Chapter 2
Plasmacytoma—Current Approach to Diagnosis and Management

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Introduction

Plasma cell dyscrasias (PCD) are characterized by an abnormal accumulation of monoclonal plasma cells typically producing high levels of monoclonal immunoglobulins or paraproteins. The spectrum of PCD ranges from monoclonal gammopathy of undetermined significance (MGUS) to symptomatic multiple myeloma (MM). The American Cancer Society has estimated 26,850 new myeloma cases in the USA in 2015 with an estimated 11,240 deaths [1].

A minority of patients with plasma cell malignancies present with either a single bone lesion, or less commonly, a soft tissue mass made up of monoclonal plasma cells. The solitary plasma-

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cytoma (SP) is characterized by a localized accumulation of neo-plastic monoclonal plasma cells in the absence of other features of systemic plasma cell proliferative disorder (i.e., anemia, hyper-calcemia, renal insufficiency, or multiple lytic bone lesions) [2–4].

SP can be classified into 2 groups depending upon its location; solitary plasmacytoma of the bone (SBP), if the tumor involves an osseous site and extramedullary plasmacytoma (EMP), if it involves an extra osseous site [2]. SBP mostly occurs in the bones of the axial skeleton, such as vertebra and skull [2, 5]. EMP is most often located in the head and neck region, mainly in the upper aero digestive tract such as the nasal cavity and nasopharynx, but may also occur in the gastrointestinal tract, urinary bladder, central nervous system, thyroid, breast, testes, parotid gland, lymph nodes, and skin [6–8].

The reason as to why some patients develop MM and others develop SP is not well understood, but it may be related to dif-ferences in cellular adhesion molecules or chemokine receptor expression profiles of the malignant plasma cells [9]. The diagnosis and management of patients with SP require the same range of clinical and laboratory expertise as for patients with MM, and a close liaison among the hematologist, radiotherapist, and surgeon is crucial for planning optimum care of these patients [10].

Epidemiology

SP is a rare form of plasma cell neoplasm and represents 3–5 % of all PCD according to the published literature [2]. An analysis of the surveillance, epidemiology, and end results (SEER) database from 1992 to 2004 demonstrated that the incidence of MM ($n = 23{,}544$; IR 5.35/100,000 person years) is 16 times higher than SP overall ($n = 1543$; IR = 0.34), and incidence of SBP was 40 % higher than EMP ($p < 0.0001$) [11].

The median age of the patients with either SBP or EMP is 55 years, which is much lower than the median age of 67–71 years for patients with MM. The incidence rate rises exponentially with advancing age; however, it is less prominent in older age group as compared to MM. The male to female ratio is 2:1. The incidence is highest in Blacks and lowest in Asians and Pacific Islanders [11–13].

Clinical Features

The clinical presentation is defined by the location and size of the plasmacytoma. The most common presenting symptom is pain due to bony destruction. Patients with vertebral involvement may also have evidence of spinal cord or nerve root compression [13–15]. Involvement of the base of the skull can present with cranial nerve palsies [16, 17].

SBP most commonly affects bones involved with active hematopoiesis; hence, the axial skeleton is more commonly involved than the appendicular skeleton, particularly the vertebra [13–15]. The thoracic vertebrae are more commonly involved than the lumbar, sacral, or cervical spine [4]. Around 20 % of patients with SBP have affection of ribs, sternum, clavicle, or scapula [18].

Most patients with EMP present with symptoms related to the location of the soft tissue mass. Approximately 80 % of the EMP involve mucosa associated lymphoid tissue of the upper respiratory tract; 75 % of which involve the oro-nasopharynx and paranasal sinuses producing rhinorrhea, epistaxis, or nasal obstruction [7, 19]. Other less commonly involved sites are the gastrointestinal tract [20], lung [21, 22], pleura [23], liver [24], bladder [25], testes [26], ovary [27], skin [28], lymph nodes [29], and central nervous system [30].

Localized amyloidosis can be a feature of both SBP and EMP [31, 32]. By definition, evidence of end-organ damage attributable to PCD like anemia (i.e., hemoglobin <10 g/dL or 2 g/dL below normal), hypercalcemia (i.e., serum calcium >11 mg/dL or 1 mg/dL higher than the upper limit of normal), or renal insufficiency (i.e., serum creatinine >2 mg/dL or creatinine clearance <40 mL/min) is not present in SP [33].

Diagnosis

The evaluation of a patient with suspected SP requires the following [34, 35]:

1. Biopsy of the single lytic bone lesion or soft tissue mass.

2. Complete blood count (CBC) with peripheral smear examination.
3. Biochemical screen including serum creatinine, calcium, albumin, lactate dehydrogenase, beta-2 microglobulin, and C-reactive protein.
4. Serum protein electrophoresis (SPEP) with immunofixation (IF) and quantitation of immunoglobulins, and a serum free light-chain (SFLC) assay.
5. 24-hour urine collection for total protein, electrophoresis (UPEP) with immunofixation (IF).
6. Unilateral bone marrow aspiration and biopsy.
7. Skeletal survey and either a positron emission tomography/ computed tomography (PET/CT) scan or a magnetic resonance imaging (MRI) of the entire spine and pelvis.

The diagnostic criteria for SP require the following [33]:

1. Histopathological confirmation of a monoclonal plasma cell infiltration of a single lytic bone lesion or soft tissue mass.
2. Absence of clonal plasma cells on a random bone marrow sample.
3. No additional lesions on bone survey or MRI of the spine and pelvis.
4. Absence of end-organ damage such as CRAB lesions (increased calcium, renal insufficiency, anemia, or multiple osteolytic bone lesions on skeletal survey, CT scan, or PET–CT scan) that can be attributed to plasma cell proliferative disorder.

A biopsy of the suspected lesion can usually be obtained using computed tomography (CT) or MRI guidance. Fine needle aspiration cytology is inadequate for diagnosis [34]. Monoclonality and/or an aberrant plasma cell phenotype should be demonstrated with useful markers being CD19, CD56, CD27, CD117, and cyclin D1 [36].

The presence of monoclonal protein (M protein) in the serum or urine of patients with SP has been noted in 24–72 % of patients in various series [2, 5, 13, 37, 38]. The level of the M protein is usually low (usually <1 g/dL) and may or may not disappear with treatment. The presence of M protein is much more common in SBP than EMP [2, 8, 13]. A cohort of 116 patients with SBP were evaluated to develop a risk stratification model for progression to

MM and 47 % (*n* = 54) of the patients were found to have an abnormal FLC ratio [39]. In another series of 43 patients, 48 % of patients were found to have an abnormal involved SFLC value, and 64 % had an abnormal SFLC ratio at diagnosis [40].

Flow cytometry studies and molecular detection of heavy- and light-chain gene rearrangements may reveal clonal plasma cells in the bone marrow of some patients who have no evidence of infiltration on light microscopy. Some patients with SP may demonstrate up to 10 % clonal plasma cells on the bone marrow and are considered as having both SP and MGUS. These patients are treated in a similar fashion to SP, but have a higher risk of progression to symptomatic myeloma [35].

Like MM, SBP has a lytic appearance on plain radiographs. In most patients, the lesion is purely lytic and has a clear margin and a narrow zone of transition to normal surrounding bone. CT and particularly MRI depict the extent of lesion more clearly than an X-ray. The MRI appearance of SBP is consistent with that of a focal area of bone marrow replacement; the signal intensity is similar to muscle on T1-weighted images and hyperintense relative to muscle on T2-weighted images [2]. MRI is a useful tool to identify soft tissue disease and "breakout" lesions in which a focal area of disease breaks through the cortex of bone into the soft tissues (including epidural spread) [41]. Also, MRI is important for delineating the extra osseous soft tissue component in the vertebrae, which may impinge on the spinal cord or spinal nerve roots [42]. The role of MRI of the thoracic and lumbosacral spine to seek additional foci of marrow involvement in patients with an apparent SBP was prospectively evaluated by Moulopoulos et al. MRI showed additional abnormalities in 4 out of 12 patients, with signal characteristics identical to those of the primary tumor. In all 4 patients, the abnormal protein persisted at greater than 50 % of the pretreatment value following definitive RT. In contrast, the M protein disappeared or was reduced by greater than 50 % in 5 of the 6 patients with secretory disease and without additional marrow abnormalities. One of the 4 patients progressed to MM 10 months after diagnosis with new lesions on conventional radiographs in the same areas as detected previously by MRI [43]. Also, Liebross et al. [44] reported that among 23 patients with thoracolumbar SBP, 7 of 8 patients who had SBP on plain radiographs alone developed MM as compared to only 1 of 7 patients who also had

negative results on MRI of the spine. Thus, whole-body MRI or spine and pelvic MRI (if WB-MRI is not available) should be part of the staging procedures in patients with SP to better assess the extent of the local tumor and reveal occult lesions elsewhere [42].

Focal lesions on FDG–PET or PET/CT scan are defined as well-circumscribed areas of increased uptake relative to the marrow background that are thought to represent areas of tumor involvement, measuring at least 5 mm in one dimension. Areas of focal uptake on FDG–PET images resolve very quickly with effective treatment, similar to the time course of M protein normalization in secretory disease [41]. The sensitivity of FDG–PET in detecting myelomatous involvement is approximately 85–96 %, and its specificity is approximately 77–90 % in different studies [45, 46]. Schirrmeister et al. [47] assessed the accuracy of PET scan in patients with presumed SP. Additional lesions, not identified by standard staging methods, were found in 4 of the 11 patients with SBP altering therapy.

It has been estimated that one-third of patients with an apparently SPB by bone survey have evidence of other plasma cell tumors on PET/CT or MRI of the spine; these patients are at greater risk for progression to multiple myeloma [48–50]. The relative advantages of MRI compared to FDG–PET and integrated PET/CT are its more widespread availability and superior spatial and contrast resolution, particularly for involvement of skull, skull base, and face. The relative disadvantages of MRI compared to FDG–PET are the time and expense required for a thorough examination of the skeletal system, its limited field of view to the region under examination, and its contraindicated use in some patients (such as patients with pacemakers, cochlear implants, and aneurysm clips). Also, the focal lesions seen on MRI will take, typically, months to years to resolve, and hence, although MRI is ideal to document "completeness" of response, FDG–PET or integrated PET/CT is more useful for monitoring short-term response [41].

Zamagni et al. prospectively compared 18F-FDG PET–CT, MRI of the spine–pelvis and skeletal survey for baseline assessment of bone disease in a series of 46 patients with newly diagnosed MM. Overall, PET–CT was superior to X-rays in 46 % of patients, including 19 % with negative skeletal survey. PET–CT scans of the spine and pelvis failed to show abnormal findings in 30 % of the patients with lesions on MRI. In contrast, in 35 % of

patients PET–CT enabled the detection of lesions which were out of the field of view of MRI [51]. A prospective trial compared MRI and PET/CT for appraisal of plasmacytoma and demonstrated an equivalent or higher sensitivity, specificity, positive predictive value, and negative predictive value for baseline staging of plasmacytomas with PET/CT as compared to MRI. However, this study was limited by small sample size ($n = 23$) [52].

Treatment

The standard of care for SP is radiotherapy (RT) given with curative intent. Surgery may be required for patients with retropulsed bone, structural instability of the bone, or rapidly progressive neurological symptoms from spinal cord compression. If a complete surgical resection was performed as part of the diagnosis, the role of adjuvant RT is not well defined [37].

A variety of treatment strategies have been tried in SBP and EMP as summarized in Tables 2.1 and 2.2.

Radiation

Definitive local radiotherapy (RT) is the treatment of choice for SP. The evidence comes largely from retrospective studies of small numbers of patients due to rarity of the disease. In a review of 206 patients with SBP, local relapse occurred in 21(14 %) out of 148 patients who received RT alone compared with 4(80 %) out of 5 patients who were treated with surgery with or without chemotherapy. Surgery (RT versus partial or complete resection and RT) did not influence the 10-year probability of local control [56]. The largest retrospective study included 258 patients with SBP ($n = 206$) or EMP ($n = 52$). The treatments included RT alone ($n = 214$), RT plus chemotherapy ($n = 34$), and surgery alone ($n = 8$). Five-year rates of overall survival (OS), disease-free survival (DFS), and local control (LC) were 74, 50, and 86 %, respectively. The median time to MM development was 21 months (range 2–135), with a 5-year probability of 45 %. Patients who

Table 2.1 Representative treatment results from major studies in solitary bone plasmacytoma (SBP) from the literature

Author, year	n	Therapy given	F/U	10 year LC (%)	10 year PMM (%)	10 year OS (%)
Bataille et al. [15], 1981	114	95—surgery + RT Rest—surgery/ Surgery + CT/ Unknown/no Rx	Few weeks to 24 years	88	58	68.5
Chak et al. [53], 1987	65	RT/surgery + RT/chemo	87 month	95	77	52
Frassica et al. [13], 1989	46	43—RT (median = 39.75 Gy) 3—surgery	90 month	89	54	45
Liebross et al. [43], 1998	57	RT (median = 50 Gy)	–	96	51	11 year (median OS)
Tsang et al. [54], 2001	32	Majority—RT (median = 35 Gy) Others— surgery + RT/RT + chemo/IFN	95 month	78 (At 8 year)	64 (At 8 year)	65 (At 8 year)
Wilder et al. [55], 2002	60	RT (median = 46 Gy)	7.8 year	90	62	59
Knobel et al. [56], 2006	206	169—RT 32—RT + chemo 5—surgery	54 month	79	51	50

(continued)

Table 2.1 (continued)

Author, year	n	Therapy given	F/U	10 year LC (%)	10 year PMM (%)	10 year OS (%)
Ozahin et al. [57], 2006	206	Majority—RT Others— RT + chemo/surgery/chemo	56 month	79	72	52
Kilciksiz et al. [58], 2008	57	30—RT 26—RT + surgery 1—unknown	2.4 year	94	4.1 year (median myeloma-free survival)	68

Table 2.2 Representative treatment results from major studies in solitary extramedullary plasmacytoma (EMP) from the literature

Author, year	n	Therapy given	F/U	10 year LC (%)	10 year PMM (%)	10 year OS (%)
Knowling et al. [59], 1983	25	22—RT (35—40 Gy) 3—surgery	71 month	88	28	43
Soeson et al. [60], 1991	25	RT/surgery/surgery + RT or chemo/chemo	44 month	88	–	50
Liebross et al. [61], 1999	22	18—RT (median = 50 Gy) 2—surgery 2—surgery + RT	–	95	32	56
Tsang et al. [54], 2001	14	Majority—RT (median = 35 Gy) Others— Surgery + RT/RT + chemo/IFN	95 month	93 (At 8 year)	16 (At 8 year)	65 (At 8 year)
Strojan et al. [62], 2002	26	12—RT 15—surgery + RT 4—surgery	61 month	87	8	61
Chao et al. [63], 2005	16	RT (median = 45 Gy)	66 month	100	31	54
Ozahin et al. [57], 2006	52	Majority—RT Others— RT + chemo/surgery/chemo	56 month	74	36	72
Kilciksiz et al. [58], 2008	23	10—RT 12—RT + surgery 1—unknown	2.4 year	95	7.4 year	89

received localized RT had a lower rate of local relapse (12 %) than those who did not (60 %). Younger age and tumor size <4 cm were favorable for OS; and younger age, extramedullary localization, and RT were favorable for DFS on multivariate analysis [57].

The optimal dose of radiation for SP has not been established. Tsang et al. demonstrated that the radiation was not associated with local failure (8-year local DFS was 100 % for 30 Gy, 81 % for 35 Gy, and 80 % for 40 Gy, $p = 0.50$), or progression to myeloma in patients with SP. The tumor bulk (size > 5 cm) was found to be the most significant factor negatively influencing local control [54]. Mendenhall et al. [64] observed a 6 % incidence of local failure with doses of at least 40 Gy which was superior to 31 % incidence of local failure with lower doses among 81 patients with SP. Knobel et al. [56] evaluated 206 patients with SBP out of which 148 patients received RT with a median dose of 40 Gy and found no dose–response relationship was observed for doses higher than 30 Gy regardless of tumor size. Tournier-Rangeard et al. reviewed 17 patients with EMP and depicted that the 5-year LC was 90 % for patients who received ≥40 Gy compared with 40 % for those who received <40 Gy ($p = 0.031$). Patients who received ≥45 Gy had 100 % local disease control, but there was no statistical difference for LC from those who received a dose ≥40 Gy ($p = 0.39$). Five-year OS for patients who received ≥45 Gy or <45 Gy were 87.5 and 37.5 %, respectively ($p = 0.056$) [65]. In light of all these studies, strict dosing guidelines are difficult to recommend [56]. National comprehensive cancer network (NCCN) recommends >30 Gy to the involved field for SBP while >30 Gy to the involved field followed by surgery if necessary for the EMP [57]. The United Kingdom Myeloma Forum (UKMF) [37] recommends RT of at least 40 Gy in 20 fractions for both SBP and EMP routinely with a higher dose (up to 50 Gy in 25 fractions) for bulkier disease (>5 cm).

The clinical target volume should be designed to encompass all disease shown by CT or MRI scanning with a margin of at least 2 cm. For small bones, such as vertebrae, this will include the entire bone involved, together with one uninvolved vertebra above and below. For larger bones, the clinical target volume will not necessarily include the entire bone, as this would involve unnecessary irradiation of normal tissues [37]. Prophylactic regional lymph node irradiation is not necessary in SBP, whereas its

addition to RT treatment portals in EMP provides excellent local control rates. However, in view of increased acute and late morbidity (especially xerostomia, which may not fully recover), it is not recommended routinely except for first echelon cervical lymph nodes in case of the primary sites involving Waldeyer's ring [37]. Conformal RT using parallel opposed fields is the most commonly used method to cover the PTV. However, IMRT technique might be considered in some cases to spare the critical structures, such as eyes and salivary glands [66].

After adequate radiotherapy, virtually all patients have relief of symptoms [2]. Patients not responding clinically to radiotherapy do not necessarily have residual tumor. They may have persistent symptoms and/or radiological changes as a result of existing bone destruction, and a repeat biopsy is advisable to clarify the situation in this circumstance [37].

The residual abnormalities on imaging post-treatment are invariable, difficult to assess, and do not correlate with outcome. Up to 50 % of patients show sclerosis and remineralization in up to 50 % of patients on plain radiography assessments [43]. The abnormalities of bone marrow and accompanying soft tissue mass may persist on MRI images, even after successful treatment [43]. Local control, defined as long-term clinical and radiographic stability, has been achieved in at least 90 % of cases [13, 43, 59].

Serial measurements of the monoclonal protein for at least 6 months after treatment are required to confirm disease radiosensitivity [2]. In most patients, the monoclonal protein is reduced markedly after completion of local RT. However, the rate of decline can be slow lasting several years [67]. The monoclonal protein disappears in about 20–50 % of patients, suggesting that all diseases were included within the RT field. The likelihood of disappearance of monoclonal protein is higher in patients in whom the pretreatment value is low. In many patients, the monoclonal protein persists despite adequate RT, indicating the presence of tumor beyond RT field. The condition of these patients may remain stable for a long time, and further treatment should be deferred until there is clear progression of the plasma cell disorder [2].

Surgery

Although most patients with SP can be treated with RT alone, surgical intervention may be necessary in some patients in whom the diagnosis of SP has not yet been made and they either present with or have rapid development of neurological dysfunction that requires laminectomy before radiotherapy [2]. An anterior approach usually allows the best access to the pathology, although some groups advocate a posterior approach to avoid the potential complications which can occur in trans-cavity access [68, 69]. Surgical procedures may also be required for patients with vertebral instability or a pathologic fracture of a long bone [2]. Loss of structural integrity requires some form of stabilization procedure, most frequently being posterior pedicle screw instrumentation. Vertebroplasty is likely to be of limited value in vertebral collapse due to SP because the degree of vertebral destruction renders the technique unsuitable [37].

Combined therapy is suggested when complete surgical tumor resection cannot be applied, and/or lymph node areas are affected. Alexiou et al. [7] reviewed more than 400 publications of EMP between 1905 and 1997 and reported that the median OS and DFS were better for surgery and RT compared with surgery alone for EMP involving the upper aero digestive (UAD) tract ($p = 0.0027$), but the difference was not statistically significant for non UAD EMP ($p = 0.62$). It is recommended that if surgery is required immediately or in the near future, it should be carried out before RT is commenced [37]. Surgery is more difficult in patients who have received RT. However, it is important to note that initial surgery may sometimes compromise RT, e.g., by the placing of metal supports, which may potentially shield areas of disease from effective radiation dose [69].

Adjuvant Chemotherapy

The role of adjuvant chemotherapy in SP has not been clearly defined at present. Although some studies have found that adjuvant therapy may prevent or delay progression to MM, most of the

studies have reported no benefit with the early administration of chemotherapy [2, 5, 37]. More recently, even myeloablative therapy with stem cell support has been evaluated in high-risk patients with solitary bone plasmacytoma, but results are too premature to draw any conclusions given the long natural history of this disease [70].

Aviles et al. suggested benefit of 3 years of adjuvant melphalan and prednisolone after RT in OS and time to development of MM. Though this was a randomized-controlled trial, the number of patients ($n = 28$) was small to make any conclusion [71]. Holland et al. showed that the addition of chemotherapy delays the time for progression of SP to MM. However, its use was not associated with any decrease in rate of conversion to MM. Also, after progression to MM, the patients, who received chemotherapy, had the same OS as those who did not [72]. Furthermore, it is suggested that early exposure to chemotherapy may predispose to the development of resistant subclones and, therefore, limit later therapeutic options [2]. Besides in a series, 4 out of 7 patients with SBP who received adjuvant melphalan after RT developed secondary leukemia [73].

Therefore, given the lack of consistent data proving benefit from chemotherapy, currently there is no current role for adjuvant chemotherapy in the initial treatment of SP [37]. For the patients with tumors larger than 5 cm and high-grade histology and for tumors that have not responded to RT, adjuvant chemotherapy may be considered. Treatment schedules effective against multiple myeloma shall be utilized [38].

Adjuvant Bisphosphonates

Till date, there have been no reports about the role of bisphosphonates in preventing progression of SP to symptomatic multiple myeloma in the published literature. Bisphosphonates are not recommended for patients with SP, except in the setting of osteoporosis or osteopenia on bone mineral density studies, at doses used for osteoporosis [37, 74].

Follow-up

Serial and frequent measurement of M protein is required to judge disease response and progression to MM during surveillance. CBC, serum chemistry including creatinine and corrected calcium, SPEP with IF, serum FLCA, and 24 h urine for total protein, UPEP with IF should be repeated at 6-week intervals for the first 6 months and then with prolongation of clinic visits [66]. Bone survey is recommended annually or as clinically indicated. Bone marrow aspirate and biopsy and imaging studies including CT, MRI, or PET–CT may be done as clinically required [75].

Natural History and Prognosis

The median overall survival for SP is 7.5–12 years [2, 76]. The most common pattern of progression among patients with SP consists of new bone lesions, rising myeloma protein level, and development of marrow plasmacytosis [2]. There are three patterns of failure in these patients: local recurrence, development of new bone lesions (without MM), and progression to MM [77].

SBPs have a poorer prognosis in comparison with EMPs [37, 54, 58, 78]. SBP has a higher risk for progression to MM at a rate of 65–84 % in 10 years and 65–100 % in 15 years. Even after curative therapy, the median time to progression to MM is 2–3 years [13, 43, 56, 58, 72]. About 50–60 % of patients with EMP develop MM [38, 61, 79]. The OS at 10 years is 40–50 % for SBP as compared to 70 % for EMP [2, 8, 13]. Patients with EMP that progressed to MM had a 100 % 5-year survival rate as compared to 33 % for SBP [64]. When MM evolves, most patients have features of low tumor mass disease, a high rate of response to chemotherapy, and a prolonged survival [2].

A variety of factors have been found to influence the risk and frequency of progression from SP to MM. Age and tumor size at diagnosis are important prognostic factors. Bataille et al. depicted that older mean age and spinal involvement were more commonly associated with progression to MM in his review of 114 cases of SP [15]. Tsang et al. [54] reported that age more than 63 years and

bulky tumors (>5 cm) had a much lower local control rate. A Turkish study concluded that age more than 55 years is unfavorable for myeloma-free survival in patients with SP [58]. However, the dimension of tumor at diagnosis is related to DFS and myeloma-free survival only on univariate analysis and not on multivariate analysis [58].

Histopathological factors play a key role in biology and hence the prognostication of SP. Anaplastic type plasmacytomas represents a higher histologic grade and a worse prognosis [80]. Kumar et al. studied angiogenesis in plasmacytoma and bone marrow biopsy samples from 25 patients with SP. High-grade angiogenesis was present in 64 % of plasmacytomas biopsy samples and none in bone marrow biopsy samples. Patients with high-grade angiogenesis in the plasmacytoma sample were more likely to progress to myeloma and had a shorter progression-free survival compared with patients with low-grade angiogenesis ($P = 0.02$) [81].

Reed et al. retrospectively reviewed 84 patients with SP (70 % —SBP and 30 %—EMP) who were treated with definitive RT during 1988 to 2008 and found that patients who had serum paraprotein detected at diagnosis had higher risk of progression to MM than those who did not (60 % vs. 39 %; $P = 0.016$) [82]. Low levels of uninvolved immunoglobulin may represent occult MM, and immunoparesis at presentation is found to be an adverse prognostic factor for the development of MM [83]. An abnormal FLC ratio is also independently associated with a higher risk of progression to myeloma. The risk of progression to MM at 5 years was 44 % in patients with an abnormal serum FLC ratio at diagnosis compared with 26 % in those with a normal FLC ratio in a study of patients with SBP [39].

The correlation between persistence of myeloma protein after RT and the development of MM has been demonstrated in several studies [15, 39, 84]. Dingli et al. constructed a risk stratification model using abnormal SFLC ratio at diagnosis and the level of M protein level at 1–2 years following diagnosis to identify patients with SBP at risk of progression to MM. Patients with a normal FLC ratio and M protein level less than 5 g/L (0.5 g/dL) were considered low risk; with either risk factor abnormal, intermediate risk; and with both an abnormal FLC ratio and M protein level of 5 g/L were considered high risk. The corresponding rates of progression at 5 years were significantly different in the low,

intermediate, and high groups: 13, 26, and 62 %, respectively (p < .001) [39].

A multivariate analysis of prognostic factors in 60 patients with SBP at MD Anderson Cancer Centre concluded that persistence of M protein for more than 1 year after RT is the only independent adverse prognostic factor for myeloma-free and cause-specific survival. At a median follow-up of 7.8 years, only 1 of 13 patients with resolution of the paraprotein progressed to MM while over 90 % of patients with persistent paraprotein had progressed. Age, tumor size, and level of paraprotein at diagnosis had no independent prognostic value [55].

Multiple Solitary Plasmacytoma (±Recurrent)

Multiple solitary plasmacytomas, which may be recurrent, occur in up to 5 % of patients with an apparently solitary plasmacytoma. These may involve bone or soft tissue and occur concurrently or sequentially in the absence of bone marrow evidence of MM [34].

The treatment approaches to patients with multiple solitary plasmacytomas (±recurrent) are variable and are influenced by factors such as patient age, sites of recurrence, numbers of lesions, and disease-free interval. When 2 lesions occur concurrently at sites where RT fields will be limited and non-overlapping or isolated lesions develop at long intervals (i.e., >2 years), RT alone may be administered. Patients with more extensive disease or early relapse may benefit from systemic therapy ± autologous stem cell transplantation, as indicated for MM, with small cases series suggesting long-term disease control [34, 85, 86].

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