily for 2 months with an excellent clinical response.

After 2 years and 8 months at home without complaints and receiving no medication, she was re-admitted to the Kobe University Hospital in September 1978 because of swelling and pain of the right scapula. Routine laboratory data included 425 x 10^4/mm^3 red blood cells, 16.7 x 10^4/mm^3 platelets, 4,200 white cell counts, 8.0 mg/ml serum calcium and 4.3 mg/dl serum phosphorus.

Skeletal X-rays in 1978 revealed increased numbers of osteolytic lesions in the skull, clavicles, ribs and cervical spines, compared to the X-rays in 1975 (Fig. 1). Aspiration biopsies from the sternum and iliac crest showed 2.2 x 10^4/mm^3 and 6.4 x 10^4/mm^3 nucleated cells, including 0.6–1.0% plasma cells and 5.4–6.0% immature plasma cells. Serum IgA was 43 mg/dl, IgG 987 mg/dl and IgM 33 mg/dl. Total serum protein was 6.3 g/dl with a normal electrophoretic pattern (Fig. 2). Daily protein excretions in the urine were approximately 0.2–0.4 gm. Electrophoresis showed only albumin with no abnormal spike (Fig. 2). Concentrated (20x) urine was also analyzed by immunofiffusion and was negative with all anti-immunoglobulin antisera. Hundred-fold concentrated urine gave positive reactions against anti-kappa as well as anti-lambda chain, with a conclusion of no evidence of BJP at this time.

Bone marrow biopsy was performed on the left 12th rib in November, 1978. The bony trabeculae were found to be abnormally thin. The ultrastructure of the myeloma cells from the marrow were with a large number of mitochondria, a Golgi complex, large nuclei with a distinct nucleolus, but with poorly-developed endoplasmic reticulum (Fig. 3), consistent with no evidence of BJP. Immunofluorescence study was negative on myeloma cells in 1978 from the marrow using fluorescinated anti Ig-chains, respectively. Immunoperoxidase technique was applied on the thin section of paraffin-blocked marrow materials in 1975 and in 1978. The negative results were obtained in myeloma cells in 1978 using all antisera, in contrast to the positive staining with only anti lambda antiserum on myeloma cells in marrow in 1975.

Because of bone destruction, 50 mg of cyclo-
phosphamide was given for the following one year and a half until September 1980, when an abrupt gait disturbance occurred. Osteolytic lesions became more obvious (Fig. 1), reappearance of BJP (Fig. 2) and marked proliferation of plasma cells of 96.8% out of total nucleated cells in an aspirated bone marrow were also noted. A combination therapy consisting of melphalan, cyclophosphamide, vincristine, ACNU and prednisolone was instituted with poor response. There were multiple fractures of the right humerus, left femur and lumbar spines in association of neurologic manifestations of paraplegia due to spinal cord compression, followed by gradual exacerbation. She died in May, 1982, with more than 7 years of clinical course after the onset.

In summary, the present case had osteolytic lesions by plasmacytoma with a production of lambda type BJP in June 1975. Within 2 months administration of cyclophosphamide and beta-methasone daily, a clinical complete remission with no medication was drawn until November 1978 on the basis of clinical improvements, no evidence of BJP and slight increase of immature plasma cells with poorly-developed rough endoplasmic reticulum in the marrow. However, the osteolytic lesions were progressive, irrespective of clinical course of remission and relapse.

DISCUSSION

Plasmacytoma or myeloma is generally defined as a neoplasm of plasma cells manifesting with osteolytic lesions, increased numbers of plasma cells in the marrow, and the finding of M-type serum or urinary proteins.¹ Plasmacytoma producing only BJP in the urine is much less frequently seen among patients with plasmacytoma. There are also rare cases of non-secretory and non-producing plasmacytoma, where immunochemical and ultra-structural analyses provide findings for
the differential diagnosis against other reticular malignancies or against carcinomatous infiltration of the bone marrow. Non-secretory cases were found to preserve normal synthesis of immunoglobulins, whereas non producing cases exhibit markedly decreased or no synthesis in the cytoplasm.

In vitro studies of mutation by mouse myeloma cells have shown that certain cultured cell lines convert from Ig (usually IgA) producers to non-producers at a very high rate of about $10^{-5}$ - $10^{-4}$ per cell generation. In some cell lines, a step-wise conversion is observed from IgA producers to light chain producers, then from light chain producers to nonproducers. The mutation rate of these events is also very high. If similar mutations occur in vivo in man, such mutant clones may overgrow the wild type cells because of some selective advantage or be quickly eliminated, according to Preud'homme. In any case, the incidence of nonproducers in human myeloma is very low. In two cases of human myeloma, Preud'homme described, the plasma cells first secreted a IgG-M-protein or free light chains and became apparent nonsecretors after melphalan therapy. Cyclophosphamide as well as melphalan are known to be mutagenic for M-protein production by murine plasma cells.

It is unusual in the present case that a complete remission was easily obtained only with 2 months of chemotherapy, and then persisted for the following 2 years and 8 months without medication. Although this type of long-term remission is rare, the mechanism is not clear. There are several possibilities to explain this phenomenon; (1) There was only one clone of BJP-producing cells converted into non-producing, and later again into producing cells, although this is unlikely. (2) There were initially one clone of Ig-producing cells, which was abolished by therapy. The another clone occurred to proliferate during remission, since the growth of second neoplastic clones is favored in impaired immune surveillance or by mutagenic roles of cyclophosphamide, although this is also unlikely. (3) There were two clones, the one of BJP-producing mature cells and the other of non-producing, immature cells. While the immature clones were more resistant to therapy, the former cells clones was probably markedly diminished by chemotherapy, which later proliferated.

However, the precise analyses should include the surface markers of immature cells or non-secretors to determine anaplastic cells of the cell line. It is also interesting to assay for OAF (osteoclast activating factor) in myeloma cells in a different stage in the clinical course, since OAF may have been secreted from the mature and immature plasma cells in the present case.

REFERENCES