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Original Article HEMATOLOGY

Sarcopenia in patients with multiple myeloma and autologous hematopoietic stem cell transplantation

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ABSTRACT

OBJECTIVE: Sarcopenia is defined as an age-related loss of muscle quantity as well as quality. Also, it is associated with morbidity and mortality. Multiple myeloma (MM) has a unique aspect with its bone involvement. We aimed to investigate the effect of hematopoietic stem cell transplantation on sarcopenia in MM patients using both CT and metabolic compartment of F-18 FDG PET/CT.

METHODS: Patients with MM who received first-line treatment and were eligible for autologous stem cell transplantation (ASCT) were included. FDG PET images before transplantation and after 120 days of ASCT were recorded.

RESULTS: When were grouped as below and above 60 years of age, a decrease in muscle mass after treatment was observed in both groups ($p<0.001$). For patients older than 60 years, age was observed to have a significant effect on muscle mass, independent of the treatment ($p=0.001$). Regarding metabolic assessment of muscles with PET imaging, the lumbar region was observed to be affected by treatment for both age groups ($p<0.001$). Metabolic volume measurement of the femoral region did not show such difference related to treatment or age.

CONCLUSION: We observed a loss in muscle mass in patients with MM related with treatment. Since PET / CT imaging is routinely used to evaluate disease, it may also be used for the evaluation of muscle as quantity as quality. Awareness of sarcopenia should be increased in patients with MM and caregivers and be supported by physiotherapists to preserve and even to increase muscle mass and strength.

Keywords: F-18 FDG PET; inflamm-aging; multiple myeloma; sarcopenia.

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Multiple myeloma (MM) is an incurable chronic disease of clonal plasma cells accounting for 1–2% of all cancers and the second most common hematologic malignancy. The average age of occurrence is 66, and most patients are over 60 years of age [1]. In parallel with the increase in age, the incidence of cancer in the elderly population increases, and management of comorbidities in this population, determination of the state of patients' physiological reserves, and comprehensive evaluation of their physical, social, and psychological performances are seen as an important need.

The incidence of sarcopenia increases with age. It is a progressive skeletal muscle system disease. A decrease in the amount and quality of muscle mass is observed in patients. It causes an increased risk of falls, fractures, physical disability, and mortality when untreated. It is an important part of the elderly population [2]. Sarcopenia management requires a multidisciplinary approach in both non-malignant and malignant diseases. MM is a hematological malignancy in which bone involvement, lytic lesions and pathological fractures can be observed, and the impact on muscle mass can significantly affect the quality of life in these patients.

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We have previously investigated the presence of sarcopenia using both CT and metabolic compartment of F-18 FDG PET/CT to assess both quantity and quality of the muscles in MM patients and observed that sarcopenia is indeed quite frequent and is related with disease outcomes including autonomous neuropathy and falls [3]. With this perspective, we aimed to move forward and investigate a most severe type of treatment, autologous stem cell transplantation (ASCT) and its impact on radiologic sarcopenia, both in terms of development and deterioration if present.

MATERIALS AND METHODS

Study Design and Data Collection

45 patients who were diagnosed with MM and have received first-line treatment (bortezomib-cyclophosphamide and dexamethasone, also known as CyBorD) for 4 courses and were eligible for ASCT were included. F-18 FDG PET images taken before and after ASCT (120 day) to determine remission status were examined. Patients who were ASCT ineligible or received further lines or salvage treatments were excluded. Demographic features including age, gender, comorbidities, staging, and risk categories were recorded from the patient's files. In line with these findings, the patients were genetically classified using the ISS classification.

The study was conducted in accordance with the Declaration of Helsinki, Ethical Principles for Medical Research. This study was approved by the Trakya University Faculty of Medicine Scientific Research Ethics Committee (11.03.2019/05-16).

Highlight key points

- Sarcopenia is a modifiable factor which is associated with morbidity and mortality, is defined as an age-related loss of muscle quantity as well as quality.
- MM due to the age range in which it occurs and the bone metabolism relationship of the disease.
- F-18 FDG PET/CT, which is used to show the response of the disease to treatment, can be used to evaluate sarcopenia both quantitatively and qualitatively.

Image Analysis

Before oral contrast administration (370-555 MBq (10–15 mCi) FD), blood sugar was aimed to be below 200 mg/dl in all patients and a 6-hour fast was provided before the F-18 FDG PET procedure (Discovery STE; GE Medical Systems, Milwaukee, WI).

The patients were visualized in three-dimensional mode for three minutes, ranging from vertex to mid-thigh, after scanning for attenuation correction with low-dose CT without contrast.

Re-evaluations are carried out with a break of 3 weeks after the last treatment. They were retrospectively evaluated by nuclear medicine physician (experienced and board-certified).

Pre- and post-treatment PET/CT images, the volumetric area of interest was drawn over the psoas muscle at the level of L3 vertebrae (Fig. 1) and on the medial vastus of the quadriceps femoris muscle at the mid-thigh level. Axial, sagittal, and coronal control was performed for targeted muscle tissue imaging. Metabolic volume (MV) was calculated from the Hounsfield unit (HU). Data was obtained from PET VCAR software (Advanced Worksta-

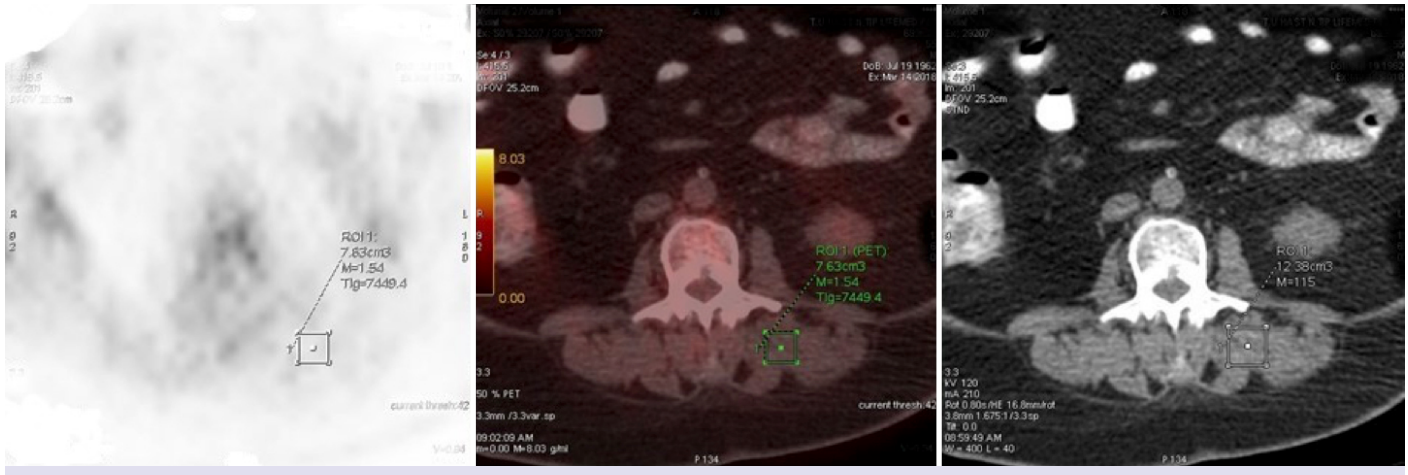

FIGURE 1. Determination of volumetric area in PET-CT, for psoas muscle.

Table 1. Characteristics findings of patients

	n (%)
Age (mean, years)	57 (SD 8.9) (28–73 years)
Age	
<60	25 (55.6)
60–70	19 (42.2)
70–80	1 (2.2)
Gender (F/M)	
Type	
IgG	32 (71.1)
IgA	11 (24.4)
Light chain	2 (4.4)
Genetic findings	
Standard	36 (80)
Poor	9 (20)
Lytic lesion	39 (86.7)
ISS stage	
I	6 (13.3)
II	12 (26.7)
III	27 (60)
Melphalan dosage (140 mg/200 mg)	4/41 (9/91)

SD: Standard deviation; ISS: International Staging System.

tion 4.4; GE Medical Systems). To reduce errors that may occur due to the patient's position, measurements were taken from both sides and their averages were calculated.

Statistical Analysis

Analyze all data with SPSS version 20 (SPSS software, IBM Corporation, Armonk, NY). Kolmogorov-Smirnov test was done to determine the distribution of the parameters. Descriptive statistics were used to examine features of patients. Also, T-test and Anova analysis were used for muscle measurements. Post-hoc analysis was performed to determine the power of the study group.

RESULTS

Patient Characteristics

45 patients were included in the study. The average age was 57 years (28–73 years). 25 of the patients were under 60 years old (55.6%), 19 (42.2%) were between 60–70 years old and 1 patient was over 70 years old. We found that the distribution of patients under the age of 60 and over was similar. 29 (64.4%) patients were male.

Six patients (13.3%) had ISS stage I disease, while 12 patients (26.7%) had stage II, and 27 (60%) patients had stage III disease. Thirty-two (71.1%) patients had monoclonal IgG secretion, while 11 (24.4%) had monoclonal IgA secretion and 2 (4.4%) had light chain secretion. Most of the patients (86.7%) were observed to have lytic lesions at the time of diagnosis. After 3–4 courses of CyBORD, almost all patients (44/45) have undergone ASCT with Melphalan 140/200 mg, as conditioning regimen (Table 1).

Muscle Assessment and Comparisons

Muscle measurements were performed from the lumbar and femoral regions of CT scans in terms of HUs. Lumbar regions mean muscle mass before the treatment was observed as 85.68 (SD 9.86), while 80.86 (SD 10.33) after the treatment ($p<0.001$). When were grouped as below and above 60 years of age, a decrease in muscle mass after treatment was observed in both groups (before treatment: 86.52–64.65, $p<0.001$; after treatment: 81.76–79.75, $p<0.001$). This difference was not observed in the femoral region (before the treatment and 94.31 (SD 10.64) after the treatment ($p=0.953$). For patients older than 60 years, age was observed to have a significant effect on muscle mass, independent of the treatment ($p=0.001$).

Regarding metabolic assessment of muscles with PET imaging, the lumbar region was observed to be affected by treatment for both age groups (5289.66 (SD 1405.13)-5053.77 (SD 1392.62), $p<0.001$) <60 years $p=0.001$, ≥60 years $p=0.039$). Metabolic volume measurement of the femoral region did not show such a difference related to treatment or age. Likewise, in total lesion glycolysis (TLG) measurements loss of lumbar muscles, but not femoral muscles were observed. In TLG measurements in the lumbar area, muscle loss was observed to be significant after treatment (4656.68 (SD 2164.84) - 3872.00 (SD 1887.12), $p<0.001$). Besides, a difference was also observed between age groups ($p<0.001$) (comparisons were summarized in Table 2, 3).

DISCUSSION

Sarcopenia is a progressive and generalized musculoskeletal disease. This syndrome can negatively affect quality of life and cause physical disability and mor-

Table 2. Effects of transplantation on muscle mass

BT based (Hounsfield Unit - HU) (SD)	Before treatment (SD)	After treatment (SD)	p
Lumbar	85.68 (9.86)	80.86 (10.33)	**0.000**
Femoral	94.37 (9.65)	94.31 (10.64)	0.953
Metabolic volume (mm^3)			
Lumbar	5289.66 (1405.13)	5053.77 (1392.62)	**0.000**
Femoral	3811.28 (1737.5)	3944.93 (1677.99)	0.409
Total lesion glycolysis			
Lumbar	4656.68 (2164.84)	3872.00 (1887.12)	**0.000**
Femoral	3257.00 (1779.58)	3251.22 (1625.51)	0.970

SD: Standard deviation.

Table 3. Treatment effects according to age factor

	<60 age	>60 age	Significance
Lumbar HU in CT			Significant with age group and treatment (0.000 and 0.000)
Before	86.52	84.65	
After	81.76	79.75	
Lumbar MV			Significant only with age factor (0.039) Only at <60 years old there is significance with treatment factor (0.001)
Before	6070.76	4313.30	
After	5508.28	4485.65	
Lumbar TLG			Significant with age group and treatment (0.000–0.000) (0.000–0.000)
Before	4998.77	4229.07	
After	3849.07	3900.65	
Femoral HU in CT			Significant only with age factor (0.001)
Before	95.68	92.75	
After	94.76	93.75	
Femoral MV			No reduction with age or treatment
Before	3501.36	4198.70	
After	3887.00	4017.35	
Femoral TLG			No reduction with age or treatment
Before	2830.01	3790.73	
After	3073.65	3473.19	

HU: Hounsfield Unit; MV: Metabolic volume; TLG: Total lesion glycolysis.

tality. It was defined as age-related muscle loss, firstly, Rosenberg mentions this syndrome in 1988 [4]. Etymologically, they are two Greek words: sarx - penia for flesh-loss [5]. It is a chronic disease with an indolent course and 1–2% decrease in muscle mass can be observed per year [6]. With the new definition, decreasing muscle strength and decreased physical performance that occur with aging are accepted as the main criteria [2]. Patients can be evaluated by direct measurement methods such as walking test, hand-grip

test, anthropometric measurements. However, there are methods such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DXA), which are indirect forms of measurement and enable us to reach a quantitative result.

There may be many underlying factors in sarcopenia. Besides its relationship with age, loss of motor units, chronic inflammation, oxidative stress, change in anabolic hormones, and decrease in physical activity are some of the causes. Secondary sarcopenia due to accompanying comorbidities should also be kept in mind [7]. Cancer-related sarcopenia, which is also an important factor in young patients for sarcopenia, is the cause of increased mortality, morbidity, hospitalization, and chemotherapy toxicity regardless of the disease. The muscle loss in colon cancer patients appears to be 15.6% per year, which is like 30 years of aging [8]. It is an important reason for non-disease morbidity and mortality. It has been shown to be associated with increased length of hospital stay, physical disability, and decreased survival [3, 9]. The role of chronic inflammation, also called "inflamm-aging", is evident here [10]. There are studies in the literature showing the importance of sarcopenia in hematological malignancies as well as in solid cancers. In the meta-analysis evaluation of studies about sarcopenia in hematological malignancies, the frequency of sarcopenia with CT was found to be 39.1% (24.6–66.1%) and was associated with low survival ($p>0.001$) [11].

Pathological process that occurs in the skeletal system with bone resorption because of osteoblast-osteoclast dysregulation are important factors affecting the quality of life and disease progression [12]. Muscle loss added to this situation as a result of the presence of chronic inflammation may cause limitation of movement and loss of balance in patients. In addition, intensive chemotherapy and frequent use of steroids in treatment can increase muscle atrophy. Resulting from chemotherapy, decreased physical activity secondary to fatigue and decreased food intake due to mucositis are also among the reasons that increase muscle atrophy and sarcopenia in MM patients [13]. It has been shown that ASCT referral is less common in MM patients with low skeletal muscle index [14]. In addition, in a study in the literature investigating the effect of sarcopenia on survival in MM patients, sarcopenia detected by CT at the time of diagnosis was shown to reduce survival in patients (in all ISS stages) in univariate analyses [15].

We observed that ASCT significantly accelerated muscle loss in patients under 60 years of age and 60 years and above, in both groups. As expected, this was more prominent in patients over 60 years of age. We could see these differences in 18-FDG PET/CT in the lumbar region, that were not present in the femoral region. Since it is considered an incurable chronic disease, maintenance treatment after transplantation and long-term exposure to steroids and chemotherapy due to relapses are inevitable in MM patients. For these reasons, the possible effects of ASCT on sarcopenia in these patients are important and should not be ignored.

Conclusion

Since 18-FDG PET/CT imaging is routinely used to evaluate disease and may also be used for the evaluation of muscle as quantity as quality. Awareness of sarcopenia should be increased in patients with MM and caregivers and be supported by physiotherapists to preserve and even to increase muscle mass and strength. Protein-based diets and vitamin D supplementation should be introduced to routine care to preserve not only bone quality but also muscle health.

Ethics Committee Approval: The Trakya University Faculty of Medicine Scientific Research Ethics Committee granted approval for this study (date: 11.03.2019, number: 05-16).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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