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MULTIPLE MYELOMA (P KAPOOR, SECTION EDITOR)

Solitary Plasmacytoma: a Review of Diagnosis and Management

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Abstract

Purpose of Review Solitary plasmacytoma is a rare plasma cell dyscrasia, classified as solitary bone plasmacytoma or solitary extramedullary plasmacytoma. These entities are diagnosed by demonstrating infiltration of a monoclonal plasma cell population in a single bone lesion or presence of plasma cells involving a soft tissue mass, respectively. Both diseases represent a single localized process without significant plasma cell infiltration into the bone marrow or evidence of end organ damage. Clinically, it is important to classify plasmacytoma as having completely undetectable bone marrow involvement versus minimal marrow involvement. Here, we discuss the diagnosis, management, and prognosis of solitary plasmacytoma.

Recent Findings There have been numerous therapeutic advances in the treatment of multiple myeloma over the last few years. While the treatment paradigm for solitary plasmacytoma has not changed significantly over the years, progress has been made with regard to diagnostic tools available that can risk stratify disease, offer prognostic value, and discern solitary plasmacytoma from quiescent or asymptomatic myeloma at the time of diagnosis.

Summary Despite various studies investigating the use of systemic therapy or combined modality therapy for the treatment of plasmacytoma, radiation therapy remains the mainstay of therapy. Much of the recent advancement in the management of solitary plasmacytoma has been through the development of improved diagnostic techniques.

Keywords Plasmacytoma · Solitary plasmacytoma · Extramedullary plasmacytoma · Solitary bone plasmacytoma · Solitary extramedullary plasmacytoma

Introduction

Plasma cell dycrasias are mature B cell malignancies. Solitary plasmacytomas represent less than 5% of plasma cell dycrasias and are further subclassified as solitary bone plasmacytoma (SBP) or solitary extramedullary plasmacytoma (SEP) depending on whether the site of involvement is the bone versus soft tissue. Soft tissue extension and spread of SBP can occur, but it is still classified as SBP, if there was initially bony involvement. SEP solely involves soft tissue and can involve any site or organ. Most commonly, SEP involves the head and neck, respiratory, and GI tract [1]. The most common presenting symptom can be pain, but other neurological symptoms can also manifest due to nerve compression.

In solitary plasmacytoma, it is important to make the distinction of whether or not minimal bone marrow clonal plasmacytosis is present (Table 1). SBP and SEP are more common in men and occur at a median age of 55. SEP is exceedingly rare. According to a review of the Swedish registry, SEP occurs with a predicted incidence of 0.063/100,000 in females and 0.078/100,000 in males. SBP occurs with a predicted incidence of 0.090/100,000 in females and 0.191/100,000 in males [2].

Diagnosis

The diagnosis of SBP or SEP requires biopsy-proven monoclonal plasma cell infiltration of a single lesion. For a diagnosis of plasmacytoma to be made, there must be an absence of end organ damage including hypercalcemia, renal dysfunction, and anemia. There must be a single site of involvement

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Table 1 Diagnostic criteria for plasma cell dyscrasias

Plasma cell dyscrasia	Diagnostic criteria
Monoclonal gammopathy of undetermined significance	Serum M protein < 3 g/dL
	Bone marrow plasma cells < 10%
	Absence of end organ damage: hypercalcemia, renal dysfunction, anemia, bone lytic lesion
Smoldering myeloma	Serum M protein ≥ 3 g/dL
	Bone marrow plasma cells 10–60%
	Absence of end organ damage: hypercalcemia, renal dysfunction, anemia, bone lytic lesion
Solitary plasmacytoma	Bone marrow plasma cells absent
	Single lesion of bone or soft tissue
	Negative whole body imaging for additional lesions
	Absence of end organ damage: hypercalcemia, renal dysfunction, anemia
Solitary plasmacytoma with minimal marrow involvement	Bone marrow plasma cells detected but < 10%
	Single lesion of bone or soft tissue
	Negative whole body imaging for additional lesions
	Absence of end organ damage: hypercalcemia, renal dysfunction, anemia
Multiple (multifocal) myeloma	Bone marrow plasma cells detected but < 10%
	Multiple sites of plasmacytomas detected on imaging
	M protein may be present
	End organ damage may be present
Multiple myeloma	Bone marrow plasma cells ≥ 10%
	Plasmacytoma may be present
	End organ damage is present: hypercalcemia, renal dysfunction, anemia, bone lytic lesion
	Without end organ damage or plasmacytoma:
	Bone marrow plasma cells ≥ 60%
	Absolute and involved: uninvolved free light chain ≥ 100

without any additional lesions demonstrated on imaging. In addition, a diagnostic bone marrow biopsy must demonstrate less than 10% of monoclonal plasma cells. Immunohistochemistry staining should be performed to ascertain the presence of a monoclonal plasma cell population. Multicolor flow cytometry can be used to detect occult marrow disease. When there is a detectable level of plasmacytosis, these cases are referred to as solitary plasmacytoma with minimal bone marrow involvement. It is important to make this distinction at the time of diagnosis as patients who have solitary plasmacytoma with minimal marrow involvement are at higher risk for progression to multiple myeloma compared to when there is no detectable plasmacytosis in the marrow. This was first demonstrated in a retrospective review of 127 patients at Mayo Clinic. It was shown that patients with plasmacytoma and detectable clonal plasma cells in the marrow were at much higher risk for progression and death. Median progression free survival was shown to be 42 months in patients with a negative bone marrow compared to 15 months in patients with detected clonal plasmacytosis [3].

While not always present, a monoclonal protein can be detected in the blood in 24–72% of solitary plasmacytoma cases [4]. Bence Jones proteinuria can also be detected but usually in a smaller proportion of patients to a far less extent.

Diagnostic Studies

^{18}F FDG PET CT

^{18}F FDG PET CT is a nuclear medicine imaging technique combined with a low resolution CT. This technique uses a glucose bound fluorine radioisotope that decays with positron emission. A combination of both PET and CT allows for

structural as well as functional assessment of various disease states. The use of PET in plasma cell dyscrasias has been somewhat limited by cost and availability.

^{18}F FDG PET CT is a useful diagnostic tool in plasma cell dyscrasias due to the high sensitivity and specificity of which it can detect lytic lesions or plasmacytomas. In addition, ^{18}F FDG PET CT has the ability to distinguish between metabolically active and inactive disease. This makes it particularly useful in the monitoring of disease activity following treatment. Traditionally, a SUVmax of 4 has been used to delineate active from inactive disease [5]. While ^{18}F FDG PET CT can also demonstrate low-grade FDG uptake following treatment, there have been no studies thus far demonstrating any prognostic impact with this finding.

There have been numerous studies comparing the sensitivity and specificity of X-ray skeletal survey, MRI, low-dose CT, and ^{18}F FDG PET CT. In essence, MRI is usually the gold standard with regard to detection of involvement in the spine. However, ^{18}F FDG PET CT imaging was shown to have the largest impact on physician's management of multiple myeloma [6]. Not unexpectedly, PET CT, low-dose CT, and MRI have a higher sensitivity and specificity than skeletal survey.

In general, there is a recommendation to incorporate ^{18}F FDG PET CT with other imaging modalities into the diagnostic work up of plasma cell dyscrasias to detect any relevant bone involvement or damage to avoid understaging patients (Table 1). ^{18}F FDG PET CT can also be used for prognostication. The presence of extramedullary disease, SUV greater than 4.2, and 3 or more focal lesions have been linked to a higher risk of disease progression and poorer outcomes for multiple myeloma [7].

Some studies have demonstrated that ^{18}F FDG PET CT has revealed numerous foci of disease or occult lytic lesions, not seen in about 30–50% patients originally diagnosed with solitary plasmacytoma. MRI, however, appears to be more sensitive with regard to detecting bone marrow involvement of the spine and pelvis as well as assessing anatomical extent of disease [8].

Another utility of ^{18}F FDG PET CT appears to be the ability to discern minimal residual disease negativity based on comparing pre-treatment and post-treatment imaging. Cell- and molecular-based methods to detect and assess disease in the bone marrow have also improved dramatically. Multiparametric flow cytometry immunophenotyping and oligonucleotide PCR can be performed to detect minimal residual disease in the bone marrow. Coupling this with ^{18}F FDG PET CT to detect extramedullary disease represents an invaluable management technique at diagnosis and throughout treatment.

MRI

MRI not only remains the preferred imaging modality to detect plasmacytoma involving the spine, but also has great utility evaluating disease throughout the body. Solitary plasmacytoma has an appearance of low signal intensity on T1-weighted imaging and high signal intensity on T2-weighted imaging. There is a homogenous enhancement with gadolinium contrast. The ability to discern soft tissue involvement and bone marrow infiltration is a characteristic unique to MRI. SBP is treated with radiation therapy in the majority of cases, so clear delineation for the delivery of radiation with margins is essential. Therefore, MRI is an important diagnostic tool in the primary staging of plasmacytoma as well as radiotherapy treatment planning.

It has previously been demonstrated that obtaining an MRI in addition to traditional imaging studies can upstage patients by demonstrating additional foci of disease in as many as 30% of patients [8]. Other studies have compared the efficacy of whole body MRI to that of low-dose CT. It was found that low-dose CT had understaged 11 patients out of 41 in a comparison with whole body MRI [9]. Another study compared whole body MRI with skeletal survey X-rays. In this study, 19 of 60 patients were understaged, and 10 of those 19 patients had alterations in their proposed therapies as a result of being upstaged. MRI can also detect bone marrow enhancement which may act as a surrogate marker of disease activity, but this has not yet been validated [10].

Salaun et al. assessed 24 patients with SEP using a combination of ^{18}F FDG PET CT and MRI. Overall, ^{18}F FDG PET CT had a higher performance for initial staging of patients due to its broader scope in evaluating different tissue types. MRI missed 18 lesions located outside of the intended study areas. In addition, MRI could not differentiate between appropriately treated lesions and active disease [11]. Overall, it is largely accepted that MRI is the preferred imaging modality to detect disease involving the spine or pelvis. However, whole body MRI is still not widely used due to limited availability and prohibitive cost. It may be used to supplement ^{18}F FDG PET CT in cases that may represent false positive lesions.

Management

Radiation

Radiation is the mainstay of therapy for plasmacytoma, which is highly radiosensitive. Local control rates can be achieved in 80–90% of cases with radiation therapy alone. Historically, a local control rate of 94% has been reported with radiation doses over 40 Gy, but local control rates were less than 70% when the delivered dose was less than 40 Gy [12]. In clinical practice, it is common for higher doses close to 50 Gy to be used, especially for bulky disease > 5 cm. A study from MD Anderson demonstrated a 5-year local control rate of 92% in 84 patients treated with definitive radiation [13]. However, the 5-year rate of progression to multiple myeloma was 47%. This was demonstrated to be higher for patients with SBP at 56%

and 30% for SEP. The 5-year overall survival for both SEP and SBP was 78%, and there was no difference in overall survival in this study.

A large retrospective analysis was performed in Europe, which evaluated the outcomes of 258 patients with solitary plasmacytomas between 1977 and 2001. Two hundred fourteen patients received radiation with a median radiation dose of 40 Gy while a smaller proportion received chemoradiation and a few received surgery alone. The 5-year overall survival was 74%, while the local control rate was 86%. Not unexpectedly, patients had a 5-year probability of 45% for progressing to multiple myeloma. The median time to develop multiple myeloma was 21 months [1]. Younger patients, those with plasmacytomas less than 4 cm and those with extramedullary disease, tended to fare better with lower risk of progression to multiple myeloma. Another cohort from Princess Margaret hospital evaluated 46 patients with solitary plasmacytoma treated between 1982 and 1993. This study demonstrated that a radiation dose less than 35 Gy did not impact local control rates. The 8-year local control rates were 100% for patients treated with 30 Gy or less, 81% for patients treated at 35 Gy, and 80% for patients treated with a dose of 40 Gy or more. However, it was shown that large, bulky plasmacytomas greater than or equal to 5 cm in diameter were at much higher risk of recurrence, with an 8-year local control rate of only 38% [14]. A larger European cohort of 206 patients with SBP was evaluated between 1977 and 2001. In this study, the 5-year local control rate was 88%. There was neither a dose-dependent response nor prognostic impact with SBP greater than 5 cm in diameter [15]. These cohorts did not demonstrate a dose-dependent response to radiation and suggest that a moderate dose of radiation can be used to effectively treat solitary plasmacytoma.

However, a study from the University of Florida did establish a dose-dependent response with higher local control rate of 94% when a dose above 40 Gy was used compared to 69% when a dose less than 40 Gy was used [16]. It is important to note that this study followed only 15 patients with solitary plasmacytoma treated between 1962 and 1978. Similarly, a French cohort evaluated 17 patients with SEP involving the head and neck treated between 1979 and 2003. The 5-year local control rate was 100% in patients treated with a greater than 45 Gy and 50% for patients treated with a dose less than 45 Gy [17]. The optimal dose of radiation remains somewhat controversial, and consensus recommendations exist to provide clinicians with guidance and suggested dose ranges.

When delineating gross tumor volume during treatment planning, the most precise imaging modality is MRI, but CT can also be used. The clinical target volume includes a margin around the gross tumor volume in which there is suspected microscopic disease. In general, a margin of at least 2–3 cm is used for sites with long bone involvement. If there is any uncertainty regarding bony involvement, the entire bone can be included in the clinical target volume. For SEP, margins of 0.5 to 1 cm are acceptable. In vertebral disease, margins are extended to the vertebral body above and below the original target [18•]. If patients have undergone hardware fixation, then the margins are usually extended so that the clinical target volume includes any implanted surgical hardware. Regional lymph node coverage in the treatment field is usually not required in treatment of SBP. However, nodal irradiation can be considered in the treatment of extramedullary disease and is common practice when high-risk regions are involved, such as the head and neck or Waldeyer's ring [19]. For SBP less than 5 cm in size, a dose of 40 Gy, in 1.8 to 2 Gy fractions is recommended by NCCN. For SBP greater than 5 cm in size, a dose of 40 to 50 Gy is recommended. A dose of 40 to 50 Gy is suggested for SEP as well.

Surgery

Surgical resection of plasmacytoma is usually not required as these malignancies are radiosensitive. For the most part, surgical excision is reserved for cases where there is loss of anatomic structural integrity or emergent decompression, and resection is required due to the spinal cord or nerve root compression [18•]. If surgery is performed, it is usually done before radiation therapy and as an adjunct to definitive radiation.

A retrospective review evaluated 155 cases of SEP not involving the upper aerodigestive tract, treated with either surgery alone, radiation alone, or combined surgery and radiation. The 2 year overall survival between all three groups was similar at around 50% [20]. These results are difficult to interpret due to this being an older published data cohort from a time period without modern radiotherapy techniques.

Systemic Therapy

The utility of adjuvant chemotherapy in SBP and SEP has been examined, and there has largely been insufficient data to recommend the use of adjuvant chemotherapy in order to improve disease control or prevent progression to multiple myeloma following radiation. Holland et al. performed a retrospective review of 46 patients with SBP and SEP treated between 1961 and 1988. There were 14 patients in the series who received adjuvant chemotherapy. The median time of progression to multiple myeloma was improved from 29 months without chemotherapy, to 59 months with chemotherapy. However, adjuvant chemotherapy did not affect the rate of progression to multiple myeloma, as 64% of patients receiving chemotherapy still progressed, and 41% of patients who did not receive chemotherapy had progressive disease [21].

A retrospective review from 4 French institutions evaluated 52 patients with SBP, treated with either combined chemoradiation or radiation alone. Chemotherapy regimens were

varied and had included Melphalan, velcade, or thalidomide. There was no difference seen between either group in terms of progression free survival and overall survival at 5 years [22].

Bisphosphonates have been shown to be beneficial when used in patients with multiple myeloma to reduce the incidence of skeletal-related events and bone pain. There is also the perceived possibility of bisphosphonates propagating anti myeloma activity. A Cochrane meta-analysis showed a benefit in overall survival with zoledronate compared to placebo, with a hazard ratio of 0.67 [23].

With the advent of new immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies for the treatment of multiple myeloma, there is great interest as to whether these agents can be incorporated into the treatment of solitary plasmacytomas. The role of adjuvant systemic chemotherapy for plasmacytoma requires further investigation.

An intergroup trial, NCT02516423, was designed in the USA as a randomized trial of adjuvant treatment following definitive radiation in patients with solitary plasmacytoma of the bone with high-risk features. Patients were randomized to zoledronate alone or lenalidomide, ixazomib, dexamethasone with zoledronate for 6 months post radiation. The trial was closed prematurely in 2018 due to poor accrual.

Surveillance

For patients treated with definitive radiation, it is important to first assess for a complete response. This is done with laboratory evaluation that would include a complete blood count, complete metabolic panel, LDH, beta-2-microglobulin, urine protein electrophoresis, serum protein electrophoresis, free light chains, and serum quantitative immunoglobulins. Laboratory evaluation should be performed roughly every 3 months for the first 2 years following radiation treatment and then every 6 months. ^{18}F FDG PET CT with or without MRI should be performed at 3 months after completion of radiation and then every 6–12 months thereafter (Table 2).

Prognosis

Despite excellent local control rates, the majority of patients with solitary plasmacytoma will eventually progress to multiple myeloma. Knobel et al. demonstrated a 5-year overall survival rate of 70% and a 5-year disease-free survival rate of 46%. In addition, the median time to development of multiple myeloma was 21 months, with a 5-year probability of 51% [15]. Some of these statistical results were obtained prior to the use of PET CT or MRI; therefore, a proportion of patients included in these data cohorts may have actually had asymptomatic myeloma with undetected systemic or disseminated disease at the time of diagnosis.

An MD Anderson cohort evaluated 60 patients with SBP between 1965 and 2000. While the presence of a serum M protein at diagnosis does not affect the prognosis of patients, the persistence of serum M protein for greater than 1 year after definitive radiation therapy was shown to be a negative prognostic factor [24]. The M protein can disappear in up to 50% of patients after definitive therapy, but some patients will have a persistent monoclonal gammopathy of undetermined significance. The 10-year myeloma-free survival was 91% in patients with a detectable serum or urine M protein that resolved within 1 year following radiation therapy. This is in comparison to a 10-year myeloma-free survival of 29% when patients had a persistence of their M protein beyond 1 year following radiation therapy. Similarly, Dingli et al. performed a retrospective review of 116 patients with SBP at Mayo Clinic between 1960 and 1995. It was found that serum M protein assessment in combination with serum-free light chain evaluation could be used to effectively stratify patients into a low, intermediate, and high-risk category. Low-risk patients had normal free light chains at baseline and an M protein less than 0.5 g/dL at 1–2 years following diagnosis. Intermediate risk patients had either abnormal free light chains at baseline or an M protein greater than 0.5 g/dL at 1–2 years following diagnosis. High-risk patients had both abnormal free light chains at baseline and an M protein greater than 0.5 g/dL at 1–2 years following diagnosis. The 5-year rate of progression was 13% in the low-risk group, 26% in the intermediate risk group, and 62% in the high-risk group [25].

Table 2 Suggested diagnostic studies for work up and management of solitary plasmacytoma

Laboratory studies	Imaging studies
CBC with differential	Whole body imaging: PET CT or MRI whole body
Complete metabolic panel	MRI or CT of involved site for treatment planning
LDH	If vertebral involvement present: MRI of the cervical, thoracic, lumbar, sacral spine
Serum protein electrophoresis with immunofixation	
Urine protein electrophoresis with immunofixation	
Serum-free light chains	
Bone marrow biopsy with flow cytometry	

The role of fluorescence in situ hybridization (FISH) and cytogenetics in risk stratifying patients with SEP has also been examined. Boll et al. performed FISH analysis of 26 patients with SEP. It was found that SEP is characterized by similar cytogenetic features found in multiple myeloma. Monosomy 13 was evident in 33% of patients, and IGH rearrangement was present in 53% of cases. Interestingly, there was a lower incidence of *t*(11;14), which is commonly seen in multiple myeloma and systemic amyloidosis. More importantly, no clinically significant prognostic factors were identified [26].

More recently, two different groups have separately demonstrated the utility of multiparameter flow cytometry in risk stratifying patients in order to predict the likelihood of disease progression. Paiva et al. followed 35 patients with SBP and 29 patients with SEP. Median follow-up for the cohort was 3 years, during which 38% of SBP patients and 14% of SEP patients progressed to multiple myeloma and required therapy. In the SBP population, it was demonstrated that 71% of patients with bone marrow involvement by flow cytometry eventually had disease progression to multiple myeloma at 3 years, compared to 8% of patients with negative bone marrow by flow cytometry. In patients with SEP, 20% of patients with positive flow cytometry eventually progressed compared with 6% when flow cytometry performed on bone marrow was negative. However, this difference was not statistically significant in the SEP population [27•].

Hill et al. evaluated 50 patients with a confirmed diagnosis of SBP between 1998 and 2008. There was a monoclonal plasma cell population detected on bone marrow flow cytometry in 34 of 50 patients. Overall, progression occurred in 72% of patients with occult marrow disease detectable by flow cytometry compared with 12% in patients who did not have any demonstrable bone marrow involvement by flow cytometry. In addition, this study also evaluated patients with urine protein electrophoresis and found a similar correlate. Disease progression occurred in 91% of patients when monoclonal urine light chains were detected and in 44% of patients without a detectable monoclonal urine light chain [28•]. When both factors of bone marrow negativity by flow cytometry and absence of a urine monoclonal protein were combined, it highlighted a population with low risk of disease progression and better outcomes.

Conclusion

Solitary bone plasmacytoma and solitary extramedullary plasmacytoma represent a rare subgroup of plasma cell dyscrasias. As such, it has been difficult to accrue large cohorts and perform clinical trials that would change the treatment paradigm of solitary plasmacytomas. Radiation therapy remains the mainstay of treatment. With sophisticated, modern radiotherapy techniques, treatment is extremely effective with minimal toxicity. There have been numerous advances in terms of the systemic treatment options available for multiple myeloma, but no evidence exists on whether adjuvant systemic therapy with any of these new agents would offer any additional benefit. The most notable advances have come in the form of diagnostic tools and imaging techniques available when staging and assessing plasmacytomas. Ultrasensitive imaging techniques will now likely isolate a proportion of asymptomatic myeloma, which may have been understaged and diagnosed as solitary plasmacytoma in the past. These tools will also allow for more accurate assessments regarding prognosis, treatment response, and ultimately surveillance for disease progression.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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