Original Research Article

CLINICAL PRESENTATION AND TREATMENT OUTCOMES OF A RARE HEMATOLOGIC MALIGNANCY, SOLITARY PLASMACYTOMA: SINGLE CENTER EXPERIENCE

ABSTRACT

Aim: Solitary plasmacytoma(SP) is a rare hematological malignancy. In our study, we aimed to present the clinical presentation of this disease and the effects of radiotherapy on local control and survival as a single center experience.

Methodology: Case records of patients diagnosed with solitary plasmacytoma treated in our clinic between 2010-2022 were evaluated retrospectively. Kaplan-Meier method was used for survival analysis and Cox univariate regression analysis was used for comparison of other data.

Results: Thirty-five of 44 patients whose files were screened met the inclusion criteria. Of these, 26 (74.3%) were solitary bone plasmacytoma (SBP) and 9 (25.7%) were extramedullary plasmacytoma (EMP). The thoracic vertebrae were the most common sites of SBP, while EMP most frequently occurred in the upper respiratory tract. The most common symptoms were pain and spinal compression. Median follow-up was 46.9 months. Multiple myeloma developed in 12 patients (34.3%) and secondary malignancy developed in three patients (8.6%) during follow-up. 1, 3 and 5-year survival rates were 94%, 80% and 76% respectively; median progression-free survival was 34.4 months.

Conclusion: We think that this study, in which we shared the data of a single center in the rare disease group, contributes to the literature in terms of detecting prognostic factors and managing the treatment process more accurately. Our results can be supported by multicenter studies that will include a larger number of patients.

Keywoords: Plasmacytoma, Radiotherapy, Treatment outcomes, Presentation

INTRODUCTION

Solitary plasmacytoma (SP) is a localized and rare hematological neoplasm that accounts for 3% of all plasma cell neoplasms. The clinical presentation is in two different forms as solitary bone plasmacytoma (SBP) and solitary extramedullary plasmacytoma (SEP).

Its diagnosis have requires with a plasma cell percentage in the bone marrow of <10%, along with imaging confirmation of a solitary tumour with no other evidence of organ or tissue damage and only minimal serum or urine level of monoclonal immunglobuline [1-3]. Diagnostic analysis consist of physical examination, complete blood count, serum protein electrophoresis, evaluation of the urine for myeloma protein, skeletal survey and bone marrow biopsy.

Skeletal survey is beneficial to detect osteoblastic response to bone destruction. Low-dose whole body computed tomography can be used as an initial imaging tecnique for detecting small (<5mm) lytic bone lesions in especially patients with multiple myeloma [4, 5]. MRI is the gold standard for detecting soft tissue lesions, bone marrow involvement and spinal cord compression, especially diffusion-weighted MRI is a highly sensitive technique [3, 5, 6]. 18F-FDG (fluorine -18-fludeoxyglucose) PET/CT and ^{99m}Tc-MIBI are other imaging techniques used in diagnosis and evaluation of treatment response [3, 6, 7].

Our knowledge of prognosis is based on retrospective series. In small retrospective studies, risk factors for progression were reported as: bone localization (SBP), advanced age (>60), tumor size >5 cm, persistence of a paraprotein >1 year after treatment, and abnormal serum free light chain ratio at diagnosis[2, 8, 9]. Strong retrospective study results and prospective studies are needed to more accurately define the risk factors affecting prognosis.

Radiotherapy(RT) or/and surgery were the most used treatment modalities. Solitary plasmacytoma is highly radiosensitive tumor [9-11]. Surgery is controversial based on the results of retrospective studies. LiQW et al. reported that the results of RT alone were superior to those of SP patients who underwent surgery alone [10, 12].

In this retrospective study, we examined the results of solitary plasmacytoma treated in a hospital with one of the largest oncology clinics in Turkey. We also aimed to identify risk factors for progression to myeloma, local control, and overall survival.

MATERIAL and METHODS

Patients and Treatment Characteristics

A retrospective analysis of cases with solitary plasmacytoma treated in a single center between 2010- 2022 was performed.

Inclusion criteria were: 1) histologically proven plasma cell tumor, 2) solitary bone plasmacytoma or solitary extrameduller plasmacytoma, 3) plasma cell percentage in the bone marrow of <10%, 5) being treated with external radiotherapy, with either 3D-Conformal or (Intensity modulated radiation therapy) IMRT or Volumetric arc therapy (VMAT) techniques;

Exclusion criteria were: 1) Previous history of radiotherapy for treatment area, 2) secondary malignancy at the time of treatment, 3) less than 3 months of follow up, 4) solitary tumor with evidence of organ or tissue damage.

In all patients, physical examination, complete blood count, serum protein electrophoresis, evaluation of the urine for myeloma protein, skeletal survey, tissue and bone marrow biopsy were routinely performed, and in most patients, magnetic resonance imaging(MRI)/18-fluorodeoxglucose positron emission tomography(PET) was used.

The parameters evaluated in the study; age, sex, initial sypmtoms, extrameduller or bone origin, tumor size, tumor localization, treatment modality, surgical resection, radiotherapy tecnique

and dose, treatment response rate with RECIST criteria and the effects of these factors on LPFS, MFS, DSS, OS were investigated.

Study was approved by the ethics committee of University of Health Sciences, Kartal Dr Lutfi Kirdar City Hospital 2022/514/160/2.

Radiotherapy Technique

All patients were properly immobilized according to tumor localization. The thermoplastic head nad neck mask was used for immobilization of tumor in the head and neck area and computed tomography (CT) images were taken in 2,5 mm slice thickness. Target volumes were delineated as follows: GTV (gross tumor volume): either primary tumour visible on CT/ MRI/ PET-CT. CTV (clinical target volume): 1-3 cm margin was applied to tumor according to tumor localization. PTV (planning target volume): 3-5 mm margin was applied to CTV. Critical structures were contoured according to the tumor site.

The IMRT plan was designed as three to nine fields technique and VMAT plan was designed as 2 to 4 arc technique. Plans were normalized so that 100 % of the PTV received more than 95% of the prescription dose. RTOG(radiation therapy oncology group) and QUANTEC(Quantitative analysis of normal tissue effect in the clinic) dose constrains were used to control critical structure doses in different anatomical locations. Different fractionation schemes were used (total dose/ fractions/ dose per fraction); (54-50-46- 40Gy/ 27-25-23-20fr / 2Gy); (30-36Gy/ 10-12fr/ 3Gy); (20Gy/ 5fr/ 4Gy), respectively.

Treatment area accuracy was evaluated by performing image guided radiotherapy using kV-kV images and /or cone beam CT every day or every other day throughout the entire treatment period.

Follow-up statistical analysis:

During the treatment period acute toxicities were assessed weekly. Patients were examined at 1 and 3 months after the completion of radiotherapy for treatment-related toxicities, and every 3 months thereafter. RTOG/EORTC scales were used to assess acute and late side effects [13].

Data analysis was performed with SPSS (version 17.0; IBM, Armonk, USA). Local progression free survival (LPFS), myeloma free survival (MFS) and overall survival (OS), disease spesific survival (DSS) rates were calculated using the Kaplan–Meier method. The LPFS rates were calculated from the last day of RT until either disease recurrence or progressive disease or death. MFS, DSS and OS was calculated from diagnosis until death or censoring at the last follow-up visit. Cox univariate regression analysis was performed to identify factors affecting survial. Statistical significance was set at $p < 0.05$.

RESULTS

Thirty-five of 44 patients met the inclusion criteria and included in this analysis. Pain was the most common symptom in clinical presentation. Spinal compression, dyspnea, fracture and mass related complaints were other symptoms. Median follow-up was 46.9 months (range: 4.4-103 months). The median age was 62 years(range: 30–86). There were eight (22.8%) patients with solitary ekstrameduller plasmocytoma and twenty-seven (77.2%) with solitary bone plasmocytoma. The median time interval between the onset of multiple myeloma (MM) was 32.4 months (range: 2.7–103). Axial skeleton and upper respiratory tract (paranasal sinuses) were the most common sites of the solitary bone plasmacytoma and of solitary extramedullar plasmacytoma, respectivly.

The median RT dose was 46 Gy (range: 20–54). Twenty three lesions (65.7%) were treated with high RT-doses (> 40Gy) [commonly applied in upper respiratory tract(nasal/paranasal localization). The other twelve lesions (34.3%) were treated with lower RT-doses up to 40 Gy (median: 30 Gy).

Ten patients (28.6%) received systemic therapies prior or after RT course. Patients, treatment and tumor characteristics are summarized in Table 1. and Table 2.

Overall and Disease Spesifik Survival

Although eight patients had died at the time of the analysis, only four patients died due to plasma cell tumors. Four cases had died due to causes unrelated to plasma cell tumors (1 patients had secondary primary cancer, 2 had cardiovascular events, one patient died of an unknown cause with

primary tumor under control at last control). The patients' time of death from unrelated plasma cell neoplasm were 4.4, 9, 37.5, 62.8 months, respectivly. OS and DSS rates were 80% and 88.3%, respectively at 3 years (Figure 1). The estimated 5 and 8 year OS was 76%.

OS was significantly lower in patients older than fifty years old (p=0.045). OS and DSS were 67.2%- 86.2% in the RT arm and 86-91.7% in the S+RT group in the 5th years, but no statistically significant difference was found between treatment modalities.

Tumor size ≥5 cm and the patient who underwent biopsy group had higher death rates than the others, but significant p value could not be detected.

Disease-specific survival was found to be significantly shorter in the patients who received a radiotherapy dose of <40 Gy, (p=0.017), but OS was not affected by the dose.

In treatment response assessment, OS rates at 5 year in >90% response:(total or near total response)/90-stable:(responsible-stable disease)/progression groups were 95%, 54%, 0%, (P=0.022); DSS was 100%, 85.7%, 0% (p=0.0001), respectively.

As expected, DSS was found to be significantly shorter in patients who developed recurrence (p=0.001) and patients who progress to myeloma (p=0.029).

None of other treatment or disease characteristics had a significant impact on OS (gender, SBP or SEP type of plazmocytoma, localization, treatment modalities, surgical resection status, radiotherapy tecniques, tumor size, progress to the myeloma; p>0,05 for all comparisons). Prognostic factors affecting disease spesific survival and overall survival were detailed in Table 3.

Secondary cancers were seen in 2 (5.7%) cases; one was breast and the other one was lung cancer.

Disease control

Isolated systemic recurrence was detected in 8 (22.8%) patients, both local and systemic recurrence in four (11.4%) patient. The 3- 5 year local progression free survival were 91 – 85.6%. Three and 5 year myeloma free survival rates were 74.3% and 53.7%, respectively.

LPFS and MFS were significantly better in the ≤ 50 years old group. LPFS was similar for patients treated radiotherapy or surgery+radiotherapy for five years (LPFS 88.2% vs. 84.4%, p>0,05). Statistically significant factors affecting LPFS; tumor size ≥5 cm, radiotherapy dose <40 Gy, response to treatment. Similarly gender, SEP or SBP, treatment modality, surgical resection type, radiotheraphy tecnique had no statistically significant effect on local progression free survival (p>0.05 for all comparisons). There was no progression to MF in the SEP group. Prognostic factors affecting local control and myeloma free survival were detailed in table 3. Three-5 years LPFS and MFS were 91-85.6 % and 74.3-53.7%. Patient who had undergone surgery prior to radiotherapy had a 5-year LPFS of 84.4% as compared to 88.2% in patient whose primary treatment was radiotherapy.

Similarly gender, sep or sbp, treatment modality, surgical resection type, radiotheraphy tecnique had no statistically significant effect on local progression free survival (p>0.05 for all comparisons). There was no progression to MF in the SEP group.

Systemic Therapy

It was observed that chemotherapy was administered at different times and with different regimens in 10 (28.6%) cases. It was observed that systemic treatments were preferred in cases with bone marrow involvement or in cases where only biopsy or subtotal resection was performed in surgery. Bortezomib, lenolidamide or melphalan were utilized in systemic therapy. Using systemic therapy at any time in addition to RT and/or surgery did not contribute to LPFS, DSS, or OS (p>0.05); It was observed that it contributed significantly to MFS (p=0.005). In the subgroup analysis, the highest MFS rates were achieved with Lenolidamide, but no significant difference was found in terms of systemic treatment regimens (p=0.055).

Side effects

Grade 3-4 side effects were not observed in any patient.

DISCUSSION

SBP and SEP are rare malignant plasma cell tumors. According to 2020 GLOBOCAN data, 176,404 (0.9%) newly diagnosed plasma cell tumors and 117,077 (1.2%) deaths due to these tumors have been reported under the title of multiple myeloma in the world. In our country, 2680 (1.1%) new cases and 1970 (1.6%) deaths were reported among all cancer diagnoses[14]. Due to the rarity of the patient group and the lack of prospective studies, we will try to discuss our study based on the results presented to us by the retrospective series.

The most common tumor localizations in the literature for SBP and SEP are the vertebral axis and head and neck region, respectively [1]. In our study, the frequency of tumor localizations was determined similarly. The clinical behavior of SBP and SEP differs. In the literature, more multiple myeloma progression and worse prognosis compared to SEP are reported in SBP cases. The results of our series also support the literature [3,15,16]. In solitary plasmacytoma, the MM progression rate has been reported to be 37-72% and the median progression time of 2 years [3,17]. In our study, the rate of progression to MM in our SBP cases was 44.4%, while no MM progression was found in our SEP cases.

Correct staging in diagnosis and correct use of imaging studies prevent misdiagnosis of SP and enable patients to reach the right treatment. The power of imaging tests used before and after 2001 in staging was emphasized in a study with a large patient series, and it was reported that myeloma may be subclinical in 40% of cases initially. According to the study, the progression rates of solitary plasmacytoma to MM after radiotherapy decreased over the years with the increase in the use of MRI and/or PET [18]. PET scanning is a helpful screening tool in order to examine the whole body in a single study and to clarify unclear CT or MRI abnormalities [19]. In our patient group, it was observed that the tests used in the staging of the disease were mostly PET-CT (34 pts) and/or MR (31 pts).

In a retrospective analysis of Sharpley et al. evaluating the modern era results in solitary plasmacytoma after 1986, they observed that progression to MM was inevitable in a group of patients,

even though the 5-year OS was 90.7% and improved compared to previous series [3]. Considering the factors affecting prognosis, Katoditrou et al. (2014) found that there was no difference in survival between OS or PFS in SBP and EMP patient groups, but progression to MM and worse OS detected in patients aged >60 years and patients with short plasmacytoma free survival [3, 20, 21]. Similarly, in our patient group, LPFS, DSS and overal survival were not different in SBP and SEP patients, while MFS was found to be significantly shorter in the SBP group (p=0.032). In the evaluation made in terms of age, MFS, DSS and OS were observed to be shorter in the age group >50 years, except for LPFS.

Tm size is another issue emphasized in the literature. In the study published in Princess Margaret Hospital by Tsang et al, in which they evaluated 46 cases in 2001, the tumor size range (0-18 cm, median 2.5 cm) was reported before radiotherapy, and local recurrence was reported to be more common in tm ≥ 5 cm group [3, 22]. The median tumor size detected by imaging techniques in our patients is 5cm (0.8-15cm). Evaluation was made by creating two groups with tm ≥ 5 cm and < 5 cm, which are frequently emphasized in the literature. In our study, a trend supporting shorter LPFS was observed in cases with tm ≥ 5 cm, but no significant result could be obtained (p= 0.054). In addition, it was found that tumor size did not affect MFS, DSS and OS, and it could not be shown to be a risk factor for progression to MM.

RT is the standard treatment in solitary plasmacytoma, besides, the tumor localization, tumor size, the relationship of the tumor with the surrounding tissue, and conditions requiring urgent intervention due to instability (neurological deficit, spinal compression) have been factors in the selection of other treatment options, such as surgery. [10, 23, 24]. For patients treated with gross tumor excision, RT is still indicated because of a high likelihood of microscopic residual disease [18]. Some studies have reported that local control is higher in patients in surgery plus radiotherapy [18, 25] and some studies have reported high control rates with only radiotherapy [26, 27]. In our series, no difference was observed between RT & surgery + RT in terms of recurrence, MFS, DSS, and OS.

In terms of radiotherapy technique, there was no difference between our results with the 3D-conformal technique and IMRT techniques. Regarding the radiotherapy dose, doses above 40 Gy were defined as radical doses in the literature, and doses of >40 Gy were recommended even after surgical resection [3, 28]. Mendelhall et al. reported local recurrence results after ≥40Gy and <40 Gy as 6% versus 31% [28]. When ≥40Gy and <40 doses were compared in our patient group; LPFS, MFS and DSS (0.003, 0.0001 and 0.017, repsectively) rates were significantly worse in the group with treatment dose <40 Gy. There was no difference between the doses in terms of OS.

Systemic chemotherapy in treatment is usually delayed until disease progression, and the role of chemotherapy during treatment is controversial. Katoditrou et al. think that chemotherapy does not affect survival and is toxic and of limited benefit [20]. It has been reported that there may be a limited contribution to MFS in the patient group receiving chemotherapy [29]. Finsinger et al. recommends chemotherapy after surgery/RT in SBP because of the high risk of progression to MM [16]. In our series, while the effect of chemotherapy applied at any part of the treatment on LPFS, DSS and OS was not observed, it was concluded that it could contribute significantly to MFS (p=0.005).

In evaluation of treatment response; The importance of serum monoclonal M protein, especially after radiotherapy, has been shown in many studies in the literature. It has been emphasized that especially its detection/increase may indicate the conversion to MM [1, 5, 6, 23]. In our study, we reviewed the prognostic significance of the tumor's response to RT & RT+Surgery instead of monitoring the M protein level. There are currently no guidelines for the assessment of treatment responses in SP. In the literature, Caers et al. suggested using the RECIST criteria for evaluation of treatment response, but did not report prognostic results [5]. In our study, we first evaluated the response based on the RECIST criteria [30] and grouped them. >90% tumor response (complete-near complete response), 90- stable disease (responsible-stable disease), progressive disease groups were evaluated. We found that LPFS, MFS, DSS, and OS were associated with worse survival times in cases that did not respond to treatment or progressed during treatment (Table 3).

CONCLUSION

We think that this study, in which we shared the data of a single center in the rare disease group, contributes to the literature in terms of detecting prognostic factors and managing the treatment process more accurately. Our results can be supported by multicenter studies that will include a larger number of patients.

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Table 1: Patients and treatment characteristics

Base line characteristics		Frequency	Percent
Age	Median 62 (30-86)	n	%
	≤ 50	8	22.9
	>50	27	77.1
Sex			
	Male	18	51.4
	Female	17	48.6
Treatment			
	Radiotheray	18	22.9
	Surgery+Radiotherapy	17	48.6
Surgery			
	Biopsy	18	51.4
	Subtotal excision	7	20
	Total excision	10	28.6
Radiotherapy			
	Tecniques		
	3D konformal	21	60
	IMRT/VMAT	14	40
	Dose		
	<40Gy	12	34.3
	≥ 40 Gy	23	65.7
Treatment Responce			
	90%(complete/near complete respose)	20	57.2
	90-stable disease(response+/stable disease)	11	31.4
	Progression	4	11.4
Progression to Myeloma			
	Yes	12	34.3
	No	23	65.7
Local failure			
	Yes	4	11.4
	No	31	88.6

Table 2: Tumor characteristics

		n	%
Tpye			
	Solitary bone plasmacytoma	27	74.3
	Solitary extrameduller plasmacytoma	8	22.8
Tumor size			
	< 5cm	16	45.7
	≥ 5 cm	19	54.3
Localization			
	Bone (SBP)	27	77.2
	Axial skeleton	19	54.2
	Apendiculer skeleton	8	22.8
	Extrameduller (SEP)	8	22.8
	Upper airway tract	5	14.3
	Lung	1	2.9
	Breast	1	2.9
	Soft tissue	1	2.9

Table 3: Univariye Analysis for Prognostic factors affecting LPFS, MFS and DSS, OS

	Worse prognotic factors	LPFS	MFS	DSS	OS
Age	>50	NS	***0.0047***	***0.069***	***0.045***
Tumor size	≥5 cm	***0.054***	NS	NS	NS
SEP or SBP	SBP	NS	***0.032***	NS	NS
Radiotherapy dose	<40 Gy	***0.003***	***0.0001***	***0.017***	NS
Treatment responce	>stable-progressive disease	***0.0001***	***0.0001***	***0.0001***	***0.022***

Figure 1: Survival curves of the patients.