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Management of Extramedullary Plasmacytomas

James A. Bonner, MD,* Jadranka Dragovic, MD,‡ and Michael P. Abrash, MD‡

From 1965 through 1982, 12 patients with solitary, biopsy-proven extramedullary plasmacytomas (EMPs) were treated at our institution with surgery alone or biopsy followed by radiation therapy. The median age of the patients was 67 years, and the median follow-up was 58 months. Of the seven patients who were treated by primary surgery, three developed recurrent or distant disease. Five patients underwent biopsy followed by radiation therapy, and none of their tumors progressed. Our series and a review of the literature show that occasionally EMPs will incompletely regress even after high doses of radiation (greater than 65 Gy); however, we recommend that doses of 45 to 50 Gy be used for most tumors, with greater doses being reserved for bulky or inaccessible tumors. Each tumor was classified histologically as well differentiated, moderately differentiated, or poorly differentiated. Patterns of pathology appear to be of no prognostic significance. Five patients (42%) were noted to have second neoplasms. (Henry Ford Hosp Med J 1987;35:245-50)

Extramedullary plasmacytomas (EMPs) are rare plasma cell neoplasms that occur in the soft tissues outside of the skeletal system. In a study from the Birmingham Regional Cancer Registry, the crude annual incidence rate for EMPs was 0.04 per 100,000 people as compared to 1.9 per 1000 for medullary plasma cell tumors (1). The incidence of EMPs in relation to multiple myeloma was 1:40. In a large review of 228 cases of EMPs by Wiltshaw (2), 76% of EMPs presented in the upper air passages, 6% in the lower air passages, 4% in lymph nodes and spleen, 3% in the gastrointestinal tract, 3% in the thyroid, 1% in the testes, and 4% in other sites. Presenting symptoms correspond to the tumor location and often include dysphagia, hoarseness, stridor, and a lump in the throat, and less often include lymph node enlargement, cutaneous lesions, abdominal pain, or gastrointestinal bleeding (2-14).

EMP is defined as a biopsy-proven plasma cell tumor in one or two extraskelatal foci without evidence of disease following bone marrow and radiological evaluation of the skeletal system (1,15,16). In Wiltshaw’s series (2), 33% to 40% of patients with EMPs developed disseminated disease (metastatic spread beyond lymph node involvement), with those tumors which had recurred locally having the higher rate of dissemination and, in contrast, the majority of solitary plasmacytomas of bone having progressed to multiple myeloma. Wiltshaw (2) suggested that solitary plasmacytomas of bone are indeed an early manifestation of multiple myeloma, whereas EMPs represent a separate clinical entity.

Numerous studies have established that surgery, radiation therapy, or a combination of these treatments represent appropriate management of EMPs (2-10,13,17-24). Local control rates of 60% to 80% have been reported (2-10,13,17-24). This study reviews the pathology, treatment, and clinical course of 12 patients with biopsy-proven EMPs that were diagnosed at Henry Ford Hospital from 1965 to 1982.

Materials and Methods

Twelve cases of biopsy-proven EMPs were seen at Henry Ford Hospital from January 1, 1965, to December 31, 1982. This endpoint was selected to allow for a minimum of four years of follow-up of all patients. All cases of biopsy-proven EMPs were identified through the computerized file of Henry Ford Hospital’s pathology department. Cases were included in the study if the following criteria were met: 1)extraskeletal plasma cell tumor proven by biopsy with no more than two foci, 2) normal bone marrow with less than 10% plasmacytosis, and 3) no evidence of bony metastasis on skeletal x-rays. All diagnostic evaluations included serum protein electrophoresis. Patients were included regardless of their M protein status. One patient was excluded from the study because no bone marrow biopsy was performed.

The pathology slides were reviewed in each case with a Henry Ford Hospital pathologist. Cases were identified as true plasmacytomas by the methods outlined by Batsakis (25). Three cases, which were considered plasmacytomas at the time of diagnosis, were excluded from the study because a review of the

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histology showed that plasma cell granuloma could not be ruled out. After these exclusions, a total of 12 patients were included in the study. The pathology of each tumor was graded by the method of Kapadia et al (26) as well differentiated (mature plasma cells with uniform size [Fig 1]), moderately differentiated (larger nuclei with less peripheral chromatin clumping and less abundant cytoplasm), and poorly differentiated (large pleomorphic nuclei with scant cytoplasm [Fig 2]). Unfortunately, surgical margins could not be adequately assessed retrospectively.

All cases were treated by surgery, radiation therapy, or a combination of these treatments. All cases include follow-up to the present time or to the patient’s death. Case 4 was previously reported in the literature without follow-up (11).

Results

Table 1 outlines the clinical presentation, treatment, course, and pathological classification of EMP for each of the 12 patients in this study. Age at presentation ranged from 44 to 88 years, with a median age of 67 years. The ratio of males to females was 10:2. Follow-up ranged from three to 242 months following initial treatment. The median follow-up time was 58 months.

For this series of patients with EMPs, the site of presentation was the upper airway in 33% (four cases), the thyroid in 17% (two cases), a cutaneous lesion in 17% (two cases), and one case each in the spleen, the prostate, a posterior cervical node, and a hilar lymph node. The presenting symptoms were related to the site of the primary tumor. Patients with upper airway EMPs had symptoms of nasal obstruction, sore throat, and hoarseness. Both patients with thyroid EMPs presented with enlarging neck masses, and one patient also complained of dysphagia. One patient with a cutaneous EMP presented with a breast mass, and the other patient presented with a draining ulceration of one year duration. The patient with a left hilar lymph node EMP presented with a mass on chest x-ray, and the patient with a cervical lymph node EMP presented with a posterior neck mass. The patient with a prostatic EMP presented with urinary obstruction, and the patient with a splenic EMP presented with a traumatic splenic tear following an automobile accident.

M protein was present in three cases. In two of these cases, the M protein was present at the time of diagnosis. One case (case...
Table 1
Course of Patients with Extramedullary Plasmacytomas

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)/race/sex</th>
<th>Diagnosis (month/year)</th>
<th>Site</th>
<th>Bone marrow</th>
<th>Other tumor</th>
<th>Presenting symptom</th>
<th>M protein</th>
<th>Treatment</th>
<th>Result</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71/W/F</td>
<td>1962</td>
<td>Left nasal vestibule</td>
<td>Negative, 1% plasmacytosis</td>
<td>Basal cell cancer</td>
<td>Left nostril obstruction</td>
<td>Positive</td>
<td>Surgically resected twice (1962, 1966); 8/67 recurred, 3,000 rads/21 days; 12/69 recurred, 3,000 cGy/21 days; 2/72 recurred, 3,600 cGy/21 days</td>
<td>Died 12/74 of myocardial infarction, acute myeloblastic leukemia</td>
<td>Died 4/72 of myocardial infarction, no clinical evidence of disease</td>
</tr>
<tr>
<td>2</td>
<td>44/W/M</td>
<td>10/65</td>
<td>Posterior cervical lymph node</td>
<td>Negative</td>
<td>Folicular cancer of thyroid, kidney cancer (2/66)</td>
<td>Posterior neck mass</td>
<td>Draining lesion for one year</td>
<td>Negative</td>
<td>10/65 surgically resected</td>
<td>No clinical evidence of disease</td>
</tr>
<tr>
<td>3</td>
<td>56/B/M</td>
<td>7/67</td>
<td>Cutaneous lesion, posterior axillary line</td>
<td>Negative, 1.2% plasmacytosis</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td>Died 4/72 of plasmacytosis</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>4</td>
<td>76/W/M</td>
<td>11/68</td>
<td>Right cutaneous breast mass, right anterior axillary mass</td>
<td>Negative</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td>Died 10/78 of plasmacytosis</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>5</td>
<td>77/B/M</td>
<td>7/75</td>
<td>Prostate</td>
<td>Negative, 5.6% plasmacytosis</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td>Died 10/81 of plasmacytosis</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>6</td>
<td>61/W/M</td>
<td></td>
<td>Left hilar lymph node</td>
<td>Negative</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td>Died 10/81 of plasmacytosis</td>
<td>Moderately differentiated</td>
</tr>
</tbody>
</table>

9) Serum electrophoresis was not performed until two years after the diagnosis, and at that time it was positive. (The quantitative values for immunoglobulin were normal at diagnosis and remained normal two years later.) Of the cases with positive M protein at diagnosis, one developed multiple myeloma in three months, one died of unrelated causes in two months, and one has no evidence of disease after seven years (continues to have M spike). No correlations were made between M protein and survival because of the small sample size.

Seven of the 12 patients had primary surgical therapy. Three tumors recurred: one locally after four years, one metastasized to regional lymph nodes at four months, and one progressed to regional lymph nodes at four months, and one died of unrelated causes in two months, and one has no evidence of disease after seven years (continues to have M spike). No correlations were made between M protein and survival because of the small sample size.

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Extramedullary Plasmacytomas—Bonner et al 247
multiple myeloma at three months. The remaining four patients were disease-free at the last follow-up visit. One patient (case 1), in whom a local recurrence developed in 1966 following a surgical resection of her nasal tumor in 1962, had a second surgical excision of tumor in 1966. She was referred to our institution in 1967 when she had a second recurrence of tumor. Her course at Henry Ford Hospital included three recurrences in 1967, 1969, and 1972, and these episodes were treated with radiation doses of 3,000 cGy, 3,000 cGy, and 3,600 cGy, respectively. She died of acute myeloblastic leukemia in 1974, with no clinical evidence of multiple myeloma; however, her nasal tumor never completely regressed following her last radiation dose in 1972. (She refused to consider any further treatment.) Another patient (case 4) developed a regional (right axillary) lymph node metastasis following the initial surgical resection of his right breast mass. He subsequently underwent an excisional biopsy of this anterior axillary lymph node recurrence. His axillary node mass recurred in 1970, and he received radiation therapy to the involved areas (2,200 cGy/16 days). He was free of disease when he died of a myocardial infarction almost four years after presentation. Another patient (case 2) was noted to have multiple myeloma at autopsy three months following surgical resection of his posterior cervical lymph node EMP. He died of a pulmonary embolus, and the bone marrow at autopsy, although negative at the time of diagnosis, was consistent with multiple myeloma.

The group of patients treated primarily by surgery included two unusual cases: a prostatic EMP, and an EMP involving a left hilar lymph node. The patient who developed prostatic EMP presented with urinary obstruction and was found to have an enlarged prostate on physical examination. He underwent a transurethral resection of his prostate, and plasmacytoma was diagnosed. He died 39 months after diagnosis with no clinical evidence of disease. The other patient, whose left hilar lymph node EMP was discovered on chest x-ray, underwent a thoracotomy with removal of the involved lymph node. No extension of tumor was noted at surgery. This patient died of a myocardial infarction in 1972. (She refused to consider any further treatment.) Another patient (case 2) was noted to have multiple myeloma at autopsy three months following surgical resection of his posterior cervical lymph node EMP. He died of a pulmonary embolus, and the bone marrow at autopsy, although negative at the time of diagnosis, was consistent with multiple myeloma.

Five patients in this study were initially treated with biopsy followed by radiation therapy. Four of these patients had excisional biopsies, and one had a needle biopsy. None of the tumors recurred locally or progressed to multiple myeloma. The patients received doses of radiation therapy ranging from 4,000 cGy/31 days to 6,000 cGy/60 days. The average follow-up for these five cases was 53 months.

As noted, each tumor was classified according to its histological differentiation. Three tumors were classified as well differentiated, five as moderately differentiated, and four as poorly differentiated. All of the patients with EMP developed recurrence following the initial treatment. The second neoplasm was discovered synchronously with the EMP in two cases (cases 9 and 12), prior to the diagnosis of EMP in one case (case 11), and following the diagnosis of EMP in two cases (cases 1 and 2). None of these second neoplasms fell in the category of multiple myeloma, and no evidence of multiple myeloma was noted in any of the patients.

### Table 2

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Total No. of Patients</th>
<th>No. of Patients with M Protein</th>
<th>No. of Local Recurrences</th>
<th>No. of Lymph Node Involvement</th>
<th>No. of Patients Developing Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

The radiations for treatment of EMPs were EMPs. Surgery, radiation therapy, or a combination of these treatments have proven to be efficacious in various series (2-10,13,17-23). Following appropriate management, it remains unclear as to which tumors will recur locally or progress to disseminated disease. Progressive increase in M protein, bone destruction, local recurrence, and unusual site of presentation have been indicated as significant prognostic factors regarding decreased survival or eventual development of multiple myeloma (1,2,8,21). The presence of M protein on serum electrophoresis and lymph node involvement have not shown prognostic significance (2,8,21). These prognostic factors were not evaluated in our study because of the small population.

In a review of 272 cases from the Royal Marsden Hospital and other institutions, Wiltshaw (2) established that the rate of local recurrence for EMPs was similar for surgery (40%) or radiation therapy (34%) as primary treatments. Radiation doses were not specified in Wiltshaw's study. It was also evident that combined treatment (surgery and radiation therapy) resulted in fewer local recurrences (16%) than either single treatment alone. Disseminated disease occurred in 35% of all cases and was unrelated to

### Discussion

Many reports have commented on appropriate treatment of EMPs. Surgery, radiation therapy, or a combination of these treatments have proven to be efficacious in various series (2-10,13,17-23). Following appropriate management, it remains unclear as to which tumors will recur locally or progress to disseminated disease. Progressive increase in M protein, bone destruction, local recurrence, and unusual site of presentation have been indicated as significant prognostic factors regarding decreased survival or eventual development of multiple myeloma (1,2,8,21). The presence of M protein on serum electrophoresis and lymph node involvement have not shown prognostic significance (2,8,21). These prognostic factors were not evaluated in our study because of the small population.

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the mode of therapy. In our series, five cases (cases 8-12) were originally treated with radiation therapy (either as primary treatment or in combination with surgery), and none of the tumors progressed. Of the seven cases originally treated with surgery, one patient’s tumor failed locally after four years and was subsequently resistant to several attempts of surgery and radiation therapy (case 1), one patient developed a regional lymph node metastasis which required surgical resection in 1969 and subsequent radiation therapy in 1970 (case 4), and one patient went on to develop multiple myeloma at three months (case 2). Case 2 was most likely a case of multiple myeloma which presented as a solitary lesion. In our small series it is difficult to make any conclusions about the benefits or risks of surgery versus radiation therapy; however, consideration of Wiltshaw’s (2) data leads to the recommendation that radiation therapy be given following surgical excision of EMPs. Conversely, surgical excision should be considered for residual tumor following primary radiation therapy.

The radiosensitivity of EMPs has been given much consideration in the literature. Harwood et al (21) evaluated 23 cases of EMP and recommended that a dose of 3,500 cGy in three weeks be given for good local control and a low rate of disseminated disease. Corwin and Lindberg (8) recommended doses of 4,000 to 5,000 cGy. Mendenhall et al (23) reported a review of the literature of 81 patients with solitary plasmacytomas (skeletal and soft tissue) and noted a significant improvement in local control rates at doses above 4,000 cGy. Local failures occurred in 6% of patients with doses greater than 4,000 cGy and in 31% for doses less than 4,000 cGy. Mill and Griffith (22) analyzed 43 patients (16 patients from their institution and 27 patients from the literature) with plasmacytomas of bone and soft tissues (22 cases were EMPs). They recommended doses of 5,500 to 6,000 cGy over six weeks for the EMPs. However, they also recognized that local failures occurred in the EMPs up to a dose of 6,750 cGy and noted that their statistics were based on a small number of cases. In a series of EMPs by Bush et al (4), local disease was noted in one of their ten cases following a dose of 6,075 cGy/41 days. In our series the nasal tumor of case 1 recurred following two surgical resections, and the patient subsequently received radiation doses of 3,000, 3,000, and 3,600 cGy at approximately two-year intervals. Tumor was still present on physical examination at the end of treatment, and the patient refused further therapy. Five other cases in our series received radiation therapy in doses ranging from 4,000 cGy/31 days to 6,000 cGy/60 days with no local failure or dissemination of disease. All of the aforementioned series suggest that EMP tumors occasionally will incompletely regress even with high doses of radiation. However, we recommend that doses of 4,500 to 5,000 cGy over three to five weeks be given for adequate local control of most tumors and that greater doses may be necessary to irradiate bulky or inaccessible tumors (case 11).

Knowing et al (18) reported the University of Toronto experience with EMPs and found that seven of 25 cases of EMP presented with lymph node involvement. Also, regional lymph nodes were the initial site of relapse in three other patients. In our series, case 4 (11) was the only case with regional lymph node metastasis. As noted, this patient presented with a subareolar breast mass plasmacytoma, which initially was surgically resected and subsequently recurred in a right anterior axillary lymph node two months after diagnosis. This recurrence responded to surgical resection and radiation, and no evidence of disease was present at the time of death 41 months after presentation. In the Toronto series (18) all three patients who developed node metastases following treatment to the primary site died with evidence of tumor. In their study, Knowing et al raised the question of whether prophylactic regional lymph node irradiation should be instituted at the time of initial treatment. This question needs to be further investigated to determine if added benefits exist for early treatment of regional lymph nodes.

Several studies have reviewed the pathology of plasmacytomas (25-29), and Batsakis and colleagues (25-29) concluded that histological appearance cannot be used as a reliable indicator of biological activity. This conclusion is corroborated by our series, in which two tumors showed aggressive biological behavior (one local recurrence and one progression to multiple myeloma), and both were well differentiated by the criteria noted previously. Two of the four patients whose tumors were poorly differentiated are still living after six to eight years of follow-up. One patient died of pneumonitis, and another died of pneumonia. Neither patient showed evidence of a plasmacytoma recurrence at the time of death. Our data showed no correlation between pathology and biological behavior of tumor; however, it is apparent that well-differentiated tumors can lead an aggressive course.

Also corroborated by this series is the association of plasmacytomas with other carcinomas, which has been documented in several reports (29-32). In an autopsy series, Weitzel (33) noted that the coexistence of other carcinomas with plasma cell neoplasms was markedly higher (19.3%) than the incidence of carcinoma associated with lymphoma leukemia (7.96%) or the incidence of multiple primary carcinoma (4.2%). In our series, 42% of patients had evidence of other malignancies during their lifetime. Hosley (31) hypothesized that plasma cell neoplasms and second cancers in one patient could have a common etiological factor, such as an inherited defect, or a common carcinogen. He also suggested that plasma cell neoplasms in the presence of other cancers may represent a plasma cell hyperplastic response which has undergone malignant transformation. In his series it was unusual to find both the plasma cell neoplasm and the second carcinoma to be widely disseminated in a single patient. Usually one process remained localized while the other process disseminated. Therefore, it is possible that patients will be adequately cured of their EMP only to encounter a battle with a second neoplasm.

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