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Review Article

Morphological Aspects of Plasma Cells in Multiple Myeloma

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Abstract

Multiple myeloma is a hematological malignancy characterized by excessive, uncontrolled proliferation of plasma cells, leading to bone marrow clonal expansion. Cytological diagnosis is based on the identification of plasma cells in the bone marrow using May-Grunwald Giemsa (MGG) staining, which exceed 10% of all bone marrow cells. The morphological study of plasma cells in biological haematology has a dual purpose: diagnostic orientation and assessment of the prognosis of multiple myeloma. The progression of the disease is characterized by the appearance of morphological changes in plasma cells, which can affect both the cytoplasm and the nucleus. Nuclear morphological changes: nuclear immaturity, irregular contours and plasmablasts are closely linked to malignancy. Abnormalities of the cytoplasm: Mott cells, flamed cytoplasm, crystalline inclusions, Dutcher bodies, essentially correspond to disorders of immunoglobulin synthesis within the plasma cell and can be encountered in multiple myeloma as well as in monoclonal gammopathies of undetermined significance (MGUS) or other reactive disorders, and are therefore non-specific for malignancy.

In this article, we review the history of the discovery of the plasma cell as an immune cell and of multiple myeloma as a hematological malignancy, the morphological aspect of an immune cell and the role of the plasma cell in the development of myeloma.

Keywords: *Plasma Cells; Multiple Myeloma; Morphological Changes; Immaturity; Nucleo-Cytoplasmic Asynchronism; Prognosis*

Introduction

Plasma cells (PC) are part of the lymphoid line, corresponding to terminally differentiated B lymphocytes found in bone marrow and lymph nodes. Their involvement in the immune defense process is linked to the synthesis and secretion of immunoglobulins. Any deregulation of the genome can lead to uncontrolled proliferation and clonal expansion of plasma cells, resulting in plasma cell neoplasia [1].

Multiple myeloma or Kahler's disease is a hematological malignancy that accounts for around 80% of malignant monoclonal gammopathies, 15% of hematological malignancies and 1% of all cancers. The disease tends to affect people over the age of 40, with a peak frequency between 67 and 70. It involves abnormal and excessive monoclonal plasmocyte proliferation in the bone marrow, biochemically manifested by hypergammaglobulinemia with a narrow peak migrating most often into the gamma globulin zone (more rarely into the

beta globulin zone) on protein electrophoresis in the case of secretory myeloma, or hypogammaglobulinemia associated with positive Bence Jones proteinuria in light chain myeloma. In bone marrow, the diagnosis of multiple myeloma is confirmed by a plasma cell count of over 10% [1-3].

Plasma cell morphology appears to be of value in the morphological diagnosis and prognostic evaluation of multiple myeloma. It is normal in 30 - 50% of cases. However, abnormalities of nuclear or cytoplasmic shape, size or content may be encountered [1].

The importance of plasma cell morphology in the discovery of multiple myeloma

In a series of articles published between 1846 and 1850, John Dalrymple, Henry Bence Jones, and William MacIntyre described all the essential features of the disease now known as multiple myeloma, initially considered to be an inflammatory disease named 'Mollities Ossium' in 1844 by Solly [4,5]. These articles discussed the clinical aspects of the disease, the properties of the Bence Jones protein, and also the cyto-histological appearances made on post-mortem findings, describing the different morphological aspects of the plasma cells encountered with each newly diagnosed case of this disease. For some, they were medium-sized cells, with rounded or oval nuclei eccentric to the nucleus, and basophilic, granular cytoplasm. For others, plasma cells were twice as large, containing up to three nuclei, which may have nucleoli [1,4].

Cytology of a normal plasma cell

The morphology of plasma cells from normal bone marrow is defined by May-Grünwald and Giemsa (MGG) staining on bone marrow smear slides. These cells, also known as Marschalko cells, appear as spheres or ellipsoids, varying in size from 15 to 30 um in diameter. The nucleus is small, with a nuclear-cytoplasmic ratio of 0.30, eccentrically located and ovoid: its axis is perpendicular to the cell axis. Chromatin is highly agglutinated, and dense masses of chromatin display typical features: a "spoked wheel" or "clock face" or "clock dial" appearance. The nucleolus is not visible. Cytoplasm is abundant, always basophilic and generally deep blue. A large, well-defined colorless peri-nuclear zone is present in almost all plasma cells and corresponds to the unstained golgi apparatus [6]. Although there are a few exceptions, there is no cytoplasmic inclusion apart from a single, round, small white vacuole corresponding to Gall's body [7].

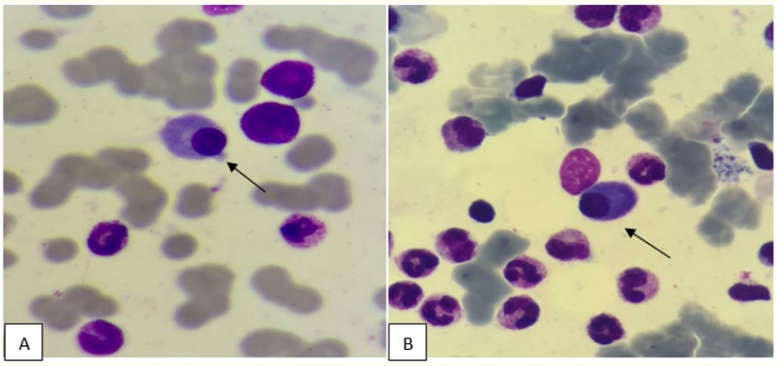


Figure A and B: *Images of a normal bone marrow smear (MGG X 100 stain) showing the normal morphological appearance of a plasma cell. The cell is oval, with a small, eccentric, oval nucleus and densely packed chromatin. The cytoplasm is abundant, basophilic, with an ill-defined, lighter area near the nucleus: the archoplasm.*

Source: Department of Hematology, Central Laboratory, Hassan II University Hospital, Fez.

Different morphological variations of plasma cells in multiple myeloma

Although plasma cells are absent in normal peripheral blood, their presence in certain cases may correspond to plasma cell neoplasia such as multiple myeloma, which is the subject of this article, but also to plasmacytoma or plasma cell leukemia.

So far, plasma cell morphological abnormalities can be divided into two categories: Nucleus-related abnormalities and cytoplasm-related abnormalities.

Nucleus-related abnormalities correspond to an abnormal chromatin network, an obvious nucleolus, an irregular nuclear contour or numerical anomalies, and are mainly related to malignancy. Such criteria, which correspond to nucleo-cytoplasmic asynchronism, have been used in several cases and classified into several subtypes to assess the prognosis of multiple myeloma. In contrast, cytoplasmic abnormalities, including color (Flamboyant cells), round inclusions (Mott cells, Russell bodies), Auer rod or crystalline inclusions, are reported in myeloma as well as MGUS and sometimes in reactive disorders. They do not correspond solely to malignant changes in the plasma cell, but are also linked to abnormal synthesis, trafficking or excretion of immunoglobulin stored in excess in the cytoplasm [6].

Plasma cell morphology in multiple myeloma is also assessed by the maturity of the cell, which may have a maturity similar to that of a normal plasma cell, or an immature character apart from plasmablasts, which are encountered in 10 - 15% of cases.

Two major classification systems, Greipp and Bartl, are designed to account for the morphological spectrum of myeloma cells (Table 1).

Reference	Year	Subtypes	Median survival (months)
Bayrd	1948	Differentiated Intermediate Poorly differentiated	> 60 < 12
Wutke., *et al*. [11]	1981	Plasmocytic Mixed cellular Plasmoblastic	40 16 10
Fritz., *et al*. [14]	1984	Morphology score I Morphology score II Morphology score III	43 31 9
Greipp., *et al*. [13]	1985	Not plamablastic (mature, intermediate, immature) Plasmablastic	35 10
Bartl., *et al*. [12]	1987	Marshalko Smal cell Cleaved Polymorphous Asynchronous Plasmablastic	38 44 21 20 19 8
Paul., *et al*. [16]	1988	Plasmacytic Plasmacytic/Plasmablastic Plasmablastic	Not reached 42 9
Murakami., *et al*. [33]	1992	Mature Intermediate Immature Plasmablastic	62 40 20 14
Goasguen., *et al*. [9]	1999	Mature Immature Plasmablastic	52 31 20

Table 1: *Cyto-morphological typing in multiple myeloma.*

The Greipp system comprises mature, intermediate, immature and plasmablastic subtypes.

The Bartl system comprises three levels with seven subtypes. The low grade includes the small-cell variant and the Marschalko type, the intermediate grade includes the polymorphic, asynchronous and cleaved types, and the high grade includes the blastic and sarcomatous types.

Bartl also described 6 infiltration patterns: interstitial, interstitial with para-trabecular sheets, interstitial/nodular, nodular, packed and sarcomatous.

Recognition of the different subtypes helps distinguish mimic myeloma. For example, the asynchronous or blastic subtype may resemble acute monoblastic leukemia. The polymorphic type of myeloma with multinucleated neoplastic cells and fibrosis may be confused with primary myelofibrosis or acute panmyelosis with myelofibrosis. The small-cell variant closely resembles low-grade B-cell lymphoma or leukemia with plasmacytosis [7].

Mature plasma cells in multiple myeloma

The number of MM patients included in the "mature" PC subtype varies from 40% to 50%. In this subtype, also referred to as the "Marschalko" subtype, plasma cells exhibit condensed chromatin and a nucleolus that is either absent or inconspicuous, as in normal plasma cells [8].

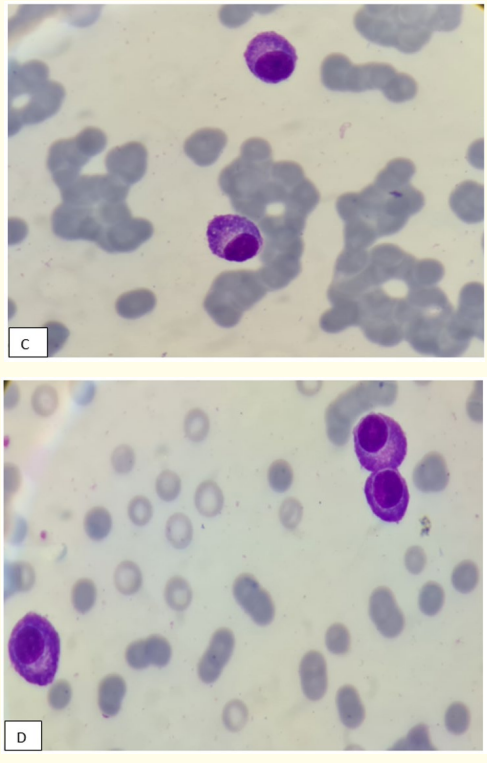


Figure C and D: *Images of a bone marrow smear (MGG X 100 stain) from a 52-year-old subject with confirmed IgG multiple myeloma in hypocellular, heterogeneous bone marrow with 41% plasma cells. The plasma cells were of very heterogeneous morphology, including the above plasma cells, which were of normal size, with oval, basophilic cytoplasm, eccentric nuclei and condensed chromatin, suggestive of morphologically mature plasma cells.*

Source: Department of Hematology, Central Laboratory, Hassan II University Hospital, Fez.

Immature plasma cells in multiple myeloma

Immaturity of a plasma cell is defined by the existence of morphological changes related to the nucleus, notably: the presence of a prominent nucleolus, a dispersed chromatin pattern and/or a larger-than-usual nuclear size. Immature plasma cells correspond neither to mature subtypes (mature chromatin lattice, low nucleo-cytoplasmic ratio, no nucleolus or invisible nucleolus) nor to plasmablastic subtypes (obvious nucleolus, immature chromatin lattice and high nucleo-cytoplasmic ratio) and account for 20 - 50% of cases [8].

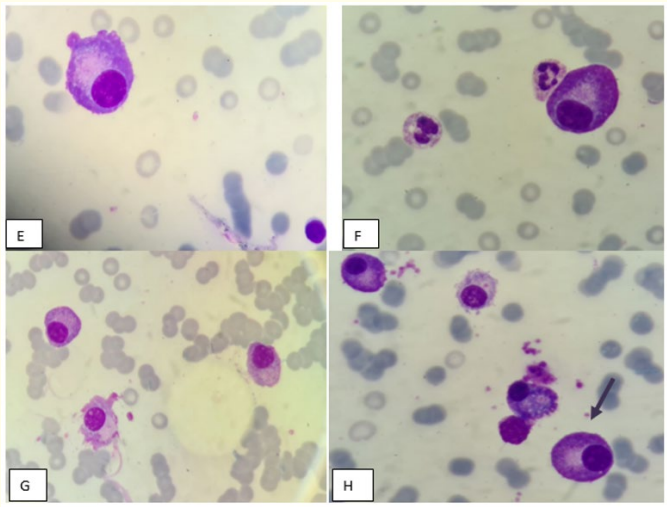


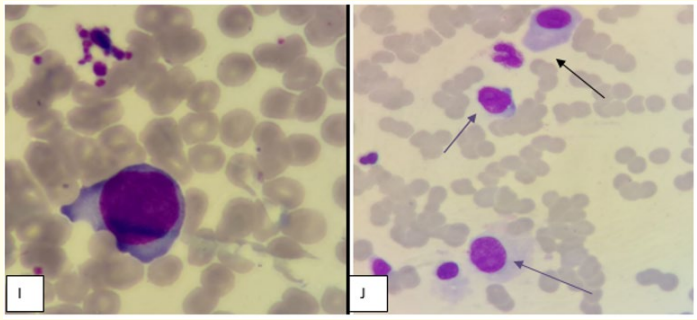
Figure E-H: *Images of a bone marrow smear (MGG X 100 stain) from a 52-year-old subject with confirmed IgG multiple myeloma in a hypocellular, heterogeneous bone marrow with 41% plasma cells. The plasma cells were very heterogeneous in morphology, including the above plasma cells, which were large, with loose, nucleated chromatin, suggesting morphologically immature plasma cells.*

Source: Hematology Department, Central Laboratory, Hassan II University Hospital, Fez.

Plasma cells in multiple myeloma

Plasmablasts represent the most immature form of plasma cell, characterized by a large nucleus, diffuse, uncoiled chromatin, a prominent centrally located nucleolus and basophilic cytoplasm (nucleocytoplasmic ratio > 0.6) [9-13].

The plasmablastic subtype is encountered in 2 - 18% of multiple myeloma cases [19,14].



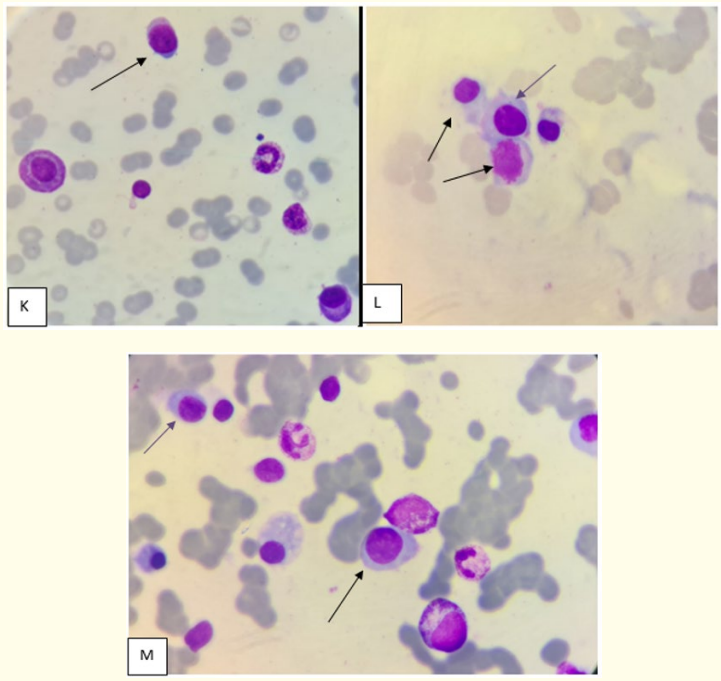


Figure I-M: *Images of bone marrow smears (MGG stain X 100) from two patients with multiple myeloma. The first (I, J, K) is a 52-year-old patient with IgG multiple myeloma in whom 41% bone marrow plasma cells were objectified. The second (M, L) is a 76-year-old patient with IgG multiple myeloma in whom the bone marrow smear showed a plasma cell population of 34%. The above blasts are of the plasmacytic type: plasmablasts; which are large, with nuclei with unbound and nucleolated chromatin and variable abundance of basophilic cytoplasm.*

Source: Hematology Department, Central Laboratory, Hassan II University Hospital, Fez.

Morphological abnormalities related to the nucleus

Nuclear irregularity

Plasma cells from patients with multiple myeloma generally show an irregular, round or oval nuclear contour. However, red cell, notched, cleaved, folded, multilobed, dumbbell or cloverleaf shapes have been mentioned in case reports and also as morphological criteria in the prognosis of multiple myeloma according to Bartl., *et al.* having objectified this nuclear irregularity in 8% of cases [14,15].

Bi- or multi-nucleated forms

In some cases of multiple myeloma, bi- or more rarely multinucleated forms have been described, although Ghevaert., *et al*. reported up to 50 nuclei in the same plasma cell in a patient with multiple myeloma [16]. In many cases, the two nuclei of the same binucleated plasma cell are of similar size and chromatin network. Malignancy can be inferred if multi-nucleated plasma cells show at least one of the following characteristics: three or more nuclei of different size with a nucleolus, chromatin lattice, finely dispersed chromatin [1].

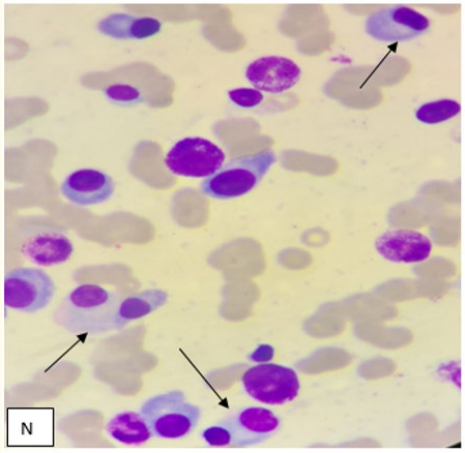


Figure N: *Medullary smear image (x100) in a patient with IgG multiple myeloma, showing a plasma cell with an irregular nucleus and two binucleated plasma cells containing two nuclei of variable size, shape and chromatin network.*

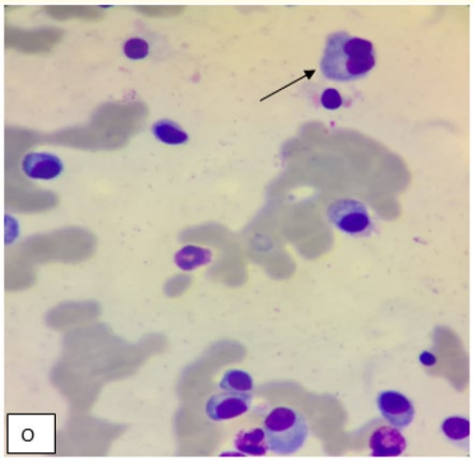
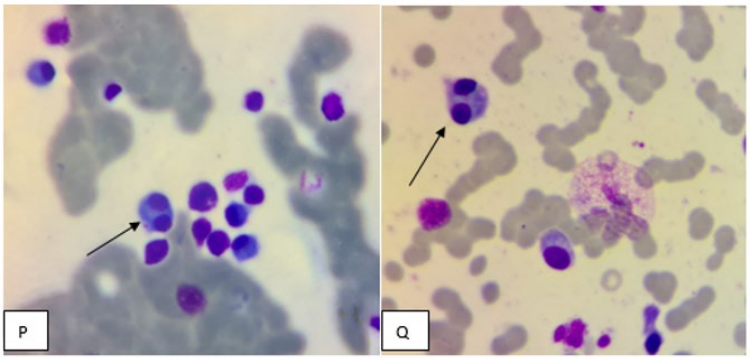


Figure O: *Medullary smear image (x100) in a patient with IgG multiple myeloma, showing a bilobed plasma cell.*



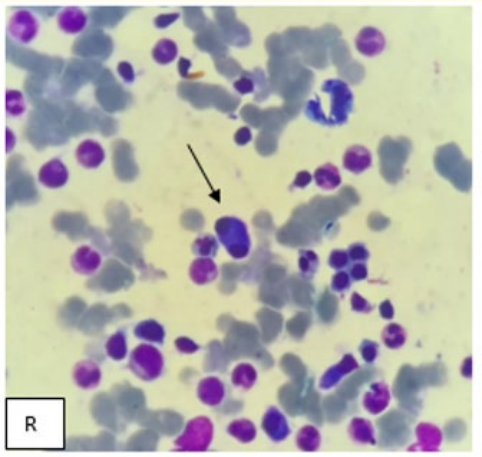


Figure P-R: *Images of bone marrow smear (x100) in a patient with lambda light chain multiple myeloma, showing binucleated plasma cells.*

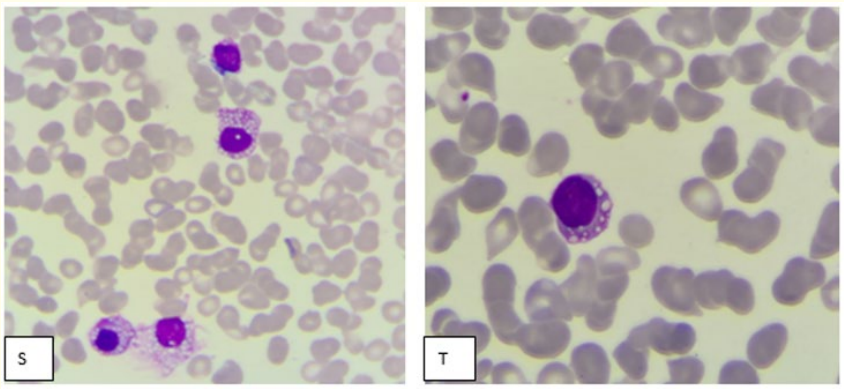
Source: Department of Hematology, Central Laboratory, Hassan II University Hospital, Fez.

Cytoplasmic morphological abnormalities

Of the various cytoplasmic aberrations described to date, most have been reported in monoclonal gammopathies, either of undetermined significance (MGUS) or malignant (Multiple Myeloma). Many of these changes can also be found in reactive conditions and are linked to abnormal immunoglobulin (Ig) synthesis or trafficking, and correspond to excess storage of the whole molecule or part of it by the plasma cell.

Mott cells

Mott cells, also known as morular cells or grape cells, are plasma cells with a variable number of spherical inclusions (up to 100) packed into their cytoplasm. Inclusions vary in size from 1 to 5 um in diameter, and may or may not be of uniform size within the same plasma cell. They are most often pale blue, but can also be colorless, gray, pink or eosinophilic. Occasionally, these inclusions can be seen on or in the nucleus. Such cells are occasionally seen in mainly infectious or inflammatory reactive processes, as well as in MGUS and multiple myeloma. In the latter case, the number of affected plasma cells can vary from < 1% to > 20% of the total number of plasma cells. They correspond to an excess of immunoglobulin synthesis by the plasma cell [17,18].



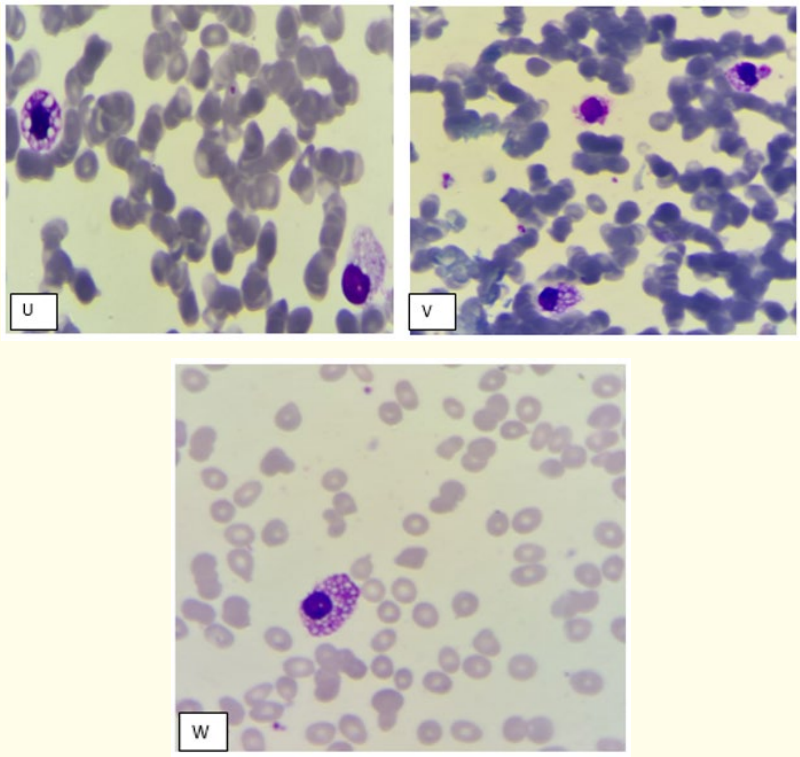


Figure S-W: *Images of a bone marrow smear (x100) after MGG staining in a 49-year-old patient with kappa light chain multiple myeloma suggestive of Mott cells. Plasma cells of variable size, with reduced basophilic cytoplasm and riddled with vacuoles.*

Source: Hematology Department, Central Laboratory, Hassan II University Hospital, Fez.

Plasma cells with flaming cytoplasm

Undritz was the first to draw attention to flaming plasma cells. These plasma cells have an intense red cytoplasm after MGG staining. The red color is linked to the presence of an anomaly in the structure of the carbohydrate fraction of immunoglobulin, whose synthesis is initiated in the endoplasmic reticulum before being modified and completed in the Golgi apparatus. The cytoplasm of flamboyant plasma cells contains numerous dilated endoplasmic reticulum cisternae, which are distended by Ig. These cells were first described in patients with IgA gammopathies, but can be seen in gammopathies of other Ig classes or even in reactive conditions [19-21].

Other cytoplasm-related morphological changes in plasma cells

Dutcher bodies

Dutcher bodies are light-gray intranuclear inclusions, which may be close in size to the nucleus, or resemble a large nucleolus. They may be single or multiple, and vary in size and location within the nucleus. They result from cytoplasmic invagination or cover the nucleus and contain highly packed immunoglobulins. They are seen mainly, but not exclusively, in multiple myeloma [22,23].

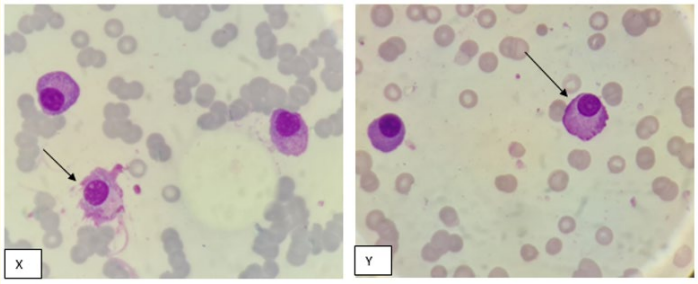


Figure X and Y: *Cells with flaming cytoplasm from a bone marrow smear (x100) in a patient with lambda light chain multiple myeloma.*

Crystalline inclusions

In addition to Russell or Mott inclusions, various other changes known as crystalline inclusions or Auer rod inclusions have been reported in multiple myeloma. Cases presenting this morphological aspect remain very rare [1]. In some cases, they correspond to needle-shaped inclusions, called Auer's rods because they more or less mimic those seen in acute promyelocytic leukemia; they are elongated, thin, either dispersed in the cytoplasm or grouped in bundles, colored red (azurophilic) but sometimes pink, blue-violet or even colorless [24]. In other cases, these inclusions are heterogeneous, either translucent (colorless), red or pink, and are generally thicker than the needle-shaped, elongated, angular, rhomboid or polymorphic crystals [25-27]. In some cases, the inclusions correspond to small azurophilic granules, dispersed in the cytoplasm [28]. Although such inclusions have been reported under normal and reactive conditions, most cases correspond to monoclonal gammapathies, whether MGUS or multiple myeloma involving in almost all cases the Ig Kappa light chain [29].

Significance of plasma cell morphological changes in the prognosis of multiple myeloma

In a series of 41 patients (1948), Baryd reported on the relationship between plasma cell morphological changes in multiple myeloma and its prognosis [1].

By classifying malignant plasma cells into three subtypes: Differentiated (17% of patients); intermediate (59% of patients) and poorly differentiated (24% of patients), median survival was greater than five years in the differentiated group and less than one year in the poorly differentiated group [30].

Several groups had previously published prognostic, cytomorphological or histological classifications (Table 1) confirming Baryd's observations: multiple myeloma patients with mature plasma cells had a much better clinical outcome, whereas multiple myeloma patients with the most immature subtype had a poorer prognosis.

To date, morphological criteria for prognostic classification in multiple myeloma have been based primarily on the identification of mature plasma cells on the one hand, and on the discovery of varying degrees of nucleo-cytoplasmic asynchrony on the other. This asynchrony is linked mainly to changes in the nucleus, including diffuse chromatin patterning, prominent nucleoli, irregular membrane contours and/or large nuclei. All these criteria correlate with immaturity or aggressiveness of the plasma cell clone. Several other morphological abnormalities, notably those corresponding to the presence of cytoplasmic inclusions or particular changes related to the outer membrane, have been reported in multiple myeloma as well as in MGUS and reactive disorders. These changes are linked to Immunoglobulin synthesis or behavior, and are not prognostically detrimental [1].

Conclusion

In addition to determining the percentage of plasma cells in bone marrow, which is necessary for the diagnosis of multiple myeloma, the study of plasma cell morphology may prove useful in the diagnosis and prognosis of multiple myeloma.

Morphological changes can affect both nucleus and cytoplasm. Those related to nucleo-cytoplasmic asynchrony are highly suggestive of malignancy, and thus point to the diagnosis. Most cytoplasmic changes correspond to abnormal behavior of immunoglobulins synthesized in plasma cells, and are observed in multiple myeloma and reactive disorders, and are not related to malignancy.

The mature nature of the plasma cell is often a criterion of good prognosis, and the therapeutic response is generally favorable; in contrast, immaturity of the plasma cell is associated with a more unfavorable prognosis and a limited lifespan.

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