Ultrastructural Studies on Human Myeloma Plasmacytes

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SUMMARY

Myeloma plasmacytes were studied in six untreated patients to obtain more information on the nuclear ultrastructural abnormalities in these cells. Asynchrony of nucleolar, nuclear, and cytoplasmic maturation was frequently observed in pleomorphic myeloma plasmacytes. Immature and mature myeloma plasmacytes of two patients contained intranuclear rodlets which consisted of fine filaments arranged in parallel. Myeloma plasmacytes in mitosis often contained persistent nucleoli, nucleolar fragments, and small nucleolus-like bodies. The mitotic division of the nucleus was also noted in differentiated cytoplasm. In some cells in mitosis, the cytoplasm was differentiated and apparently functional.

INTRODUCTION

The ultrastructure of both mature and immature human neoplastic plasmacytes has been studied (3, 8, 14, 17, 31, 32, 35) but only a few reports have appeared on the ultrastructural abnormalities of these cells (7, 17, 21, 31, 35). According to these studies, the ultrastructural morphology of myeloma plasmacytes may be variable and the abnormal plasmacytes may contain unusual nuclear and cytoplasmic inclusion bodies, although the basic general ultrastructure of these cells is apparently preserved (7, 17, 21, 31, 35).

The present study was undertaken to provide more information on the nuclear ultrastructure in myeloma plasmacytes of untreated patients. In addition to the known abnormalities of myeloma plasmacytes (3, 7, 17, 21, 31, 35), the present study demonstrated further abnormalities of the nuclear ultrastructure of these cells such as the presence of intranuclear rodlets and maturation asynchrony of the nucleolus and other structures.

MATERIALS AND METHODS

The samples of the bone marrows of 6 therapeutically untreated patients were fixed in osmium tetroxide. The specimens dehydrated in ethanol containing uranyl acetate (29) were embedded in Epon-Araldite mixture (18) and sectioned with a Porter Blum II ultramicrotome. The ultrathin sections stained with uranyl acetate and poststained with lead citrate (37) were observed with a Philips 200 electron microscope.

RESULTS

The general ultrastructural morphology of less (Fig. 1) and more mature (Figs. 2 and 3) myeloma plasmacytes did not differ from previous descriptions of neoplastic plasmacytes in the literature (14, 17, 32).

Nucleoli of myeloma plasmacytes were either relatively compact with a relatively uniform distribution of nucleolar ribonucleoprotein components (Fig. 4), composed of more as well as less distinct nucleolonemas (Figs. 1, 3, 5, and 6), or ring shaped (Figs. 2, 5, and 6). As in leukemic lymphocytes (30), the relatively compact nucleoli and nucleoli with less or more distinct nucleolonemas (Figs. 1 and 4 to 6) were characterized by the presence of numerous granular components, the number of which was apparently reduced in ring-shaped nucleoli (Fig. 5). Presumably, transitional nucleoli between those nucleoli and nucleoli with more or less distinct nucleolonemas (8, 30) were also noted in some cells (Fig. 5). Such nucleoli usually contained 1 large fibrillar center with chromatin clusters at the periphery which resembled the central light area of ring-shaped nucleoli (Fig. 5). The discontinuous shell of the perinucleolar chromatin seemed to be less developed in large, relatively compact nucleoli with less distinct nucleolonemas as compared with ring-shaped nucleoli (Figs. 1, 2, 4, and 6). The ultrastructural morphology of nucleolar ribonucleoprotein, deoxyribonucleoprotein, and protein components was not different in comparison with their previous descriptions (2, 8).

Compact nucleoli (Figs. 1 and 4 to 6) were usually present in less mature cells. However, in patients with pleomorphic cells, such nucleoli were frequently seen in mature myeloma plasmacytes with well-developed and occasionally dilated rough endoplasmic reticulum (Fig. 3). In these cells the perinucleolar chromatin around nucleoli with less or more distinct nucleolonemas was frequently composed of large chromatin clusters (Figs. 3 and 5). The presence of relatively compact nucleoli and nucleoli with more or less distinct nucleolonemas and ring-shaped nucleoli in one and the same nucleus was not rare in pleomorphic myeloma plasmacytes (Figs. 5 and 6).

Received April 18, 1973; accepted June 11, 1973.

1This work was supported by Cancer Research Center Grant CA-10893-P.5.

2Five of these patients died approximately 1 year after the bue marrow biopsy taken for the electron microscopy; one is surviving after 10 years.
In 2 patients with pleomorphic plasmacytes, the nuclei of mature as well as immature cells contained solitary rodlets (Figs. 4, 7, and 8), the maximal length of which was 3.4 µm (Table 1). These rodlets consisted of fine filaments arranged in parallel (Table 1; Figs. 7 and 8) which occasionally terminated at chromocenters (Figs. 7 and 8).

As shown by light microscopy (9), mitotic figures of myeloma plasmacytes (Figs. 9 to 12) are rare. They were found only in 2 patients with pleomorphic myeloma cells, and in one of these patients 2% of the plasmacytes observed were in the mitotic division. The mitotic cells frequently contained persistent nucleoli, nucleolar fragments, and small nucleolus-like bodies. Nucleoli or nucleolar fragments in prophase cells usually were composed mainly of granular components (Fig. 11). Nucleolus-like bodies of fibrillar structure were noted in further mitotic stages (Figs. 9 and 10). The morphology of the mitotic microtubules was essentially the same as that of other cells (6). The width of the fine mitotic filaments (Fig. 12) was 87 Å (S.D. ± 6.3) and was similar to that of filaments described in the kinetochore region (6). A persistent mitotic chromosome was found in 1 interphase nucleus (Fig. 13). However, mitotic nuclei were frequently found in mature differentiated cytoplasm with well-developed and often diluted cytoplasm (Figs. 9 and 14). Perichromatin granules in mitotic cells were often closely associated with the chromosomes (Fig. 14).

**DISCUSSION**

The present study provides additional information on the ultrastructural abnormalities of myeloma plasmacytes which were investigated in bone marrow of therapeutically untreated patients (Table 2).

The intranuclear rodlets in immature and mature myeloma plasmacytes were similar to those found in other cell types. The natural occurrence of these structures was reported in neurocytes in various animal species (28), dog epididymis (13), human neurocytes of diseased patients (20), human glioma cells (23), and human mature neoplastic β-pancreatic islet cells (1). The function of the intranuclear rodlets is still unknown at present despite the fact that their formation occurred under various experimental conditions in developing chicken neurocytes (27), in actinomycin D-treated amphibian oocytes as well as embryonic cells (16), in golden hamster brain cells treated with dibenzanthracene (22), and in electrically stimulated sympathetic neurons (26). In addition, the formation of the intranuclear rodlets in cultured cells was also related to viral infections (4, 10, 11). Similar fine filaments were also observed in dividing myeloma plasmacytes and in the cytoplasmic fibrillar body of myeloma plasmacytes, which was associated with the external layer of the nuclear membrane (4, 31, 35). Cytochemical analysis was not carried out on the fine filaments of the intranuclear rodlets and fine mitotic filaments or cytoplasmic filaments in myeloma plasmacytes, because the number of cells containing these structures was very limited and the specimens were prepared for the electron microscope by means of routine procedures. The relatively low electron density and width of these filaments were similar to those of intranuclear rodlets of cat neurons which, as cytochemical studies showed, were composed of proteins and not RNA or DNA (26).

The presence of large nucleoli with more or less distinct nucleolonemas rich in nucleolar granular components in myeloma plasmacytes with “mature nuclei or cytoplasm” can be interpreted as maturation asynchrony of these cell components in multiple myeloma as in other neoplastic blood diseases (7). Such nucleoli are usually present in less mature blood cells and plasmacytes (8, 29, 30, 32). The presence of large compact nucleoli with varying distinctness of their nucleolonemas reflecting an active RNA synthesis (8) in mature myeloma plasmacytes is in agreement with some autoradiographic studies on these cells (12, 25). According to these studies, RNA synthesis persists even in mature myeloma plasmacytes in contrast to the “normal” mature plasmacytes in which the RNA synthesis is apparently inhibited by the cell maturation (12).

The present study also demonstrated that nucleoli can persist in mitotic myeloma plasmacytes. The relatively large nucleoli in prophase consist predominantly of granular components. However, the small persistent nucleolus-like bodies in mitotic myeloma plasmacytes rich in fibrillar structures were similar to those described in other cell types (5, 33, 34). In addition, the investigation of mitotic cells in the present study suggested that myeloma plasmacytes with mature cytoplasm can divide. On the other hand, the possibility cannot be eliminated that such cells contained immature nuclear structures or active nucleoli before the mitotic division of nuclei. Moreover, mitotic division of nuclei need not be accompanied by simultaneous cytoplasmic division and 2 or more nuclei in mature cells in pleomorphic plasmacytomas are not uncommon (38).

**Table 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>No. of measured rodlet filaments</th>
<th>% of cells with rodlets*</th>
<th>Maximal length of rodlets (µm)</th>
<th>Width of rodlet filaments* (Å)</th>
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<tr>
<td>1</td>
<td>20</td>
<td>4</td>
<td>3.4</td>
<td>70 ± 5.0*</td>
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<tr>
<td>2</td>
<td>50</td>
<td>8</td>
<td>3.2</td>
<td>84 ± 3.6</td>
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</table>

* Fifty sections were evaluated in each case.

* Measured at different magnifications.

* Mean ± S.E.

**Table 2**

Ultrastructural abnormalities of myeloma plasmacytes in 6 patients

<table>
<thead>
<tr>
<th>Ultrastructural abnormality</th>
<th>No. of patients</th>
</tr>
</thead>
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<tr>
<td>Maturation asynchrony of cell components</td>
<td>3</td>
</tr>
<tr>
<td>Nuclear rodlets</td>
<td>2</td>
</tr>
<tr>
<td>Persistent nucleoli in mitotic cells</td>
<td>2</td>
</tr>
<tr>
<td>Mitotic chromosomes in mature cytoplasm</td>
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</table>
REFERENCES


Fig. 1. An immature myeloma plasmacyte with a large nucleolus (arrow) composed of nucleolonemas, numerous interchromatin granules (I), and a relatively fine chromatin structure of the nucleus. × 17,350.

Fig. 2. A maturing myeloma plasmacyte with a ring-shaped nucleolus (arrow), large chromatin clumps at the nuclear membrane (small arrows), and large cytoplasm. M, mitochondria; E, rough endoplasmic reticulum. × 20,700.
Fig. 3. A mature myeloma plasmacyte with dilated rough endoplasmic reticulum (E). The nucleolus, however, is composed of less distinct nucleolonomes compared to those in Fig. 1 (arrow). Pointer, large chromatin cluster in the region of the perinucleolar chromatin. × 15,600.

Fig. 4. A compact nucleolus composed mainly of granular components in an immature myeloma plasmacyte. Note the 3 extranucleolar fibrillar centers, the perinucleolar chromatin (small arrows), and the intranuclear rodlets (arrow). × 22,000.
Fig. 5. The nucleolus on the right (large arrow) has 2 clusters (small arrows) of intranucleolar chromatin at the periphery of the central light area. The relatively compact nucleolus on the left contains a fibrillar center with a chromatin cluster (small arrow) at its periphery. × 32,000.

Fig. 6. A ring-shaped nucleolus (arrow) and 2 nucleoli with less distinct nucleolonemas of a myeloma plasmacyte. The perinucleolar chromatin of the ring-shaped nucleolus (pointer) appears to be more abundant than that of nucleoli with less distinct nucleolonemas. × 25,600.
Fig. 7. A maturing myeloma plasmacyte containing intranuclear rodlets (arrow). × 15,000.

Fig. 8. The intranuclear rodlet (pointers) is composed of fine filaments, one of the terminal ends of the rodlet is adjacent to a chromocenter (arrow). × 32,500.
Fig. 9. A mitotic division of a mature plasmacyte with dilated cisternae of the rough endoplasmic reticulum. Fibrillar body that may be a "pronucleolus" (arrow). × 11,250.

Fig. 10. Fibrillar body of Fig. 9 (arrow). The high-contrast prints were underdeveloped to demonstrate the fibrillar structure of this body. × 38,700.
Fig. 11. A persistent prophase nucleolus (arrows) which is composed mainly of granular components and is juxtaposed to several chromosomes (pointers). × 22,000.

Fig. 12. Fine filaments juxtaposed to a chromosomal mass (pointers) in a mitotic plasmacyte. × 88,500.
Fig. 13. A persistent "mitotic" horseshoe-shaped chromatin mass (pointers) associated with a nucleolus (arrow) in an interphase nucleus of a mature myeloma plasmacyte. × 37,500.

Fig. 14. Perichromatin granules closely associated with a chromosome (arrow) in a mitotic myeloma plasmacyte. E, rough endoplasmic reticulum. × 11,250.
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