

Myeloma Protein Kinetics Following Chemotherapy

By Peter McLaughlin and Raymond Alexanian

The effects of chemotherapy were evaluated in 43 multiple myeloma patients with high monoclonal globulin levels in both serum and urine. In responding patients, Bence Jones protein excretion declined more rapidly and markedly than the serum myeloma protein. Bence Jones protein excretion was reduced by 50% within 2 mo in responders, remained unchanged in nonresponders, and declined with a slow halving time of 2–7 mo in patients with partial disease

control. Three patients with clinical resistance to treatment showed atypical protein changes and progressively more Bence Jones protein excretion relative to their serum monoclonal component. Serial measurements of Bence Jones protein excretion provided an early and reliable index of tumor mass change in patients with multiple myeloma.

IN MOST PATIENTS with multiple myeloma, changes in serum myeloma protein production rate have provided the best available index of tumor mass change from chemotherapy.^{1,2} The utility of systematic Bence Jones protein (BJP) quantitations in defining remission and relapse has been less clear, primarily because the relation of changing BJP excretion to variations in tumor mass has not been defined. Thus, the significance of a specific reduction in BJP excretion following chemotherapy is unknown. Such knowledge would also provide a more realistic appraisal of remission and relapse in the 20% of myeloma patients with light chain excretion as their only protein abnormality.

This study evaluated serum myeloma proteins and Bence Jones protein excretion simultaneously in a large number of patients receiving chemotherapy. Results indicated that a rapid and marked decline of BJP excretion provided the earliest evidence that a remission would develop, sometimes months before definitive changes in the serum myeloma protein had occurred. With rare exceptions, the eventual magnitude of tumor reduction was predicted from the rate of BJP decline during the first 2 mo of treatment.

MATERIALS AND METHODS

The records of 525 consecutive, previously untreated patients with multiple myeloma referred to the University of Texas M.D. Anderson Hospital between September 1965 and December 1980 were reviewed. Only patients with both serum myeloma protein exceeding 2.0 g/dl and BJP excretion greater than 1.0 g/day were eligible for study. Only those patients with at least 4 myeloma protein measurements in both serum and urine for at least 6 mo following the start of chemotherapy were analyzed. Patients with renal abnormalities (i.e., BUN >40 mg/dl or 24-hr urinary albumin >1 g) were analyzed separately. Among patients with marked albuminuria, those with a urine monoclonal component of the same electrophoretic mobility as the serum myeloma protein were excluded because light chain excretion could not be quantitated. All patients received intermittent courses of an alkylating agent with prednisone, many also receiving vincristine and doxorubicin in accordance with specific protocols.³

Changes in the serum myeloma globulin concentration were measured from the electrophoretic strip in patients with IgG and high IgA peaks, and from the direct immunoglobulin quantitation in patients with IgA monoclonal globulins falling to less than 2.0 g/dl.

Variations in myeloma tumor mass were calculated from changes in serum myeloma protein production rate using techniques described previously.^{1,2} BJP excretion/day was determined simultaneously from the product of the 24-hr urine protein excretion and the percent light chain globulin on urine electrophoresis.

Patients were classified into three response groups depending on the magnitude of reduction in serum myeloma protein production as an index of tumor mass change, as described previously.^{1,2} Responders eventually reduced serum myeloma proteins by at least 75%, "improved" patients by 50%–74%, and nonresponders showed less than a 50% reduction. The response of three atypical patients was difficult to classify and these patients were analyzed separately. Survival was calculated from life-table calculations with statistical comparisons by the Wilcoxon technique.

RESULTS

Because of the specific pretreatment and serial myeloma protein measurements required, the analysis was limited to those 43 patients who had complete data for at least 6 mo. The clinical features of these patients are summarized in Table 1. In these selected patients with high monoclonal globulin levels in both serum and urine, the median serum peak was 4.7 g/dl and the median BJP was 2.1 g/day. Since the kinetics of serum myeloma protein and BJP change in the 12 patients with renal disease were similar to those without renal abnormalities for each response category, these patients were included in the analysis.

In each patient, the percentage change in BJP excretion following chemotherapy was compared with the percentage decline in serum myeloma protein production as the primary index of tumor mass change.¹ As indicated in Fig. 1, 16 of 20 responding patients reduced serum myeloma protein by 50% within 2 mo, the serum peak disappearing from the electrophoretic strip in 4 of these patients. All responding patients showed a rapid reduction of BJP excretion

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Submitted July 13, 1981; accepted May 20, 1982.

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0006-4971/82/6005-0008\$01.00/0

Table 1. Clinical Features of Patients*

	Respon- sive	Improved	Un- responsive
No. of patients	20	9	11
Median age	57	60	55
No. Hb <8.5 g/dl	4	2	1
No. calcium >11.5 mg/dl	2	1	0
No. BUN >40 mg/dl	3	1	1
No. high tumor mass	8	4	5
Median survival (mo)	48	23	12
Myeloma proteins			
No. IgG peak	14	7	6
Median g/dl	4.8	4.6	5.6
No. IgA peak	6	2	5
Median g/dl	4.7	6.4	4.4
Median BJP excretion (g/day)	2.0	2.5	2.2

*Three patients with atypical changes were excluded.

by at least 50% within 2 mo and by 90% to less than 200 mg/day within 4 mo. Among 4 patients with very slow declines in serum myeloma protein (i.e., halving time 4–8 mo), all showed a more rapid decline of BJP

excretion, with a halving time of 0.5–2 mo; the serum peak concentration had declined by only 15%–30% by the time that BJP excretion had been reduced by more than 50%.

Unresponsive patients showed a different pattern of myeloma protein change (Fig. 1). None of the 11 unresponsive patients reduced either the serum myeloma proteins or BJP excretion by 50%, a clear plateau in BJP excretion being evident in all within 4 mo of treatment.

In “improved” patients, myeloma proteins fell in a pattern intermediate to that found in responsive and unresponsive patients (Fig. 2). All reduced their serum myeloma protein by 50%–74% and their BJP by more than 50%, but BJP excretion declined slowly with a median halving time of 4 mo (range 2–7 mo). BJP disappeared eventually in 2 “improved” patients but persisted at more than 250 mg/day in the remaining 7 (Fig. 2).

The median survival times for responders, improved patients, and nonresponders were 48, 23, and 12 mo,

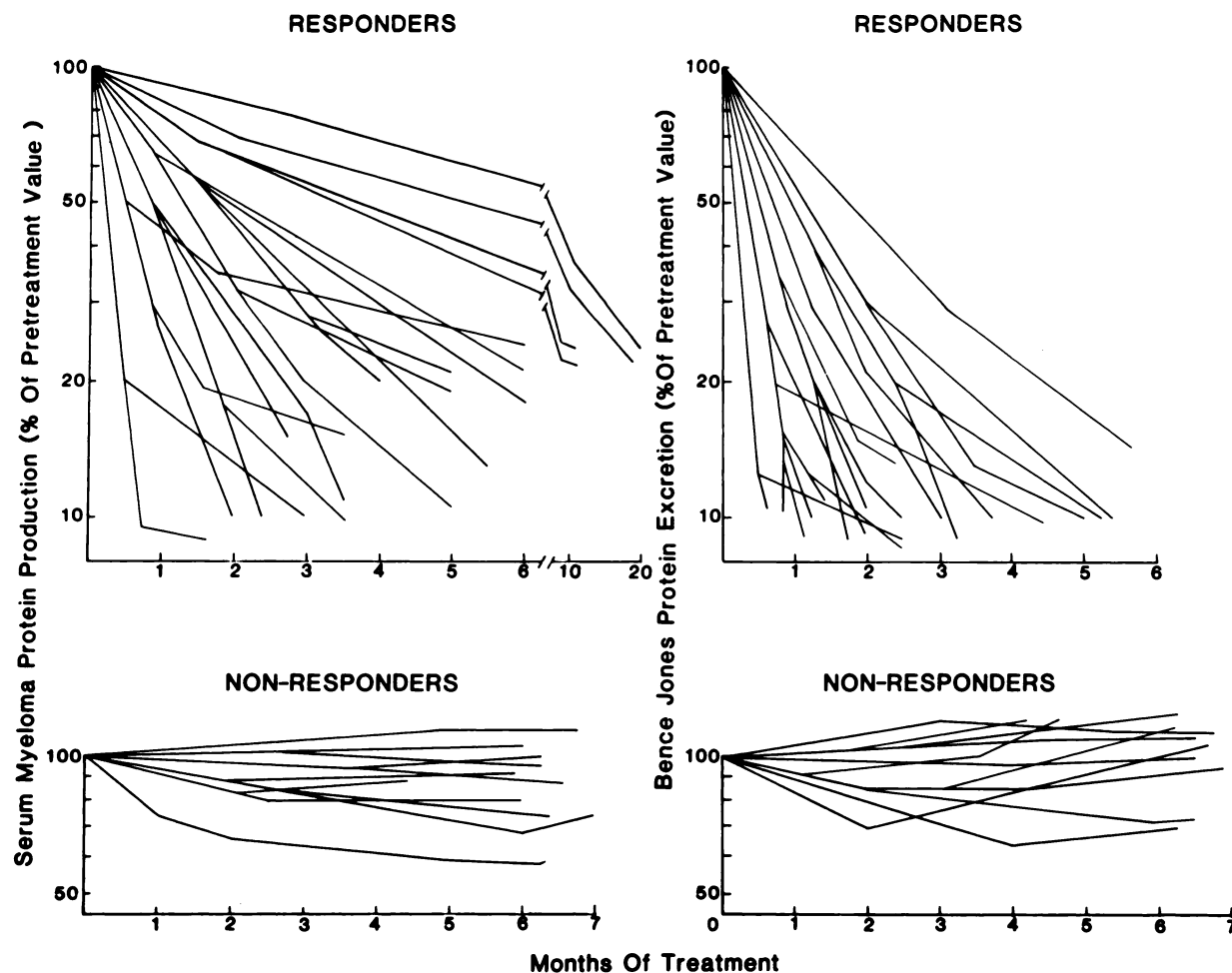


Fig. 1. Upper panels indicate responders, showing the slower fall in serum myeloma protein (left) compared to the rapid decline and disappearance of urine Bence Jones protein (right). Lower panels show absence of change in unresponsive patients.

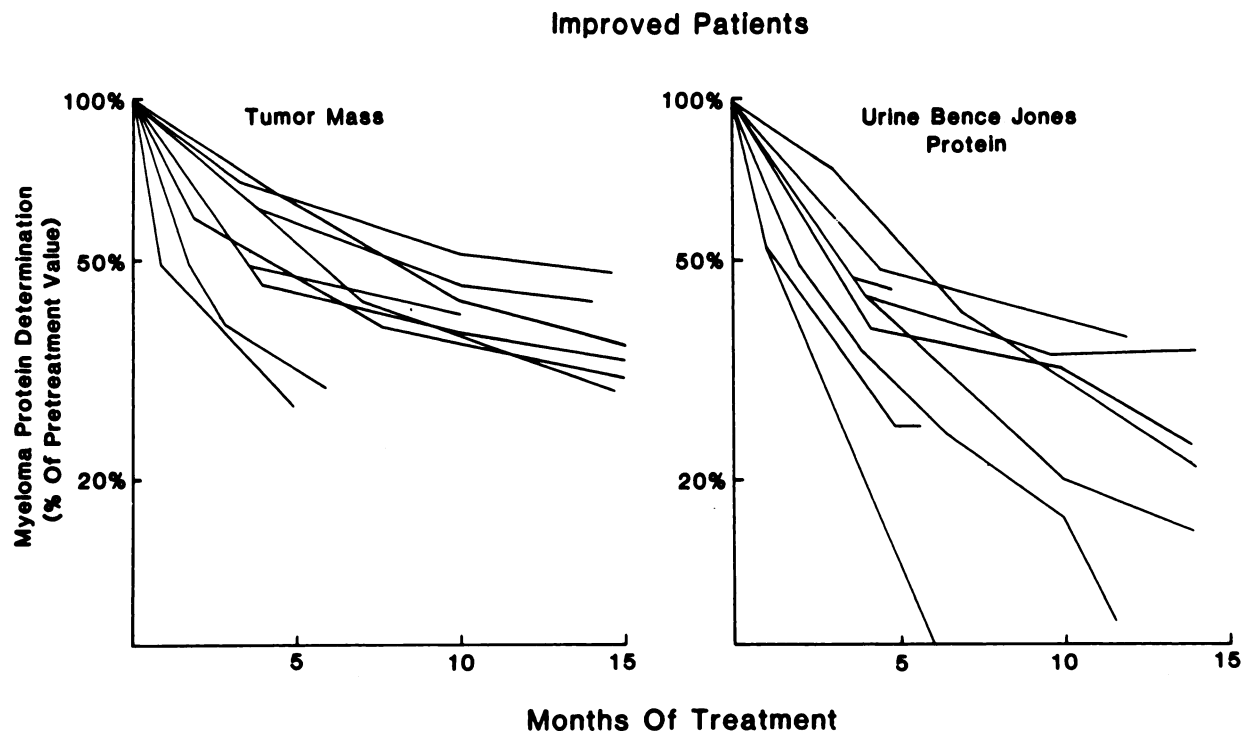


Fig. 2. "Improved" patients showed less marked reductions of tumor mass to 25%–50% of control (left) with slow reductions of urine BJP (right).

respectively. The survival for responders was significantly better than that for the combined group of nonresponders and improved patients ($p < 0.01$). Insufficient patients were available to define whether responders with very rapid reduction of myeloma proteins lived longer than slow responders.

The rate of BJP reduction was compared among the three different response groups whose tumor mass response had been defined from the serum myeloma protein data. Figure 3 shows clear separations in the rate of BJP decline for each response category that were obvious within several months of treatment.

Three patients showed atypical protein changes. One responder had an unusually slow fall of BJP, which paralleled a very slow, but eventually marked, fall of the serum IgA component (Fig. 4C). One patient had an initial reduction of the serum IgG peak by 50%, with a rapid reduction of BJP to 200 mg/day within 2 wk (Fig. 4A); early clinical relapse with enlarging subcutaneous and pleural tumors were then associated with rapid elevations of both protein components. Both of these patients were atypical only in the speed of their protein changes. One other atypical patient had persistent urinary BJP despite a decline in the IgG peak by 75% (Fig. 4B). In this patient, only the persistent BJP identified him as a nonresponder. These patients had most clinical features similar to those of the other patients. However, two were hypercalcemic

with a high tumor mass, and the serum peak was less than 3.2 g/dl in all, in comparison with the median of 4.8 g/dl for all other patients.

The kinetics of protein reduction were also evaluated in 35 consecutive patients who produced only BJP that had disappeared following identical chemotherapy programs. The clinical features of myeloma had resolved and the patients were considered in remission. As in responding patients with serum myeloma proteins, the BJP halving time was less than 2 mo in all. However, more than 4 mo of treatment was required in 10 patients before BJP disappeared from the urine, and all had very high pretreatment excretion levels (median 10 g/day). In one patient with 26 g/day of lambda light chain excretion, disappearance of BJP excretion occurred only after 18 mo of treatment.

DISCUSSION

While a reduction in serum myeloma protein has been an accepted measure of the total tumor response,^{1,2} the significance of a specific decline in Bence Jones protein excretion (BJP) has been less clear. The role of BJP was evaluated from serial assessments of both serum and urine protein markers in a large number of patients with both abnormalities who received a standard program of chemotherapy. Changes in Bence Jones protein excretion provided the earliest index of either a marked plasma cell reduction

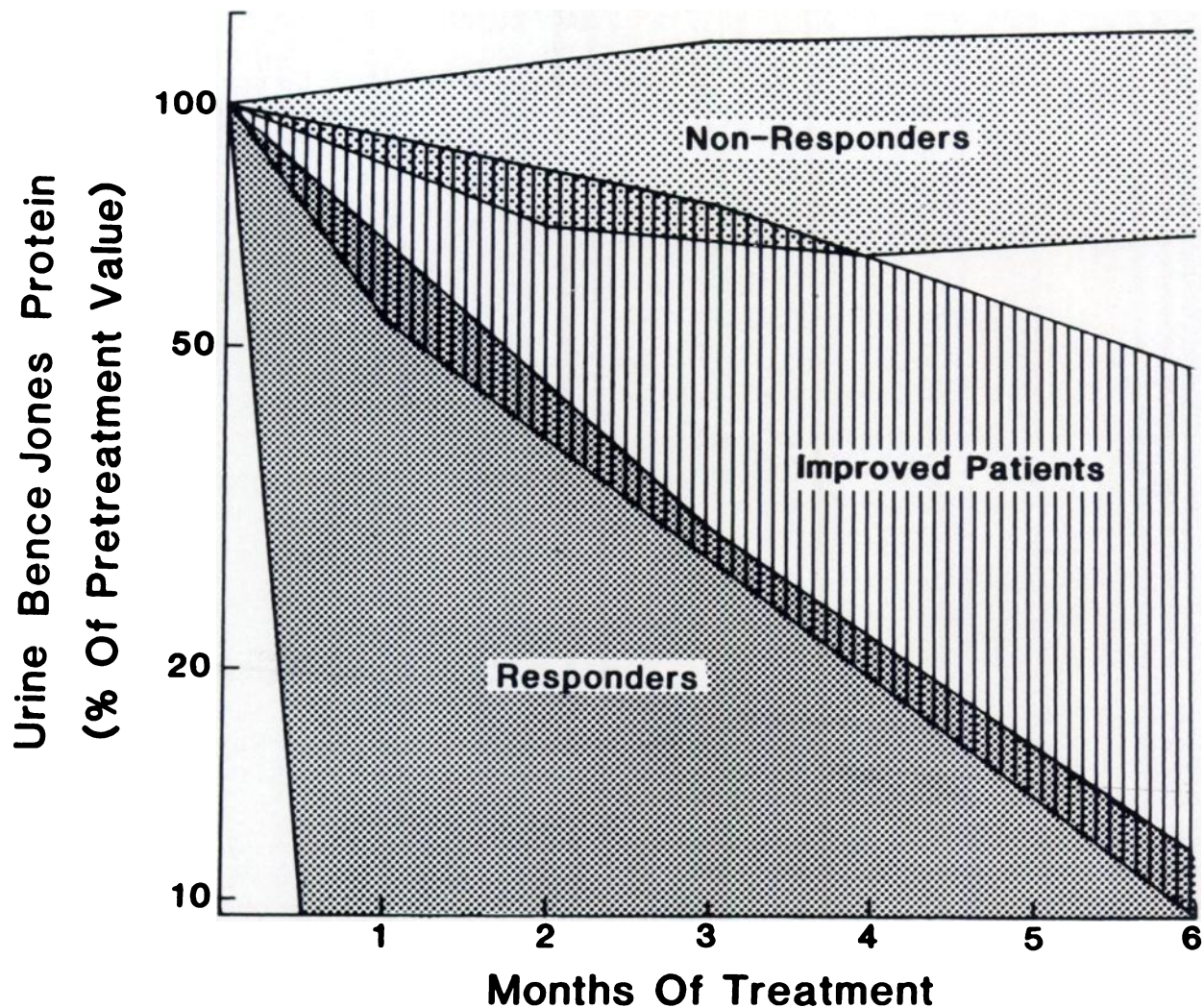


Fig. 3. Degree of BJP decline as a percent of the pretreatment value in the three response categories defined from the degree of serum myeloma protein reduction. A rapid reduction occurred only in responding patients, while nonresponders were recognized within several months.

or a resistance to chemotherapy. Thus, BJP excretion was reduced rapidly and disappeared in responding patients, but persisted at more than 50% of the pretreatment value in all nonresponders, differences that were obvious within several months of treatment. Patients with an intermediate tumor reduction showed slower and usually less complete reduction of Bence Jones protein than achieved in responders. BJP changes correlated well with other accepted criteria of remission, even in the presence of renal failure and/or nephrosis, and patients responding by this criterion had longer survival times. The failure to reduce BJP by 50% within 4 mo after the start of chemotherapy identified patients with therapeutic resistance in whom different treatments should be instituted early, especially when advanced disease is present and the prognosis is poor.⁴ Each of the infrequent exceptions to this pattern appeared to be clinically resistant to chemo-

therapy and showed progressively less heavy chain and more light chain production per cell in the manner described by Hobbs.^{5,6} More frequent measurements of Bence Jones protein excretion, such as weekly after the start of chemotherapy, might have confirmed response and resistance trends even earlier in some patients. Such data could also clarify the important question of whether the speed of protein reduction has any correlation with prognosis.

The rapid metabolism of Bence Jones protein probably accounts for its prompt elimination from the urine following a marked reduction of the myeloma cell population. The half-life for heavy chain immunoglobulins ranges from 6 days for IgA to 23 days for IgG components, and their catabolism is largely independent of the kidney.⁷ In contrast, the half-life of Bence Jones protein is less than 1 day, and the kidney is the major site of catabolism.^{8,9} Since the capacity for

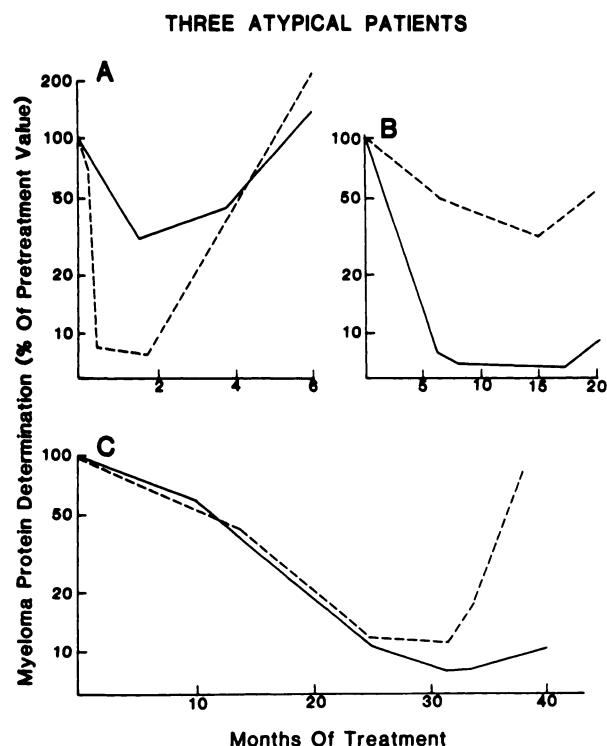


Fig. 4. Lower panel indicates an atypical patient with slow declines and eventual disappearance of both urine BJP (dotted line) and IgA myeloma protein (solid line). With relapse, only BJP excretion increased markedly. Upper right panel shows a patient with a marked reduction of serum myeloma protein but little change in urine BJP (dotted line). Upper left panel indicates an atypical patient with a temporary fall in urine BJP (dotted line) that was followed by early progression of both protein markers and of multiple tumor masses.

renal catabolism may exceed 30 g/day in some myeloma patients with high production levels, the urinary excretion of Bence Jones protein presumably represents the excess production that escapes renal catabolism. Thus, the disappearance of urinary BJP reflects a less marked decline of total BJP production and of the myeloma cell mass than does a comparable decline in serum myeloma protein production.

In patients with Bence Jones protein excretion as

their only abnormality, precise criteria for remission have been difficult to define. Some centers have defined remission as a 50% reduction in BJP excretion, while others have required disappearance. No studies have considered the rates of protein change or the time to disappearance as a factor. Our studies indicated that only patients with a rapid rate of BJP reduction "responded" in terms of a 75% reduction of serum myeloma protein production. Because some patients may have a very high basal BJP excretion, especially when Bence Jones protein constitutes the only abnormality, the eventual disappearance of BJP may require many months of chemotherapy. Those patients with slow reductions should be considered resistant to chemotherapy and should be offered promising new agents, especially if they are symptomatic.

Some of our patients had atypical BJP changes following chemotherapy despite a marked decline of the serum monoclonal component. Later BJP elevations with disease progression were sometimes greater than the increments in the abnormal serum protein. These patterns were similar to those of Hobbs, who proposed the concept of "Bence Jones escape" to indicate the emergence of a more primitive plasma cell subclone with less ability to produce or assemble intact immunoglobulins.^{5,6} Presumably even more dedifferentiation occurred in those uncommon relapsing patients whose disease progressed with only bone destruction and/or soft tissue tumors, but without any recurrence of the original myeloma protein. Suchman et al. have described several patients with an aggressive terminal phase of multiple myeloma with less differentiated plasma cells.¹⁰ Such atypical relapse patterns emphasize the importance of monitoring serial changes of myeloma proteins, bone lesions, and bone marrow plasmacytosis throughout a patient's course, since changes in any of these features may herald disease progression.

ACKNOWLEDGMENT

The authors are indebted to Kay Delasalle, who assisted with the analyses.

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