Emergence of B-Immunoblastic Sarcoma in Patients With Multiple Myeloma: A Clinicopathologic Study of 10 Cases

By Brunangelo Falini, Ignacio De Solas, Alexandra M. Levine, John W. Parker, Robert J. Lukes, and Clive R. Taylor

MULTIPLE MYELOMA is a malignant disease characterized by plasma cell infiltration of the bone marrow associated with multiple osteolytic lesions, usually in the presence of a monoclonal gamopathy.¹

Morphologically, myeloma cells resemble classical Marshalko plasma cells, although many authorities believe that additional distinctive features are present, such as the persistence of "immature" nuclei in cells that otherwise are typically plasmacytic, with extensive basophilic cytoplasm and a juxtanuclear hof. However, it has long been recognized that considerable variation may occur. The morphology of the myeloma cells may vary from "mature" plasma cells to immature pleomorphic cells, which may be multinucleated and may contain one or more conspicuous nucleoli. Such cases have often been termed "poorly differentiated,"² "plasmablastic,"³ or dysplastic⁴ myeloma. In addition, cases of multiple myeloma with large extraosseus masses and "sarcomatous" characteristics have been reported in the literature,⁵,⁶ with or without infiltration of the bone marrow by highly undifferentiated myeloma cells resembling "reticulum cells." These morphological features have been interpreted by some authors as evidence in support of the hypothesis that the myeloma cell is a derivative of the "reticulum cell"⁶,⁷,⁸,⁹,¹⁰,¹¹,¹² rather than a descendant of the lymphoid series. This belief stems from earlier concepts formulated by Maximow and propagated by Marshall¹³ and others envisaging the "reticulum cell" as a central stem cell, giving rise to many hemopoietic elements including plasma cells.

In succeeding years a variable and often confusing terminology developed as different investigators attempted to define and characterize these tumors histologically, coining such names as "plasmacytic reticulum cell sarcoma,"¹⁴ "plasma cell sarcoma,"¹⁵ "reticulum cell sarcoma,"¹⁶,¹⁷ and "histiocytic lymphoma."¹⁸ In related studies, several authors suggested that a relationship exists between the degree of maturity of the myeloma cells, the natural history of the disease, and the clinical state; the poorest prognosis being assigned to the patients with the most immature type of cells.¹⁹,²⁰

This article describes and discusses the clinical and pathologic features of 10 patients with multiple myeloma, in which evolution to a lymphoma of transformed lymphocytes with plasmacytoid features, an immunoblastic sarcoma of B-cell type (B-IBS) in the Lukes/Collins classification,¹⁹,²⁰ was observed. In six patients this progression occurred mainly in extramedullary sites; in the remaining four the change was confined to the bone marrow.

On the basis of immunologic and morphological findings in these 10 cases, it will be argued that the majority of the lesions described in the literature as "reticulum cell sarcoma occurring in multiple myeloma" probably represent examples of B-IBS, supervening upon preexisting multiple myeloma, a B-lymphocyte-derived neoplasm. Moreover, the suggestion is made that in these patients the progression of multiple myeloma to B-IBS probably represents a transition from a low-turnover neoplasm to a kinetically more aggressive tumor of transformed lymphocytes or B immunoblasts, with a correspondingly poor prognosis.

MATERIALS AND METHODS

Case records and material from the 10 patients described here were collected from the Hematology and Hematopathology services of the Los Angeles County-University of Southern California Medical Center, from the contributing hospitals of the Southern California Lymphoma Group, from the USC Hematopathology Consultation Service, and from the Medical Clinic of Perugia University.

From the Department of Pathology, University of Southern California, Los Angeles, Calif.

Supported in part by NIH-NCI Grant CA19449 (USA). B.F. is a recipient of a fellowship from the North Atlantic Treaty Organization.

Submitted July 31, 1981; accepted December 21, 1981.

Address reprint requests to Clive R. Taylor, M.D., Department of Pathology, University of Southern California, Los Angeles, Calif. 90033.
Perugia, Italy. As such, these cases have been subject to marked selection bias, and their occurrence cannot be taken as an indication of the frequency of the condition to be described.

At the time of diagnosis, a full clinical investigation was performed, including bone marrow biopsy and/or aspirate, serum and urine investigations for monoclonal proteins, and a total body skeletal survey including a chest x-ray. Sequential bone marrow biopsies performed during the course of the disease were available in some patients.

The morphological criteria for the diagnosis of multiple myeloma in bone marrow sections were those defined by Canale and Collins. In eight patients the initial diagnosis was consistent with multiple myeloma according to the criteria defined by SWOG. Two patients had an initial diagnosis of localized or indolent myeloma of bone.

In this study, the morphological criteria for the inclusion of cases showing the coexistence or evolution of B-IBS in myeloma were: (A) evidence of a change in the histologic picture in sequential bone marrow biopsies from typical myeloma to B-IBS, (B) the presence of a monomorphic proliferation of immunoblasts in the bone marrow with residual areas of recognizable myeloma, (C) involvement of extramedullary tissues by tumors with the histologic features of B-IBS in patients already having classical intramedullary myeloma. The morphological criteria for a diagnosis of B-IBS have been described elsewhere and are summarized briefly in the Results section. Autopsy was performed in four cases.

Patients with biopsy-proven diagnosis of B-IBS in extramedullary sites in whom a serum and/or urinary monoclonal spike was present, but in whom a bone marrow examination was not performed or, if performed, was not consistent with the diagnosis of multiple myeloma, were not included in this study.

Tissues for histology were fixed in Zenker's fluid, B5, or formalin depending on the contributing institution. Paraffin-embedded tissues were sectioned at 3–4 μm and stained by hematoxylin and eosin, peroxidase acid Schiff, Giemsa, and methyl green pyronin (MGP) methods. Bone marrow and peripheral blood smears were stained with Wright's stain. An immunoperoxidase method (peroxidase-antiperoxidase PAP procedure) was used for the demonstration of intracellular immunoglobulin in five cases. The detailed procedure has been reported previously. Electron microscopic studies were performed in three cases.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Initial Diagnosis</th>
<th>Site of Presentation of B-IBS</th>
<th>Tumor Cell Morphology (B-IBS)</th>
<th>Peripheral Blood Involvement</th>
<th>Time Interval Between Initial Diagnosis and Development B-IBS</th>
<th>Survival From Diagnosis of B-IBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53/M</td>
<td>Multiple myeloma</td>
<td>Right supraclavicular mass</td>
<td>Immunoblasts, plasmacytoid</td>
<td>No</td>
<td>36 mo</td>
<td>8 mo</td>
</tr>
<tr>
<td>2</td>
<td>53/M</td>
<td>Multiple myeloma</td>
<td>Right supraclavicular mass, bone marrow</td>
<td>Immunoblasts, plasmacytoid features present in some cells; few multinucleated neoplastic giant cells</td>
<td>No</td>
<td>32 mo</td>
<td>13 days</td>
</tr>
<tr>
<td>3</td>
<td>52/F</td>
<td>Multiple myeloma</td>
<td>subcutaneous nodules, bone marrow</td>
<td>Highly pleomorphic features; many multinucleated neoplastic cells</td>
<td>No</td>
<td>7 mo</td>
<td>19 days</td>
</tr>
<tr>
<td>4</td>
<td>61/F</td>
<td>Multiple myeloma</td>
<td>Pulmonary nodule (autopsy)</td>
<td>Immunoblasts, nonmultinucleated giant neoplastic cells</td>
<td>No</td>
<td>24 mo (autopsy)</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>77/M</td>
<td>Osteolytic lesion of the rib</td>
<td>Retropertioneal mass</td>
<td>Immunoblastic proliferation; striking plasmacytoid features present in all neoplastic cells</td>
<td>No</td>
<td>29 mo</td>
<td>Still alive after 1 yr</td>
</tr>
<tr>
<td>6</td>
<td>67/M</td>
<td>Osteolytic lesion of the skull</td>
<td>Right auxillary node</td>
<td>Immunoblasts with striking plasmacytoid features; scattered abnormal multinucleated neoplastic cells</td>
<td>No</td>
<td>52 mo</td>
<td>3 mo</td>
</tr>
<tr>
<td>7</td>
<td>46/F</td>
<td>Multiple myeloma</td>
<td>Bone marrow</td>
<td>Monomorphic proliferation; immunoblasts</td>
<td>Yes (2.5 x 10^9/liter) many immunoblasts; occasional plasma cells</td>
<td>11 mo</td>
<td>1 mo</td>
</tr>
<tr>
<td>8</td>
<td>67/M</td>
<td>Multiple myeloma</td>
<td>Bone marrow</td>
<td>Monomorphic proliferation; immunoblasts</td>
<td>Yes (20 x 10^9/liter) many immunoblasts</td>
<td>5 mo</td>
<td>21 days</td>
</tr>
<tr>
<td>9</td>
<td>36/M</td>
<td>Multiple myeloma vs B-IBS</td>
<td>Bone marrow</td>
<td>Monomorphic proliferation; immunoblasts</td>
<td>No</td>
<td>Simultaneously</td>
<td>8 mo</td>
</tr>
<tr>
<td>10</td>
<td>80/F</td>
<td>Multiple myeloma vs B-IBS</td>
<td>Bone marrow</td>
<td>Clusters immunoblasts in background of myeloma cells</td>
<td>Yes (6.4 x 10^9/liter) many immunoblasts in clusters</td>
<td>Simultaneously</td>
<td>1 mo</td>
</tr>
</tbody>
</table>
Serum and urine samples were electrophoresed on paper or cellulose acetate, followed by immunoelectrophoresis with commercial specific antisera (Hyland, Costa Mesa, Calif., and Meloy, Springfield, Va.). Immunoglobulins G, A, and M were measured quantitatively by radial immunodiffusion.

RESULTS

Clinical Findings

The pertinent clinical information on these patients is summarized in Table 1. Age at presentation ranged from 36 to 80 yr. There were four females and six males. For descriptive purposes, these patients are arranged in three groups according to the mode of clinical presentation: cases 1–4 (Table 1) showed typical multiple myeloma (stage II and III of Durie and Salmon) with secondary development of B-IBS in extraosseous sites; cases 5 and 6 (Table 1) had localized myeloma of the bone with extramedullary transformation to B-IBS; and cases 7–10 (Table 1) manifested multiple myeloma with intramedullary transformation to B-IBS.

The presenting symptom of B-IBS in four patients (cases 1–4) was the appearance of extraosseous masses during the course of the myelomatous process, concomitant with a rapid deterioration in the clinical state. The sites of presentation of these masses are summarized in Table 1.

Two other patients (cases 5 and 6, Table 1) appeared to have a low tumor mass myeloma, in that radiographic studies showed the presence of no more than three osteolytic lesions, and the bone marrow biopsy revealed less than 10% plasmacytosis with no cytologic abnormality. In one patient (case 6) there was a small monoclonal spike (IgG 1900 g/dl), while in the other patient (case 5) no detectable paraproteinemia was present. The histopathologic diagnosis of myeloma in these patients was established by biopsy of an osteolytic lesion of the skull (case 6) or rib (case 5), respectively. At the time of diagnosis of extramedullary B-IBS (5 and 2 yr after the diagnosis of myeloma), one of the patients (case 6) showed the appearance of new osteolytic lesions suggesting a progression to more generalized multiple myeloma. At that time, however, bone marrow biopsy was not repeated and the monoclonal spike was unchanged. In the other patient (case 5), serial serologic, radiographic, and bone marrow studies showed no evidence of progression to classical multiple myeloma.

The remaining four patients (cases 7–10, Table 1) manifested a rapid deterioration in clinical status, associated with a progressive loss of response to therapy. As a result, the bone marrow was reexamined, revealing so-called “anaplastic” cytologic features or “undifferentiated” myeloma.

In 8 patients the transition to B-IBS occurred at time intervals ranging from 5 to 52 mo after initial diagnosis, while in 2 patients the 2 diseases were diagnosed simultaneously (Table 1). All patients received chemotherapy, with or without local radiotherapy, for the treatment of multiple myeloma. Following the diagnosis of B-IBS, treatment was changed to various types of combination chemotherapy. None of the patients responded well to these aggressive regimens, a partial remission (8 mo) being observed in one patient only (case 1). Only one patient (case 5) remains alive 12 mo from the diagnosis of B-IBS; the median survival of the remaining cases was 4 mo after the diagnosis of B-IBS.

Histopathology

The major morphological observation in the three groups of patients is summarized in Table 1. In cases 1–4, the histologic findings in the initial bone marrow examination were typical for the diagnosis of multiple myeloma (Fig. 1). The extraosseous masses that developed subsequently showed diffuse infiltration by a mixed population of noncohesive cells. The predominant elements were transformed lymphocytes (immunoblasts), intermediate or large in size, with abundant amphophilic cytoplasm, large vesicular nuclei, often with thickened nuclear membranes. The nucleus usually contained one large nucleolus. A variable number of cells showed obvious plasmacytoid features (Fig. 2). In most cases, a distinct subpopulation of giant cells, sometimes multinucleated and bizarre, was identifiable, and contributed to the overall pleomorphism of the neoplasm. These cells varied in frequency and were particularly numerous in cases 1
and 3 (Figs. 3 and 4). Large numbers of mitotic figures were invariably present. At the moment of diagnosis of extramedullary B-IBS, sections from two patients (cases 2 and 3) also showed a similar histologic picture in the bone marrow. In cases 1 and 4, the bone marrow showed marked hypoplasia with a few small foci of myeloma cells. At postmortem examination, immunoblastic sarcoma was present in multiple sites within patients in this group, with the exception of case 4 in which the transformation to IBS could be recognized only in the lung lesion.

Sections of tissues removed from the osteolytic lesions of the rib and skull in cases 5 and 6, respectively, revealed tumors composed of myeloma cells (Fig. 5). Mitotic figures were rare. These histologic findings fulfilled the morphological criteria for the diagnosis of myeloma. The morphological findings in the extramedullary lesions that developed subsequently, namely the axillary lymph node in case 6 and the retroperitoneal mass in case 5, were striking in that the tissues from both cases showed extensive infiltration by large cells (Fig. 6) with obvious plasmacytoid features, including eccentrically positioned nuclei and strongly pyroninophilic cytoplasm using the methyl green-pyronin stain. Nuclei exhibited some condensation of chromatin along nuclear borders; often a large central nucleolus was present. Residual reactive follicles were also observed in the lymph node. In contrast to the osseous lesions, the mitotic index with extramedullary lesions was invariably high.

In two patients (cases 7 and 8) the initial bone
marrow biopsy fulfilled the morphological criteria for diagnosis of multiple myeloma. The myeloma cells were composed of small uniform cells with eccentric nuclei, amphophilic cytoplasm, and a readily discernible paranuclear hof. Only scattered immunoblasts could be identified. However, sequential bone marrow biopsies showed an increase in the number of the immunoblasts, which eventually came to represent the predominant population, justifying a diagnosis of B-IBS. The mitotic index increased in a parallel manner.

Cases 9 and 10 were peculiar in that the patients presented “ab-initio” with a histologic picture of multiple myeloma, which in some areas contained sheets of
bizarre immunoblasts, suggesting evolution to B-IBS. In one patient (case 9), the marrow was diffusely infiltrated by a population of immunoblasts. In the other patient (case 10), several discrete clusters of immunoblasts were present among the myeloma cells that formed the bulk of the tumor. Multinucleated neoplastic giant cells were also observed in case 10.

Peripheral Blood

Sequential peripheral blood studies were available for review in all patients. Plasmacytoid lymphocytes and immunoblasts (Fig. 7) in varying percentages could be identified in the peripheral blood smears of three other patients (cases 7, 8, and 10) (Table 1).

Electron Microscope Studies

Lymph node biopsies from cases 1, 5, and 6 were examined by electron microscopy (EM). All three showed plasmacytoid cytoplasmic features in varying degrees, the content of rough endoplasmic reticulum (RER) varying from case to case. In case 1, the cells showed a moderate heterogeneity in nuclear configuration and chromatin pattern. The cells ranged from those possessing large, round, or oval nuclei, with finely dispersed euchromatin and prominent nucleoli (Fig. 8), to those with nuclei more lymphocytic in appearance, with condensed heterochromatin, some of it at the nuclear membrane (Fig. 9). The latter cells, however, also contained nucleoli.

The large primitive cells frequently showed marked nuclear irregularity and possessed one to three prominent nucleoli. These cells also showed variation in the amount of chromatin and, although many cells contained dilated cisternae of RER, there was much less RER in the cells of case 1 than in the other two cases examined by EM. There were, however, large numbers of free ribosomes in the cytoplasm. The most striking feature in case 1 was the presence of compact collections of microfibrils, located focally in the cytoplasm (Fig. 9). These have been described previously in lymphocytes, plasma cells, and a variety of other cell types by several workers. However, the bundles of fibrils were larger, more discrete, and compact than those we have observed previously in lymphocytes.

The overall impression was that the nuclei of smaller cells were lymphocytic in appearance but that the cytoplasm was distinctly plasmacytoid (i.e., plasmacytoid lymphocytes). The other population of large, more primitive cells with irregular nuclei, fine chromatin, and prominent large nucleoli were classified as immunoblasts with plasmacytoid features (i.e., B immunoblasts).

In case 5, the majority of the cells were large plasmacytoid immunoblasts containing round-to-oval...
nuclei with quite large nucleoli. Euchromatin predominated, but there were small clumps of heterochromatin at the nuclear membrane. The cytoplasm was packed with markedly dilated cisternae of RER and numerous mitochondria.

Immunoblasts with plasmacytoid features also comprised the major cell population in case 6. Nuclei were round to oval with quite prominent, large nucleoli as in case 5. The cytoplasm was abundant and packed with parallel arrays and swirls of RER, the cisternae dilated and filled with a fine electron-dense granular material. There was some peripheral condensation of the heterochromatin in the smaller cell, and there were scattered small lymphocytes intermingled with the plasmacytoid immunoblasts.

In summary, the electron micrographs confirm the impression provided by the paraffin sections from these three cases (i.e., that immunoblasts with plasmacytoid features represented the predominant population in each case).

Immunologic Data

Table 2 summarizes the immunologic data in these patients. At the time of diagnosis, eight patients were found to have a monoclonal immunoglobulin component in the serum. The types of abnormal paraproteins identified immunoelectrophoretically in these patients are shown in Table 2. The remaining two patients, one with multiple myeloma and the other with localized myeloma of the bone had no detectable serum and/or urinary paraproteins. At the moment of diagnosis of B-IBS, the monoclonal spike was either increased or unchanged in those cases in which sequential measurements were available.

Immunoperoxidase studies (Figs. 10 and 11) in the five cases in which material was available for immunostaining showed that the immunoblastic population showed a pattern of monoclonal staining for immunoglobulin identical to that present in the myeloma cells and corresponding to the monoclonal immunoglobulin identified immunoelectrophoretically in the serum.

DISCUSSION

Although all 10 patients in this series developed B-IBS in a background of plasma cell neoplasia, three broad patterns of disease were observed.

In six patients (cases 1–6, Table 1) the appearance of extramedullary masses during the course of the

<table>
<thead>
<tr>
<th>Case</th>
<th>Type of Serum-Urine</th>
<th>Immunoperoxidase Staining of B-IBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IgG-x</td>
<td>Monoclonal (lymph node)</td>
</tr>
<tr>
<td>2</td>
<td>IgG-D-λ</td>
<td>λ-Monoclonal (supraclavicular mass)</td>
</tr>
<tr>
<td>3</td>
<td>IgG</td>
<td>Not performed</td>
</tr>
<tr>
<td>4</td>
<td>IgG-λ</td>
<td>Monoclonal IgG-λ (bone marrow, lymph node, lung lesion)</td>
</tr>
<tr>
<td>5</td>
<td>No paraproteinemia</td>
<td>Not performed</td>
</tr>
<tr>
<td>6</td>
<td>Low level IgG monoclonal spike (1900 mg/dl)</td>
<td>IgG-λ-monoclonal (lymph node)</td>
</tr>
<tr>
<td>7</td>
<td>No paraproteinemia</td>
<td>Not performed</td>
</tr>
<tr>
<td>8</td>
<td>λ-Light chain</td>
<td>λ-Monoclonal</td>
</tr>
<tr>
<td>9</td>
<td>IgA-λ</td>
<td>Not performed</td>
</tr>
<tr>
<td>10</td>
<td>IgA-x</td>
<td>Not performed</td>
</tr>
</tbody>
</table>

Fig. 10. Case 6. Right axillary lymph node biopsy stained for kappa light chain by immunoperoxidase (PAP) method. The cytoplasm of all of the large cells (immunoblasts) shows positive (grey-black) staining for kappa chain. Taken in conjunction with the total lack of staining of these cells for lambda light chain (Fig. 11), this suggests a monoclonal neoplastic population. In contrast, only some of the Marschalko-type plasma cells stained, suggesting the presence of a residual population of reactive plasma cells in the lymph node (immunoperoxidase stain for kappa chain, hematoxylin counterstain, ×400).

Fig. 11. Case 6. Adjacent section to that depicted in Fig. 10, showing immunostaining for lambda light chain by immunoperoxidase (PAP) method. The cytoplasm of the immunoblasts shows no evidence of positive reaction. Scattered positive reactive Marschalko-type plasma cells are present (immunoperoxidase stain for lambda chain, hematoxylin counterstain, ×400).
disease was a dramatic clinical event. Despite this similarity, it must be stressed that there were some fundamental clinical and pathologic differences between these patients. In contrast to four patients (cases 1–4) who presented with advanced stage multiple myeloma, two other patients (cases 5 and 6) were considered to have, at the time of initial diagnosis, low tumor mass myeloma with minimal bone disease (one to three osteolytic lesions), absent or low level monoclonal paraproteins, preservation of normal levels of nonmyeloma immunoglobulins, absence of hypercalcemia, and normal hemoglobin levels.

In addition, differences in the histologic pattern of the extraosseous tumors were noted. Morphologically, the tumors found in cases 1–4 fulfilled the criteria for B-immunoblastic sarcoma, formerly termed reticulum cell sarcoma or histiocytic lymphoma. The tumor masses in cases of localized myeloma (cases 5 and 6) were characterized by the presence of striking plasmacytoid features in the majority of the neoplastic cells and the absence of bizarre multinucleated cells, which made the differential diagnosis between B-IBS and extramedullary myeloma difficult. However, the presence of a very high mitotic index as compared with that observed in the primary lesion of the bone and the much more “primitive” nuclear morphology of immunoblasts in our view indicated a progression of the myeloma to the more aggressive neoplasm, B-immunoblastic sarcoma.

In all of these tumors from all six patients, the B-cell nature of the neoplastic cells was confirmed by the immunoperoxidase studies that revealed the presence within the neoplastic cells of the same monoclonal immunoglobulin (light chain type and heavy chain class) identified immunoelectrophoretically in the serum of each patient. These findings are in agreement with previous observations and provide convincing evidence that, in these patients, the supervening lymphoma of large cell type represented the evolution of the original multiple myeloma rather than the emergence of a second distinct neoplasm, as suggested by other writers.

There have been a number of other descriptions of highly aggressive lymphomas developing in patients with multiple myeloma, but with the exception of Robb-Smith’s series, these consist mainly of single case reports. Moreover, in the previous studies the developmental relationship of these tumors was usually not recognized, and they were regarded as separate entities (multiple myeloma and reticulum cell sarcoma). In comparing the clinical features of our patients to those reported by Robb-Smith, several similarities are apparent, particularly the presence of extramedullary masses and a rapidly deteriorating clinical course after the diagnosis of the lymphoma. However, certain differences do exist between the two series. In contrast to the Robb-Smith patients, who developed “plasma cell/reticulum cell sarcoma” in the phase of complete or partial remission of their primary multiple myeloma, all the present cases, especially those of group A, showed resistance to therapy and increased or unchanged monoclonal paraproteins at the time of diagnosis of B-IBS. It seems likely that in the patients observed by Robb-Smith, the “sarcoma” cells were rapidly dividing immunoblasts showing little evidence of maturation towards the plasma cell and loss of the ability to synthesize immunoglobulin. This phenomenon has been demonstrated both in human and experimental models. Also, in contrast to the present series, none of the patients reported by Robb-Smith presented with a diagnosis of localized myeloma of bone.

The remaining four cases (cases 7–10) illustrate a similar pattern of disease, but with some differences in clinicopathologic expression. In these patients, extramedullary tumor masses were not documented during the course of the disease. Nevertheless, a change in the morphological picture in sequential bone marrow biopsies or the presence “ab-initio” of foci of immunoblasts in the marrow was observed in all cases. In the past, this histologic pattern has usually been termed “undifferentiated myeloma.” Three important clinicopathologic features characterized these cases: (A) clusters or monomorphic infiltration of immunoblasts; (B) multinucleated giant neoplastic cells in varying percentages; (C) a high mitotic index. The clusters of immunoblasts and multinucleated cells were similar to those observed in the extramedullary tumors of patients 1–4.

The apparent evolution of multiple myeloma (a B-cell neoplasm) to B-IBS is analogous to the emergence of a “large cell lymphoma” in patients with chronic lymphocytic leukemia (Richter’s syndrome). In both conditions progression to a more aggressive neoplasm is heralded by the appearance in various tissue sites of clusters of “immature” cells, recognizable as immunoblasts. This point of view is in agreement with the modern concepts concerning the histogenesis of multiple myeloma, for it is currently believed that in multiple myeloma the B immunoblasts (plasma cell precursors) represent the actively dividing cell population responsible for the perpetuation and expansion of the neoplastic clone. In the bone marrow of patients with typical myeloma, these immunoblasts constitute only a small proportion of the neoplastic cells, intermingled with the predominant population of
neoplastic plasma cells or myeloma cells (for which the tumor is named) and a small number of lymphocytes.32

Thus, one might hypothesize that the change from myeloma to a more rapidly proliferating tumor (B-IBS) results in an increase in the number of the immunoblasts (proliferating cells), which in turn produces a change in the overall histologic picture.32,38,39

The variations in the histopathologic pattern (diffuse infiltration versus clusters of immunoblasts) are probably dependent on the time of the examination of the bone marrow during this progressive change.

The presence of multinucleated bizarre Reed-Sternberg-like neoplastic cells both in the bone marrow and extramedullary lung of some of our patients is also an interesting biologic phenomenon and probably accounts for the incorrect terminology—megakaryoblastic40 or megakaryocytic41 myeloma—used in the past. These cells would appear to represent additional evidence for the transition of multiple myeloma to a more kinetically active neoplasm (B-IBS). The high frequency of Reed-Sternberg cells in Hodgkin's disease lymphocyte depletion type (as compared with lymphocyte predominance type) and of Reed-Sternberg-like cells in large cell non-Hodgkin lymphomas, both arising de novo or from the transformation of a preexisting lymphoproliferative disorder, seems to indicate an association of these large bizarre cells with rapidly proliferating neoplasms.38 Thus, the histologic features observed in our patients (i.e., clusters or diffuse proliferation of immunoblasts, multinucleated giant neoplastic cells, and high mitotic index) suggest the progression from a low turnover (multiple myeloma) to a high turnover neoplasm (B-IBS). This suggestion is strongly supported by previous observations in human tumors that have demonstrated a relationship between the size of the neoplastic cells and the cell cycle kinetics.38 In particular, dual parameter flow cytometry studies42 performed on cellular suspensions of human leukemias and lymphomas seem to indicate that the "large cells" previously termed "reticulum cells," now recognized as transformed lymphocytes and immunoblasts, represent the proliferating fraction of the tumor (i.e., the faster growing cells). Consequently, the number of such cells (in a lymphoma) is indicative of the rate of proliferation of the tumor, and hence the prognosis. As pointed out in an earlier review, there is nothing new in this suggestion;38 in fact, it is implicit in many of the lymphoma classifications proposed over the years.

At the risk of oversimplification one might say that the larger the predominant cell and the more delicate its nuclear features, the poorer the prognosis.—Block41

It is not surprising, therefore, that following the diagnosis of B-IBS, the course of the disease was aggressive. The median survival from the diagnosis of B-IBS was only 4 mo. This figure is remarkably similar to that reported by Trump et al.37 in a review of a large series of patients with Richter's syndrome.

These concepts are in keeping with those expounded in a more extensive consideration of the whole range of B-cell neoplasia38 and are particularly interesting when considered in the light of the studies on cellular kinetics in multiple myeloma. Multiple myeloma has traditionally been considered a neoplasm with a low turnover rate with only a small fraction of cells showing active DNA labeling.44 Consequently, the prognosis has been related more to the tumor mass than to the kinetic behavior of the neoplasm. However, it has recently been reported45 that a high pretreatment labeling index plus a high cell mass may be associated with a particularly aggressive form of multiple myeloma having a propensity for CNS involvement. In the above studies no attempt was made to correlate the kinetic data with the morphological appearance of the myeloma cell population. However, it is known that cells in S phase generally appear large and primitive;46 in the lymphoid series, such cells have the appearances of transformed lymphocytes or immunoblasts.38 Thus, it seems likely that as the number of cells in S phase increases, one would observe an increase in the proportion of large immunoblasts and a relative decrease in differentiated plasma cell forms.

Recourse to the pertinent literature on multiple myeloma shows that the relationship existing between the morphological features of the neoplastic cells and the clinical course of the disease has been a controversial subject. Kolody, in 1927,47 noted that "among plasmacytomata one encounters a small and a large cell variety; the latter are said to be of more rapid growth and somewhat worse prognosis." Bayrd, in 1948,16 observed that "the cases (of myeloma) in which there was a marked degree of pleomorphism, often associated with frequent mitoses and notable immaturity, bore the poorest prognosis." In addition, Azar48 has reported the occurrence of uncommon forms of fulfilling myelomatosis (disseminated nonosteolytic myelomatosis) characterized by infiltration of the bone marrow by highly anaplastic plasma cells resembling reticulum cells. The nine cases of dysplastic myeloma described by Davis et al.5 as displaying cellular dysplasia, extrasosseous extension, and an aggressive course, probably represent a similar condition. Also, more recently, Woodroff18 has suggested that the cells in plasma cell leukemia are immature when compared with the myeloma cells observed in the bone marrow of
other patients with multiple myeloma. In contrast to the above studies, several authors have not been able to demonstrate any correlation between the degree of maturity of the myeloma cells and clinical course of the disease.13,30

Clearly, kinetic and immunohistologic studies have provided a new insight into the nature of multiple myeloma, in particular revealing the close relationship, in terms of cellular origin, of multiple myeloma with other B-lymphocyte-derived neoplasms, including B-IBS, B-cell chronic lymphocytic leukemia, and the follicular center cell lymphomas.38 However, areas of uncertainty persist concerning the relationship of morphological findings with prognosis. Only from additional multiparameter studies, combining the use of immunologic methods, kinetic analysis, and morphologic, can we expect to resolve some of the discrepancies currently to be found in the literature and perhaps, thereby, achieve a rational approach to a more effective form of therapy.

ACKNOWLEDGMENT

Raymond Russell performed the immunoperoxidase techniques. We are grateful to Betty Redmon for assembling the manuscript. The following physicians submitted the cases for the study: N. J. Gould, M.D., Glendale, Calif.; O. Kilinger, M.D., Mission Hills, Calif.; and Professor M. F. Martelli, Perugia, Italy.

REFERENCES

Emergence of B-immunoblastic sarcoma in patients with multiple myeloma: a clinicopathologic study of 10 cases

B Falini, I De Solas, AM Levine, JW Parker, RJ Lukes and CR Taylor