CONCISE REPORT

Coincident Chronic Lymphocytic Leukemia and Osteosclerotic Multiple Myeloma

By M. T. Jeha, T. J. Hamblin, and J. L. Smith

We report the first occurrence of chronic lymphatic leukemia (CLL) and osteosclerotic multiple myeloma (MM) in the same patient. The surface Ig of the CLL and the monoclonal serum Ig had different heavy and light chain classes, and CLL lymphocytes failed to secrete the monoclonal Ig in short-term culture. We conclude that they were entirely separate malignancies occurring together by chance.

Both chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) are B-cell tumors. On rare occasions, these tumors coexist, and in this circumstance the question should be asked as to whether this represents a progression or maturation of an existing tumor or the occurrence of two separate diseases in the same individual.

The bony lesions of MM are characteristically osteolytic, and the presence of any osteosclerosis calls for the diagnosis to be reconsidered. Osteosclerosis has been described in MM in a small number of cases, particularly around osteolytic lesions or in areas of periosteal new bone formation, but widespread osteosclerosis is extremely rare.1

We describe here the first association between CLL and osteosclerotic MM and demonstrate that they are two entirely separate diseases.

MATERIALS AND METHODS

Clinical Data

A.H., aged 64 yr. complained of tiredness for 2 mo and when examined, had palpable lymph nodes in the left axilla and right submandibular area, and a barely palpable spleen. Full blood count showed Hb 10.3 g/dl, WBC 37.5 x 10^9/liter, with 84% small lymphocytes and a blue background to the film. Erythrocyte Sedimentation Rate (ESR) was 132 mm in the first hour. Serum electrophoresis revealed a monoclonal band in the ß region, which was identified by immunoelectrophoresis as IgG. Free ß light chains were present in the urine at a concentration of 0.13 g/liter. Serum IgG was 83 g/liter, IgA 0.4 g/liter, and IgM 0.2 g/liter.

Skeletal x-rays showed widespread osteosclerotic lesions in the pelvis and dorsal and lumbar vertebrae, but no evidence of osteolysis, and a radioisotopic bone scan showed a uniformly increased uptake with no "cold" areas.

Bone marrow aspiration yielded peripheral blood only. Trephine biopsy of bone was unsuccessful on two occasions. Clinically, he had a normal prostate, and serum acid phosphatase was normal.

Needle biopsy of the prostate yielded normal prostatic tissue. Eventually, open biopsy of the iliac crest under general anesthesia demonstrated large numbers of plasma cells in the marrow.

He was treated with chlorambucil, 6 mg daily, and prednisolone, 10 mg daily, and on this regime his white count returned to normal but his serum IgG continued to rise. He was then given 4-day courses of Melphalan, 18 mg, and prednisolone, 100 mg, every 6 wk. There was no effect on his monoclonal IgG, and subsequent treatment with cyclophosphamide, vincristine and CCNU was also unsuccessful.

He became severely anemic requiring blood transfusion every 6 wk, but was able to maintain a platelet count between 50 and 100 x 10^9/liter. White count varied between 2 and 4 x 10^9/liter. Despite an adequate platelet count, he suffered from recurrent nose bleeds when his IgG level was above 100 g/liter and these were controlled by a series of 2-liter plasma exchanges. He was maintained on plasma exchange and blood transfusion at regular intervals for 18 mo without chemotherapy, during which time his chronic lymphatic leukemia was no longer manifest. After this time he left the area and died a month later.

Immunofluorescence and Immunoglobulin Synthesis

Peripheral blood from the patient and normal controls was collected into preservative-free heparin and layered over Ficoll-Trisoli. 2 Cells collected at the interface were washed three times and the final pellet was resuspended in culture medium for analysis. Viability was >90% in all preparations.

Cell suspensions were stained with fluorescein-conjugated antisera to immunoglobulin heavy and light chains. 3 Cell smears fixed in methanol and washed in saline were also stained with these antisera by the direct method. Controls were included in all experiments. The fluorescein-labeled preparations were examined using a Leitz Orthoplan microscope fitted with a HB 200 mercury vapor Poelm illuminator.

Bioisotopic labeling techniques and the subsequent characterizations and quantification of labeled Ig have been described in detail elsewhere. 1 Briefly, cells at 5 x 10^6/ml were incubated in leucine-free medium containing 1H-leucine at 50 μCi/ml for 18 hr at 37°C. Cells were separated from the supernatant by centrifugation (1500 g, 15 min) and lysed with phosphate-buffered saline (PBS) containing detergent NP40 and proteolytic inhibitors. Both the cell lysates and supernatants were spun at 35,000 g to remove cell debris and dialyzed exhaustively against PBS. The radioactivity incorporated in all macromolecules was determined by precipitation with 10% trichloroacetic acid (TCA). Labeled Ig was precipitated using a sandwich technique with sheep antiserum specific for human Ig as the first antibody and rabbit antiserum with activity to sheep Ig as the second antibody. Normal sheep serum was used as the first antibody in control precipitations. These Ig precipitates were washed three times with cold PBS prior to counting or preparation for gel analysis. Reduced and alkylated Ig precipitates were identified by immunoelectrophoresis as IgG. Free ß light chains were demonstrated by electrophoresis in the ß region, which was identified by immunoelectrophoresis as IgG. Free ß light chains were present in the urine at a concentration of 0.13 g/liter. Serum IgG was 83 g/liter, IgA 0.4 g/liter, and IgM 0.2 g/liter.

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count was chain intracellular Ig. In culture neoplastic cell preparation for a population of cells with surface light cells secreted a light to heavy chain excess of 4.4. On gel analysis the light chain, with no evidence for a population of cells with surface light chain intracellular Ig. In culture neoplastic cell preparations, synthesized 0.1 of their supernatant and 0.4 of their lysate total labeled protein. On gel analysis the only heavy chain detectable was \( \mu \). No labeled peaks in the \( \gamma \) position were noted in the supernatant or lysate.

### RESULTS

At the time of study, the peripheral lymphocyte count was \( 43.5 \times 10^9/\text{liter} \) and contained \( >99\% \) lymphocytes. Peripheral blood lymphocyte preparations stained for surface \( \text{IgM} \) (66%) and \( \text{IgD} \) (5%) heavy chains with \( \kappa \) (68%) light chain, with no evidence for a population of cells with surface \( \lambda \) light chain intracellular Ig. In culture neoplastic cell preparations synthesized 0.1 of their supernatant and 0.4 of their lysate total labeled protein. On gel analysis the cells secreted a light to heavy chain excess of 4.4 (Table 1). These data are in accord with our findings in CLL and not with myeloma. All counts precipitable with anti-Fab \( \gamma \) serum were precipitable with anti-\( \kappa \) light chain. On gel analysis the only heavy chain detectable was \( \mu \). No labeled peaks in the \( \gamma \) position were noted in the supernatant or lysate.

### DISCUSSION

Where two different tumors of the same tissue occur in the same individual it is important to determine whether or not they have the same origin, since valuable information on the biology of tumors can be derived from such an event.

A total of 16 patients with coincident CLL and MM has been described in the literature. These cases have been detailed in two reviews, although both omit the case reported by Sany et al. In most of these cases, information on immunoglobulin class is lacking. However, in the case of Preud'homme and Seligman, the light chain subtype of the surface Ig of the CLL lymphocytes was the same as that produced by the malignant plasma cells, suggesting that the tumors were related. On the other hand, in the case reported by Hoffman and Rudders the two tumors had different light chain types and antiidiotype antibody raised against the myeloma protein failed to react with the surface Ig of the CLL lymphocytes.

In our patient, both the heavy and light chain classes of the surface Ig of the CLL and the MM protein differed, and furthermore, CLL lymphocytes held in short-term culture failed to produce immunoglobulin of the class of the MM protein, thus demonstrating that the two tumors had a separate origin. In addition, the CLL responded to chemotherapy, whereas the MM progressed despite several different chemotherapeutic regimes.

Osteosclerotic MM is a rare variant that has recently been reviewed. Sixty-eight patients have been described in the literature of whom 27 had osteosclerotic lesions without osteolysis. Such widespread bony sclerosis as was seen in our patient has only rarely been reported. The syndrome carries a worse prognosis than osteolytic MM and is associated with peripheral neuropathy in approximately 50% of patients. Our patient had no neurologic abnormalities but failed to respond to chemotherapy.

In our patient, the diagnosis of myeloma was difficult to establish because the characteristic radiologic features of MM were absent, and it was not possible to obtain bone marrow samples either by aspiration or trephine.

The osteosclerotic bony lesions were thought to resemble those of metastases from carcinoma of the prostate, but this organ was clinically normal, his serum acid phosphatase was normal, and needle biopsy of the prostate yielded normal prostatic tissue.

In view of the fact that monoclonal immunoglobulins occur in between 1% and 5% of patients with CLL, it was thought necessary to culture the patient's small lymphocytes to demonstrate that they were not producing the monoclonal IgG, and armed with this information we decided to perform an open biopsy of bone to obtain adequate histology. This demonstrated heavy infiltration with malignant plasma cells.

Several series have demonstrated a high incidence of second malignancies in CLL, and others have suggested that in MM also there is a high incidence of second malignancies.

In our own recently analyzed series of 100 cases of CLL, 27 had second malignancies. It seems likely therefore that in both of these conditions there is an increased incidence of second malignancies, and by chance, they will occasionally occur together quite independently. Both may have a long latent period before they draw attention to themselves and therefore the fact that they are discovered together should not be taken to imply that they arose together.
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