Phagocytic Plasma Cells in a Patient With Multiple Myeloma

By Heinz Ludwig and Margit Pavelka

A female patient with IgG multiple myeloma and phagocytosing plasma cells is presented. Electron microscopical investigation showed an unusually large number of small mitochondria in the myeloma cells. In 21%, intracytoplasmic incorporation of one or more red cells or occasionally of erythroblasts or cells of the myeloid series were found. Uptake of platelets was seen rarely only. Studies of the in vitro phagocytic activity of myeloma cells did not reveal phagocytosis of opsonized bacteria or of latex particles by the malignant plasma cells.

PLASMA CELLS represent the terminal differentiation product of antigen-driven B lymphocytes. Their main task is antibody production, which they fulfill very effectively by secreting usually 10,000–80,000 antibody molecules/single cell/min.1 Plasma cells have been shown to be usually incapable of phagocytosis,2,3 although they may, in exceptional cases, incorporate iron intracytoplasmatically.4,5 In multiple myeloma, four patients have previously been described in whom plasma cells with phagocytic activity for hematopoietic cells were found.6–8 We describe a case with IgG myeloma with phagocytosing plasma cells that incorporated red cells, red-cell precursors, cells of the myeloid series, and platelets.

CASE-REPORT

An 84-yr-old female patient presented with fever, weight loss, and pain in the thoraco-lumbar region. Physical examination revealed an enlarged lymphnode of 2 cm in diameter in the left supraclavicular region but no generalized lymphadenopathy or splenomegaly. Multiple lytic lesions in the skull and in several vertebras were found in the x-ray examination.

Laboratory studies revealed hyperproteinaemia (11.6%) and slightly increased alkaline phosphatase (136 U/liter). Serum electrophoresis showed a paraprotein in the gamma-region (M-component 49%) and a reduced albumin fraction (39%). The paraprotein was identified by immunoelectrophoresis as IgG-κ (5200 mg/100 ml); the nonparaprotein immunoglobulin concentrations were reduced (IgA 26 mg/100 ml, IgM 34 mg/100 ml).

Normochromic, normocytic anemia was found. The hemoglobin was 8.4% and the hematocrit 25 vol%. White cell and platelet counts were slightly reduced (3.4 x 10³/liter and 1.03 x 10¹/liter, respectively). The differential count showed lymphocytosis (48%) with 2% plasma cells. The Coombs test was weakly positive (1:4); serum haptoglobin levels were reduced. Twenty-four-hour proteinuria was 640 mg. Urine electrophoresis revealed a large gamma-fraction (74%) that accounted for 470 mg IgGκ; in addition, traces of free κ light chains were found. The sediment was normal.

Examination of the bone marrow smear revealed a diminished and slightly megaloblastic red-cell series. The myeloid series appeared to be normal; megakaryocytes were present in normal numbers and they produced platelets. Plasma cells of varying degrees of maturity comprised 46% of nucleated bone marrow cells. The cells were from 15 to 50 μ in diameter and showed pronounced polymorphic morphology. In most cells, one eccentric nucleus was seen, but several polynucleated plasma cells were also observed. In 4% of the cells, between 4 and 10 nuclei with round-shaped cytoplasm were observed. In 21% intracytoplasmic incorporation of one or more hematopoietic cells was noted. Uptake of erythrocytes was seen in 18%, of erythroblasts in 2%, and of cells of the myeloid series in 1% (Fig. 1). Phagocytosis of platelets was noted only rarely.

Some of the entrapped red cells and platelets appeared to be partly degraded and fragmented into vacuoles. Erythrophagocytosis or uptake of other hematopoietic cells by monocytes and neutrophils could not be detected.

The plasma cells stained strongly for acid phosphatase and methyl green pyronine stain. More than 94% of the bone marrow plasma cells (including the phagocytosing plasma cells) were found by immunofluorescence staining to contain intracytoplasmatic IgG-κ. After an iron stain with Prussian-blue, no iron particles were seen in the cytoplasm of the myeloma cells.

In smears of buffy coat, 7% lymphoplasmacytoid and 3% plasma cells were found in addition to granulocytes, lymphocytes, and monocytes. In these peripheral lymphoplasmacytoid and plasma cells, phagocytosis of hematopoietic cells was also observed occasionally.

Another biopsy of the enlarged lymphnode in the supraclavicular region revealed mainly plasma cells and erythrocytes. However, frequency of erythrophagocytosis by the tumor cells aspirated from the lymphnode was lower (14%) than in the bone marrow.

The patient was treated with melphalan and prednisone and received 3 packed red cell transfusions. Within the following weeks partial remission was achieved, and the patient was transferred to an institution for the aged. She refused further cytostatic treatment and died shortly thereafter. Postmortem pathologic examination was not performed.

MATERIALS AND METHODS

In Vitro Phagocytosis of Myeloma Cells

A plasma-cell-enriched mononuclear cell preparation was prepared from bone marrow aspirate by Ficoll-Hypaque density gradient centrifugation. These cells were washed and divided into aliquots of 4 x 10⁶ mononuclear cells in RPMI 1640 supplemented with 10% fetal calf serum (Gibco Bio-Cult, England). Thereafter, they were incubated for either 1 or 4 hr at 37°C and 5% CO₂ with (A) 4 x 10⁶ homologous red cells, (B) 4 x 10⁶ E. coli 0.04, (C) 4 x 10⁶ staphylococci strain Washington or, (D) 4 x 10⁶ latex particles (1 μm, Serva, Germany). All particles used had been opsonized in fresh autologous serum prior to incubation.

The suspensions were gently agitated in 10-min intervals during incubation. Subsequently, the cells were washed twice in RPMI 1640 and were either prepared by cytocentrifugation on glass slides.

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for light microscopic investigation or processed for transmission electron microscopy.

**Electron Microscopy**

For ultrastructural investigation, the mononuclear cell preparation was fixed 1 hr in 2.5% phosphate-buffered saline (0.1 M, pH 7.4) buffered glutaraldehyde. Postfixation was performed in 1% veronal acetate buffered OsO4; thereafter, specimens were dehydrated in a graded series of ethanol and embedded in Epon. After staining with alcoholic uranylacetate and alkaline lead citrate, ultrathin sections were examined with a Zeiss EM9 electron microscope.

**RESULTS**

The electron microscopic studies showed a slight disparity between nuclear maturation and cytoplasmic differentiation. The nuclei exhibited little chromatin aggregation and large nucleoli, whereas in the cytoplasm, well developed organelles with an unusually large number of small mitochondria were found. Nucleated and mature red cells (Fig. 2), granulocytes and immature cells of the myeloid series (Fig. 3), and platelets (Fig. 4) were observed incorporated within wide intracytoplasmic vacuoles. The vacuoles with morphologically intact cells usually exhibited smooth surfaces, whereas in some vacuoles, predominantly in
Fig. 3. Phagocytosis of a granulocyte by a plasma cell. The tumor cell shows an immature nucleus with a prominent nucleolus and well developed cytoplasmic organelles (x 10,000).

Fig. 4. A platelet phagocytized by a myeloma cell. Note the unusual high number of small mitochondria (x 10,000).
those containing remains of degraded cellular elements, microvilli were apparent.

Studies of the in vitro phagocytic activity of the myeloma cells did not reveal uptake of opsonized E. coli, staphylococci, or latex particles by the malignant cell population. In addition, there was no significant increase in erythrophagocytosis after incubation of bone marrow plasma cells with opsonized red cells. In the few granulocytes contaminating the mononuclear cell fraction, phagocytosis of latex and bacteria was detected frequently.

**DISCUSSION**

Phagocytic activity is a characteristic feature of monocytes, macrophages, and polymorphonuclear cells but is not expected to occur in plasma cells. Indeed, no indication for phagocytic activity was seen in plasma cells of 55 carefully screened patients with multiple myeloma nor in one case of multiple myeloma treated with intravenous injection of carbon particles. Phagocytosis by tumor cells of lymphoproliferative disorders can be observed occasionally, and it was first described in 1908 in lymphoblasts in a patient likely to have suffered from acute leukemia. Subsequently, erythrophagocytosis by neoplastic lymphoid cells was found in patients with malignant lymphomas and in patients with hairy cell and acute lymphatic leukemia. In one of these studies, leukemic B lymphocytes were found to be able to phagocytose latex particles of 0.8 \( \mu \text{m} \) diameter, and a few reports suggest that rarely even normal B lymphocytes possess the capacity to incorporate latex particles, red blood cells, and microorganisms.

The hematophagocytic activity of 21% of plasma cells in our case of IgG- \( \kappa \) myeloma is therefore an interesting finding. This phenomenon could possibly be due to the malignant expansion of one of the rare normal B lymphocyte clones with inherent phagocytic activity. The remarkably large number of mitochondria observed in the myeloma cells may possibly represent a morphological characteristic of such a polyfunctional plasma cell clone that is not only able of incorporating the phagocytosed cellular elements, but also of degrading them.

At present, we have no definite explanation for the exclusive phagocytosis of hematopoietic cells nor for our inability to induce uptake of opsonized bacteria and latex particles or for our failure to increase the number of erythrophagocytosing plasma cells in vitro. Restriction of phagocytosis by plasma cells to particular cell types, extremely prolonged processes of phagocytosis by the malignant plasma cells, too few actively phagocytosing cells in culture or methodological inadequacy of our in vitro test system might all have accounted for our observation. In three of the previously described four cases with multiple myeloma and phagocytosing plasma cells, phagocytosis by myeloma cells was also restricted to hematopoietic elements. However, in these three patients, electron microscopic investigation and in vitro studies were not performed.

**REFERENCES**

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