Multiple Myeloma With Intramedullary Masses of M-Component

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The bone marrow of a patient with light chain myeloma and amyloidosis was substantially infiltrated with basophilic globular particles. The globules, which were confined to the bone marrow, ranged in size from tiny intracytoplasmic inclusions to large (100 μ) extracellular particles. Both the intra- and extracellular globules stained with fluorescent antibody directed against the light chain (κ) produced by the patient's abnormal clone, and not with other fluorescent antiserums. By electron microscopy, even the largest extracytoplasmic globules were bounded at least in part by rough membranes, suggesting that their extreme size was the result of cellular synthesis rather than extracellular coalescence.

Substantial replacement of the bone marrow compartment by abnormal plasma cells occurs with some frequency in multiple myeloma and may lead to pancytopenia, sometimes with early red and white cell forms in the peripheral blood. Intramedullary deposition of protein produced by the plasma cell tumor has not been previously recognized as occupying a significant portion of the bone marrow. The marrow of a myeloma patient, herein described, contained large accumulations of extracellular proteinaceous material with fluorescent-antibody-staining characteristics of the myeloma protein produced by the malignant clone.

CASE REPORT

A 59-yr-old black woman was admitted to the Wilmington Medical Center in December 1972 because of nausea, vomiting, diarrhea, and intermittent pain in the left shoulder and right rib cage for 6 mo. She had been admitted previously for thrombophlebitis and for a hysterectomy. In May 1971, she had been seen in the emergency room for abdominal pain, and at that time urinalysis revealed 3+ protein, and the BUN was 32 mg/100 ml.

Physical examination in December 1972 showed a BP of 200/120, signs of dehydration, and mild right rib tenderness. Hemoglobin was 7.1 g/100 ml. White blood cell and platelet counts were normal. A urinalysis showed 3+ protein. The BUN was 35 mg/100 ml; creatinine, 3.6 mg/100 ml; and calcium, 10.0 mg/100 ml. A chest x-ray showed mottling of the ribs bilaterally. Bone marrow aspiration revealed plasmacytosis with many "globules" ranging in size from 3 to 100 μ which stained blue with Wright's stain. Some globules were found within plasma cells, but most were extracellular. These globules failed to stain with periodic acid-Schiff, Oil Red O, or Sudan Black, and they did not exhibit birefringence with Congo Red. Bone marrow biopsy (Fig. 1) revealed replacement of a large proportion of the marrow with this globular material. Bone survey showed multiple lytic lesions in the skull, vertebrae, ribs, pelvis, and long bones. The heat test for Bence Jones protein was positive. Serum protein electrophoresis showed decreased γ globulin. Urine protein electrophoresis demonstrated a homogeneous spike in the γ region which was identified immunologically as free κ light chain. Total protein excretion was 3.5 g/24 hr.

During hospitalization, the patient developed transient oliguria with progressive azotemia,
necessitating peritoneal dialysis, and hypercalcemia (Ca, 12.7 mg/100 ml) which was controlled with prednisone. She was begun on cyclic phenylalanine mustard and prednisone.

In March 1974, she was admitted with lethargy, vomiting, and a calcium of 14.7 mg/100 ml. The symptom complex improved with prednisone and hydration. Her tongue was noted to be enlarged and indurated. Biopsy of a pedunculated lesion arising from the floor of the mouth showed amyloid, confirmed with Congo Red staining under polarization microscopy. Her treatment was changed to intermittent BCNU, cyclophosphamide, and prednisone.

Despite treatment she deteriorated rapidly over the next several months. The major problem was rapid enlargement of the tongue which severely compromised nutrition. An upper gastrointestinal series on one occasion showed an area of submucosal infiltration 6 cm in length in the cervical esophagus. She died quietly on June 18, 1974.

At autopsy (done by Dr. F. P. Parker), extensive myelomatous involvement of skull, vertebrae, ribs, pelvis, and long bones was confirmed. The previously described globules were seen in all areas of bone marrow. They were not found in any other organs. Amyloid deposition was present in the tongue, myocardium, kidneys, esophagus, gastrointestinal tract, pancreas, and lymph nodes. No amyloid deposits were found in bone marrow.

**SPECIAL STUDIES**

**Bone Marrow Studies**

Cover slip smears of a bone marrow aspirate were fixed in 70% ethanol for 20 min, air dried, and stained with fluorescent antibodies specific for the \( \gamma \), \( \kappa \), and \( \lambda \) polypeptide chains. Smears were viewed with a Leitz ultraviolet microscope, equipped with a Ploem vertical illuminator.
Fig. 2. (A) Photomicrograph of bone marrow aspirate specimen stained with fluorescent anti-κ. x 156. (B) Cell containing many circumferentially staining inclusions. x 1480.

Staining of cells and inclusions occurred only with the fluorescent anti-κ preparation. As is evident in Fig. 2, staining was circumferential.

Electron Microscopy

Aspirated bone marrow particles were fixed in 2.5°c glutaraldehyde, 2°o formaldehyde in 0.05 M phosphate buffer, pH 7.4, at room temperature for 24 hr, postfixed in osmium tetroxide, dehydrated in ethanol, and embedded in Araldite-Epon. Sections (80 nm) were cut with a Sorval MT-2 microtome, stained with uranyl acetate and lead citrate, and examined with an AEI EM-6B transmission electron microscope.

Under electron microscopy, intra- and extracellular inclusion bodies were surrounded by membranes with characteristics of rough-surfaced endoplasmic reticulum. The inclusions, which varied in size from 200 nm to 100 μ, were round, homogeneous, and extremely electron opaque. Around each inclusion was a space bounded by a ribosome-studded membrane. The space, which was of approximately the same width as the flattened cisternae of rough-surfaced endoplasmic reticulum, contained a slightly electron-opaque, amorphous material resembling that found in the cisternae.

Inclusions were also seen in senescent plasma cells, and many inclusions, some as large as 100 μ, were observed outside of cells (Fig. 3), but always a membrane was adherent to all or a portion of the surface of the structure.

DISCUSSION

Inclusion bodies similar to the ones which occupied so much of our patient’s marrow were considered by Russell3 to represent the etiologic agent of cancer. Russell bodies are usually eosinophilic, although basophilic or neutral-staining bodies are occasionally observed. They are electron-dense accumulations of plasma cell secretory products,4 the surfaces of which stain with fluorescent anti-κ.
immunoglobulin. Plasma cells with multiple basophilic staining inclusions have been termed "grape cells" for horticultural similitudes, but intramedullary accumulation of extracellular basophilic inclusions as extensive as that of this patient has not to our knowledge been described.

Since the inclusion bodies did not stain with Congo Red, the relationship between the amyloid deposits in this patient and the inclusions was unclear. Previous authors attempted to correlate Russell bodies with presence of primary and secondary amyloidosis. In a large series of myeloma patients studied by light and electron microscopy, we did not find this correlation.

The mechanism by which the extracellular bodies arose is not certain. The presence of ribosome-studded membranes suggests, however, that the bodies are formed within the rough endoplasmic reticulum of myeloma cells and are released upon death and lysis of the cells. In spite of the extremely large size of some of the bodies, our morphologic observations indicate that each globule arose in a single cell and did not form by coalescence of several extracellular bodies.

In neoplastic processes the effective increase in tumor cell mass reflects the difference between rates of tumor cell division and of tumor cell death. In most instances, tumor cell death is an unheralded event, and, following phagocytosis, nothing remains to mark the passing of the cell. In the case described herein the massed concretions of immunoglobulin appeared to be remnants of the tumor.

Fig. 3. Electron micrographs of bone marrow. (A) A senescent myeloma cell at the bottom contains several large electron-opaque inclusions within cisternae of the rough endoplasmic reticulum. The younger cell above contains smaller inclusions of varying size. × 5070. (B) Membrane of rough endoplasmic reticulum (arrow) remains adherent to extracellular electron-opaque globular deposit. A portion of a lymphocyte (L) is visible. × 7800.
cell mass which constituted by their presence a kind of tombstone for the departed cells. It is unclear why these bodies were not phagocytized as effectively as were other remnants of the decaying cells.

This case illustrates yet another way in which the products of plasma cells may be injurious to the myeloma patient.

REFERENCES

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