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Skeletal muscle and solitary bone metastases from malignant melanoma: multimodality imaging and oncological outcome

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Malignant melanoma solitary metastases to bone or skeletal muscle occur in 0.8% of patients. The aim of this study was to evaluate features of skeleton and muscle metastases with multimodality imaging and review the oncological outcome. Thirteen patients with melanoma metastases from January 2006 to February 2016 were included. Histologic confirmation was obtained. Imaging studies included computed tomography (CT), MRI, and/or positron emission tomography/CT. Treatment received and BRAF status were recorded. Differences in BRAF status and overall survival (OS) were analyzed using the χ^2-test. Associations between OS and metastases were analyzed using Cox proportional models. Nine (69%) patients showed osseous involvement. Lower extremity bones were affected in three (23%) patients: first toe, right calcaneal spurs, and knee. The spine was involved in three (23%) patients. In two (15%) patients, the pelvic bones were involved. In one (8%) patient, the temporal bone was affected. Nine (70%) patients had a history of malignant melanoma, with a median time to progression of 28 months. The median OS was 18 months: 24 months in patients with a history of melanoma and 3 months in patients with metastases at first diagnosis. The median follow-up duration was 28 months. BRAF mutant versus wild-type tumors showed significant differences in OS ($P = 0.03$). The hazard ratio for death in the metastatic group at diagnosis was 6.83, 95% confidence interval: 1.060–144.072 ($P = 0.04$). Solitary metastases from melanoma to the skeleton and muscle are rare. CT, MRI, and positron emission tomography/CT are useful for the evaluation of musculoskeletal findings. Image findings are not definitive for diagnosing a malignant solitary lesion; thus, a pathologic confirmation with a biopsy is recommended.

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Introduction

The incidence of melanoma of the skin, the most commonly fatal form of skin cancer, is increasing faster than any other potentially preventable cancer [1]. Most cases are diagnosed at an early stage, some patients have metastatic disease at presentation, and others develop metastases after their initial definitive treatment. Imaging studies play an essential role in the initial staging and subsequent management [2] and radiologic evaluation should be focused rather than exhaustive. Patients with metastatic melanoma should undergo a detailed evaluation before treatment to assess the extent of disease.

The work-up in these patients includes whole-body imaging [computed tomography (CT) of the chest, abdomen, and pelvis and MRI of the brain], serum lactic dehydrogenase, and pathologic confirmation of metastatic disease. Malignant melanoma usually metastasizes to regional nodes and skin. Nevertheless, hematogenous spread occurs mainly to the lungs, brain, bone, small bowel, and a variety of other tissues [3]. The differential diagnosis for unsuspected lesions found anywhere on imaging studies in patients with known melanoma almost always includes melanoma.

Solitary melanoma metastases to skeletal muscle occur in 0.8% of patients [4], although skeletal muscle represents nearly 50% of the total body weight and receives an abundant blood supply [5]. It provides a rather hostile environment for cancer progression, but melanoma metastases to skeleton and muscle are suggested to occur more frequently than usually recognized [6]. The aim of this study was to evaluate the features of solitary bone and muscle metastases diagnosed in our institution with multimodality imaging and review the oncological

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outcome with a particular focus to patterns of solitary lesions, their frequency, and impact on cancer staging.

Materials and methods

This is a retrospective cohort study that included patients who were diagnosed with malignant melanoma, treated, and followed at Hospital Universitario La Princesa from January 2006 to February 2016. We performed a search based on the CIE-9, CIE-9M, and CIE-10 codes that were or could be related to malignant melanoma. A total of 305 patients with malignant melanoma were found and 13 (4.23%) cases of solitary malignant melanoma solitary metastases to the skeleton or muscle were identified. Histologic confirmation was obtained for all patients included.

The electronic medical records of the 13 patients were reviewed, and all the patients at our institution who had images available for review were identified. Multimodality imaging included MRI, fludeoxyglucose (FDG) positron emission tomography (PET)/CT, and skeletal survey or radiography. At least two imaging techniques (skeletal survey, MRI, and/or FDG PET/CT) were performed in these patients to evaluate bone and skeletal muscle.

Clinical and pathologic features

Clinical features, dates of diagnosis of malignant melanoma metastases, and the characteristics at diagnosis of the primary malignant melanoma were recorded. A pathologist with expertise in malignant melanoma reviewed the histologic features to confirm the diagnosis. The pathology report includes the subtype and a description of cytomorphology and architecture. When available, important prognostic factors such as the greatest thickness, anatomic or Clark's level, presence of ulceration, margin status, and for vertical growth phase lesions, the presence of mitoses, lymphocytic infiltrates, microsatellites, and neural or vascular invasion are also included. Immunohistochemistry was performed with S-100 and HMB-45, as a discriminating immunomarker, in difficult cases.

Fludeoxyglucose F 18 positron emission tomography/computed tomography

PET/CT studies were carried out in the same PET/CT system using a 6-row detector CT (Biograph 6 TruePoint; Siemens Medical Solutions, Erlanger, Germany) with a theoretical spatial resolution of 3–4 mm. It is composed of four rows of detectors with lutetium oxyorthosilicate crystals and 6-row detector CT with a system of dose modulation depending on the topogram (CARE Dose; Siemens). The acquisition mode is three dimensional, with a coincidence detection window of 4.1 ns. The FDG PET/CT procedure was identical for all the patients included, as described below.

In all patients, the European Association of Nuclear Medicine procedure guidelines for FDG PET/CT for tumor imaging version 1.0 and 2.0 were followed [7,8]. On the day of the procedure, before administering FDG, all patients underwent an assessment of short and directed clinical history to obtain the most relevant information (clinical history, comorbidities such as inflammatory or infectious processes, diabetes mellitus), an explanation of the procedure was provided, and patients signed the informed consent for administration of the intravenous contrast.

Studies were analyzed by a nuclear medicine physician and a radiologist, all with experience in the field using the same workstation (Syngo software system; Siemens Medical Imaging). Both readings were performed independently with a consensus generated *post hoc* and discrepancies were resolved by discussion. Independent reading of the CT component of the PET/CT was not considered in our study as PET/CT as a whole is a technique validated more than a decade ago.

MRI study protocol, interpretation, and image analysis

An MRI study was carried out following standard protocols including contrast enhancement in certain cases. A GE 1.5T magnet [1.5T Signa HDx (GE, Waukesha, Wisconsin, USA)] was used. The sequences used include the following: (a) T1-weighted (turbo spinecho) and short time inversion recovery sequence in MRI (STIR) sequences; (b) sagittal T1-weighted and STIR sequences of the entire spine with postprocessing; and (c) diffusion sequences. Intravenous contrast was administered in patients with normal renal function.

Statistical analysis

Treatment received and BRAF status (mutant or wild type) were recorded. Overall survival (OS) was defined as day of death or last follow-up. Time to progression (TTP) was defined as TTP in patients with a previous diagnosis of melanoma. Differences in BRAF status and OS were analyzed by Kaplan–Meier curves using the log-rank analysis. Associations between OS and metastases were analyzed using Cox proportional models.

Results

Clinical and pathologic features

The selected group of patients diagnosed with skeletal muscle or solitary bone metastases from malignant melanoma included 13 (4% of the database) patients: 11 (85%) women and two (15%) men (Table 1). The mean age of the patients was 55 years. Clinical presentation: five (39%) showed mild local symptoms, four (31%) patients had a palpable mass at the time of diagnosis, two (15%) reported severe pain, and two (15%) patients were asymptomatic. There was no history of trauma to bone or skeletal muscle in any of the patients.

There was a history of malignant melanoma in nine (70%) patients, with a median TTP between the detection of malignant melanoma and metastasis of 28 months.

Table 1 Clinical and pathologic data of the 13 patients with skeletal muscle and solitary bone metastases

Patient number	Sex	Age (years)	Symptom	Location	Histologic subtype	BRAF status	Systemic treatment	OS (months)
1	Female	78	Mild local pain	Big toe	Acral lentiginous melanoma	WT	No	11
2	Female	56	Palpable mass	Gluteus muscle	Nodular melanoma	WT	c-Kit inhibitors	4
3	Female	60	Asymptomatic	Calcaneal spurs	Nodular melanoma	Unknown	No	18
4	Female	61	Mild local pain	Trochanter of femur	Superficial spreading melanoma	Unknown	Chemotherapy	37
5	Female	47	Mild local pain	Spine	Superficial spreading melanoma	Unknown	Chemotherapy	18
6	Female	24	Severe pain	Spine	Desmoplasic melanoma	Unknown	Chemotherapy	17
7	Female	47	Palpable mass	Deltoid and supraspinatus muscle	Nodular melanoma	Unknown	No	38
8	Female	53	Asymptomatic	Wing of ilium	Metastases of melanoma	Mutated	BRAF inhibitors	29
9	Male	45	Mild local pain	Spine	Metastases of melanoma	WT	No	2
10	Female	76	Severe pain	Temporal bone	Metastases of melanoma	WT	c-Kit inhibitors	2
11	Female	38	Mild local pain	Knee	Metastases of melanoma	Mutated	BRAF inhibitors	24
12	Female	87	Palpable mass	Longissimus thoracis muscle	Metastases of melanoma	Unknown	No	25
13	Male	60	Palpable mass	Supraspinatus muscle	Metastases of melanoma	Mutated	BRAF inhibitors	86

WT, wild type tumors.

Solitary skeletal muscle or bone metastasis was the initial or the only presentation of malignant melanoma in four (31%) patients.

Lower extremity bones were affected in three (23%) patients: big toe, right calcaneal spurs, and knee. The spine was involved in three (23%) patients. Two (15%) patients had pelvic bones: the wing of the ilium and trochanter of the femur. In one (8%) patient, the temporal bone was affected. Four (31%) patients had skeletal muscle involvement: right gluteus, left longissimus thoracis muscle, deltoid, and supraspinatus muscle.

Histologic findings of the biopsies of the lesions found at imaging were as follows: six (46%) patients had metastatic melanoma, three (23%) patients had nodular melanoma, two (15%) patients had superficial spreading melanoma, one (8%) patient had desmoplasic melanoma, and one (8%) patient had acral lentiginous melanoma. BRAF status was as follows: four (31%) were wild type and three (23%) were mutant. BRAF status was not analyzed in six (46%) patients because they were diagnosed and treated before 2011.

Imaging features

The image findings for solitary bone metastases are described as follows:

(1) First toe: the osseous involvement of the first toe was observed in a foot radiography showing a soft tissue mass of the first toe that disrupted the cortical bone of the distal phalange. Months later, the foot radiography was repeated in anterior posterior and oblique projections, showing increased soft tissue mass and disappearance of distal phalange. Foot MRI T1 showed a hypointense mass with higher intensity foci of melanin deposits and a moderately hyperintense mass on the STIR-weighted image with heterogeneous enhancement after the administration of gadolinium (Fig. 1a–d).

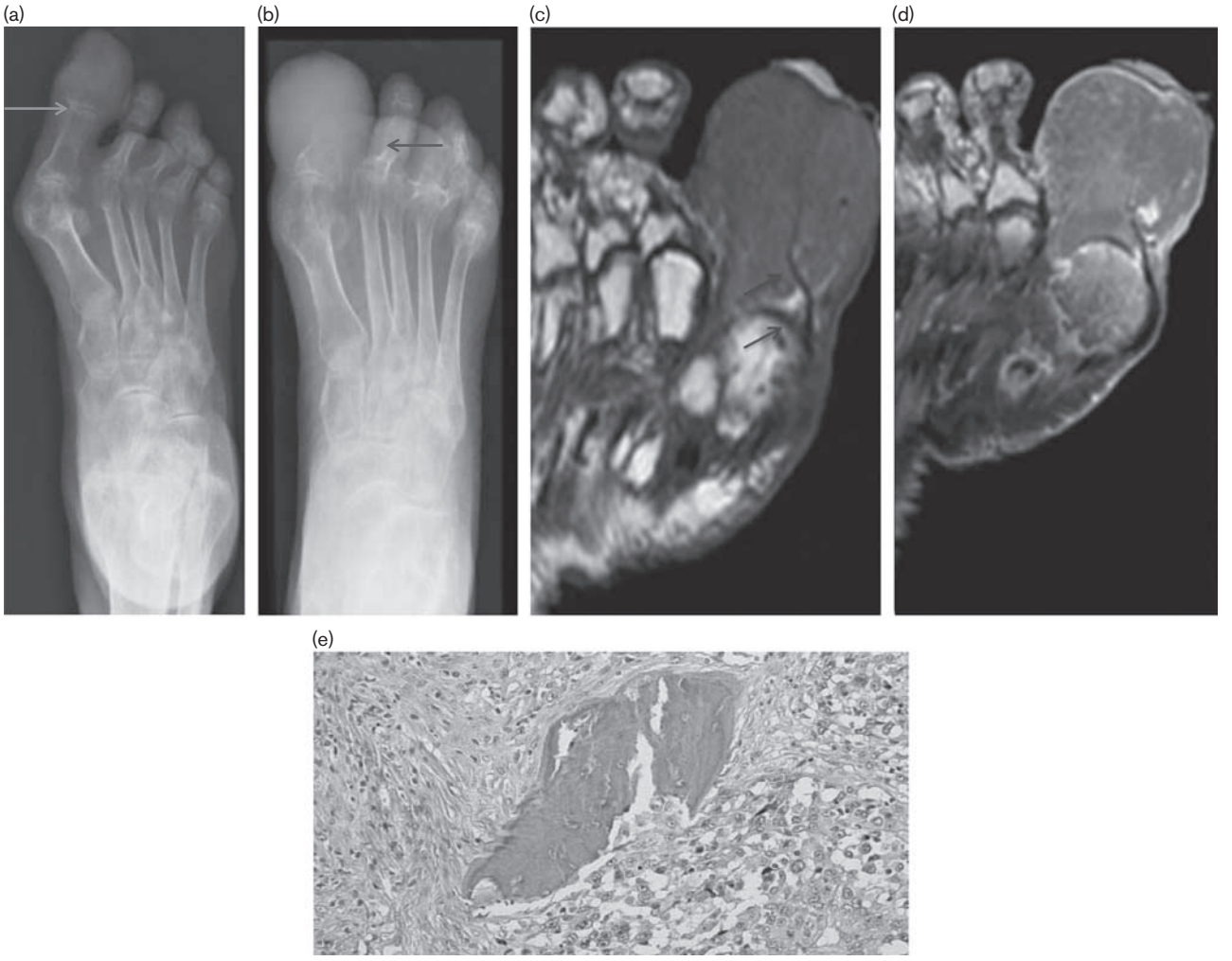
(2) Calcaneous bone: lateral foot radiography defined moth-eaten lytic lesion of the calcaneous bone. CT reconstruction showed a mixed sclerotic and lytic lesion with cortical bone interruption and soft tissue tumor. The foot MRI showed an irregular signal pattern hypointense on T1 and slightly less so on protonic density sequence in MRI. Sequential sagittal fat sat T1 + G showed aggressive bone destruction by the tumor lesion and soft tissue mass, which was enhanced in the postgadolinium sequence (Fig. 2a–d).

(3) Knee (the knee radiography): taken when symptoms began: no definable lesion was identified. Anterior view of bone CT scan featured bright uptakes in the right knee. MRI taken a few weeks later showed a signal alteration that involved the medial condyle and diaphysis, soft tissue edema, and cortical interruption that was hypointense on coronal T1 and hyperintense on fat-saturated T2 with intense enhancement after the administration of gadolinium (Fig. 3a–d).

(4) Spine column: the spine column lesion was affecting the vertebral pedicle of L2 lumbar on MRI and PET/CT lumbar. MRI T1-weighted images showed a hypointense lesion affecting the vertebral pedicle of L2 that enhanced after the administration of gadolinium. On imaging, we obtained one PET/CT reconstruction that showed the lesion's FDG-18 uptake SUV_{max} 10 (Fig. 4a–d). The other patients had a lesion in the spine that affected the dorsal vertebral body and a lumbar vertebral body, with characteristics similar to those described for the patient with exclusive involvement of the pedicle.

(5) Pelvic bone: the CT scan showed a lytic lesion in the acetabular region with a soft tissue component and a non sequential axial image of fused PET/CT showed

Fig. 1



(a) Foot radiograph with soft tissue mass of the first toe (arrow), which disrupts the cortical bone of distal phalange. (b) Months later, the foot radiography was repeated in anterior posterior, showing increased soft tissue mass and disappearance of the distal phalange. (c) Foot MR – the coronal T1 shows a hypointense mass with higher intensity foci of melanin deposits (arrows). (d) Foot MR shows a moderately hyperintense mass on STIR-weighted image. (e) The pathology slide shows that malignant melanoma cells magnified and infiltrated spongy bone.

a low to moderate FDG-18 uptake (SUV_{max} 3,2), diagnosed as metastatic.

(6) Temporal bone: CT scan showed a lytic lesion with a soft parts component and an extension to the maseterus muscle. Intracranial extension with vasogenic edema was also observed in MRI.

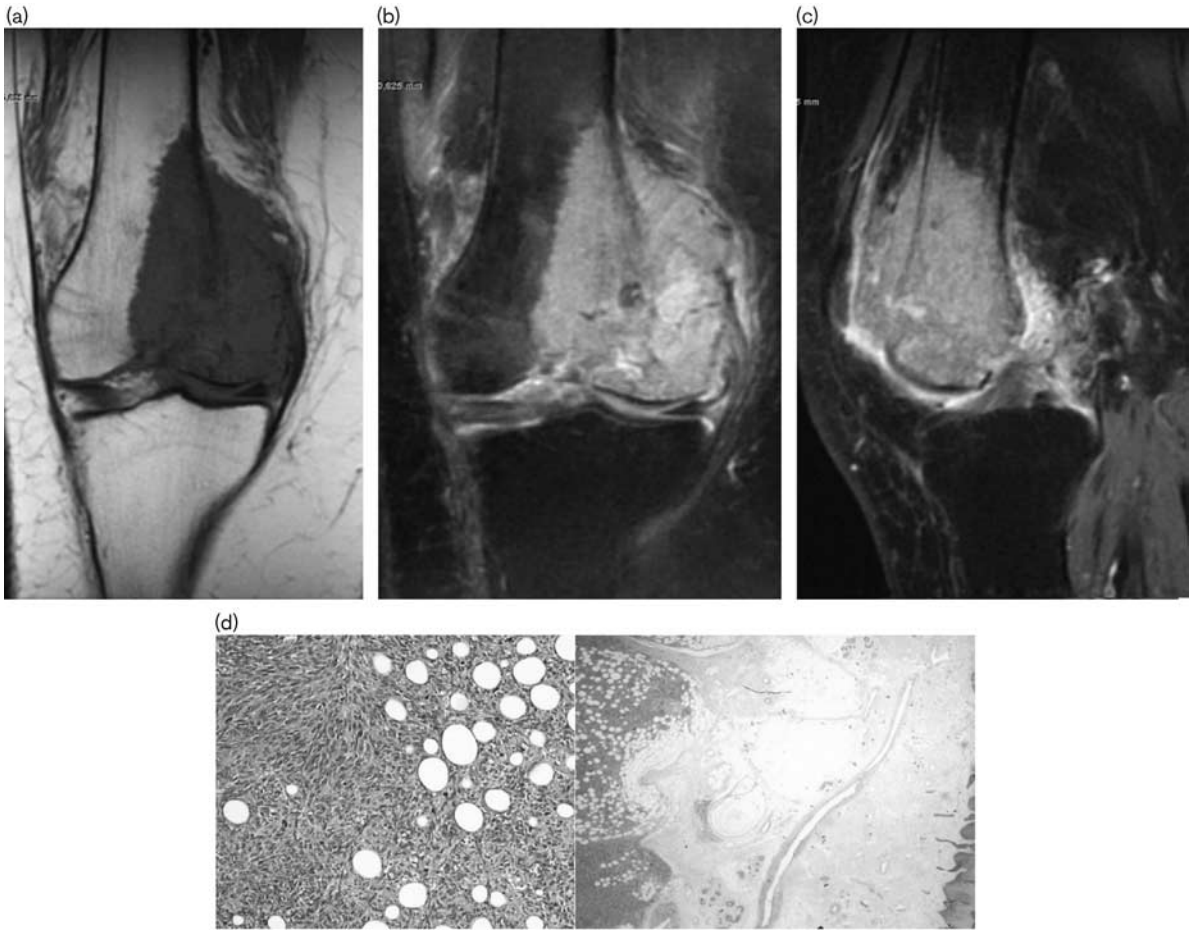
The image findings for skeletal muscle metastases are described as follows:

(1) Intramuscular metastasis of the shoulder: shoulder MRI of sequential T1 images presented an isointense muscle mass located in the deltoid, infraspinatus, and teres minor muscles, with small areas of increased signal that suggested melanin deposits. Images with contrast showed heterogeneous enhancement of the mass with perilesional edema.

(2) Supraspinatus muscle: this case showed a small rounded lesion located in the subacromial fat, isointense to muscle T1 and hyperintense on the corresponding fat-saturated T2. The fat-saturated T2 showed a high-intensity nodular lesion in the supraspinatus muscle. After the administration of gadolinium, there were multiple ill-defined hyperintense foci distributed throughout muscle tissue, axillar, and subcutaneous fat.

(3) Longissimus thoracis muscle: a small 6 mm nodule in longissimus thoracis muscle with elevated FDG-18 uptake (SUV_{max} 7, 6) was observed and it was interpreted as metastatic in origin.

Fig. 2



(a) Knee MRI showing a signal alteration that involves the medial condyle, which was observed on coronal T1-weighted images. (b) The affected bone and soft tissue mass appear hypointense and hyperintense on T2 with fat saturation. (c) Intense enhancement after gadolinium. (d) The biopsy results for this patient show malignant melanoma cells, which infiltrate the superficial epidermal layer (×20).

(4) Pectoralis major and semispanlis capitis muscles: another solitary skeletal muscle lesion, located in pectoralis major and semispinalis capitis muscles, with the same characteristics, was observed.

Statistical analysis

Eight (62%) patients received systemic treatment: three (38%) patients received BRAF inhibitors, three (38%) patients received conventional chemotherapy agents for the treatment of metastasic melanoma, and two (25%) patients received c-Kit inhibitors. Among the five (38%) patients who did not receive systemic treatment, three (60%) were not suitable for systemic treatment and two (40%) underwent curative surgery. The two patients who underwent curative surgery have not experienced relapse and are under follow-up.

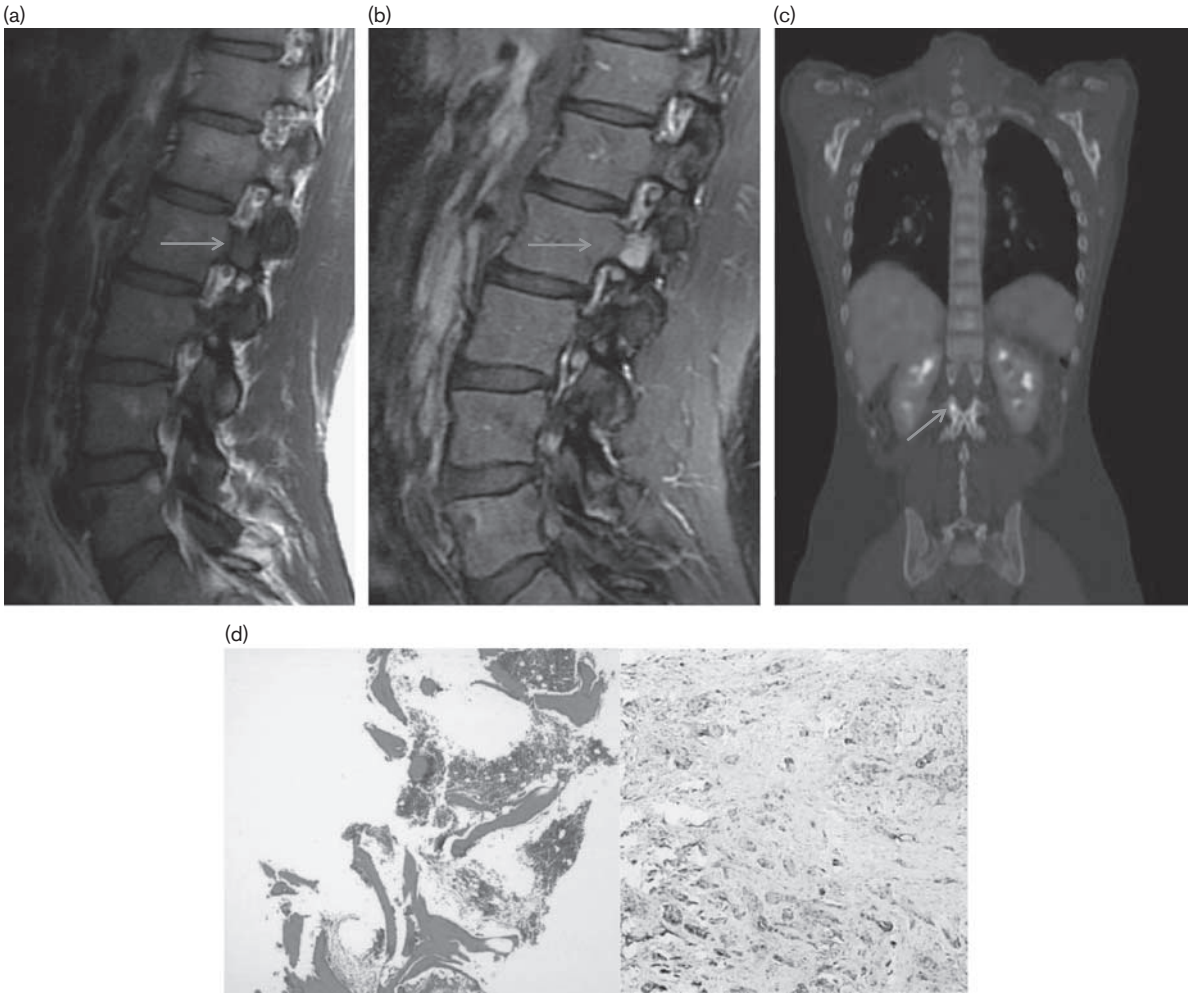
The median OS was 18 months: 24 months in patients with a history of melanoma and 3 months in patients with synchronous metastases at diagnosis (Fig. 5a). After a median follow-up of 28 months, the hazard ratio for death in the metastatic group at diagnosis was 6.83 (95% confidence interval: 1.060–144.072; $P = 0.04$). The median TTP for patients who showed progression of disease was 11 months: 28 months in patients with a history of melanoma and 3 months in patients with synchronous metastases at diagnosis ($P < 0.0001$).

BRAF mutant versus wild-type tumors showed significant differences in the median OS: 24 versus 6 months, respectively, log-rank test 5.544 ($P = 0.02$; Fig. 5b). Solitary bone and muscle metastases showed no significant differences in the OS, but patients with muscle metastases were younger at primary diagnosis.

Discussion

Malignant melanoma accounts for 1–3% of all malignancies [3,9] and they can metastasize to any organ. Like other malignancies, melanoma is well known for local recurrence as well as distant metastasis, which occurs

Fig. 3



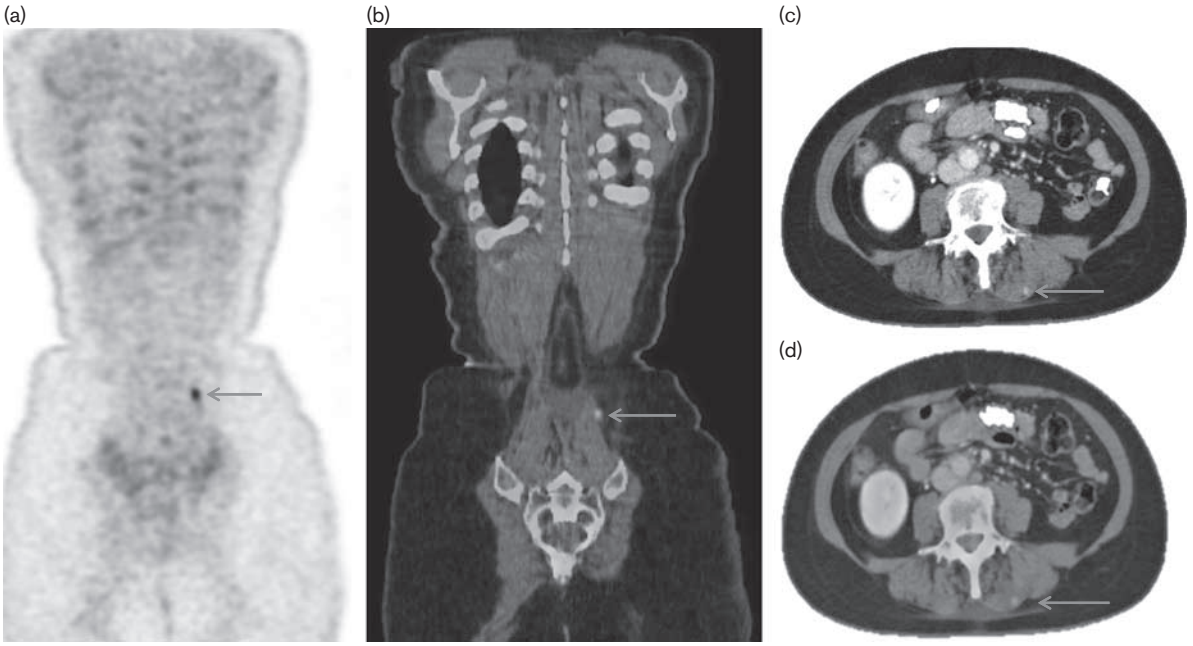
(a) Lumbar MRI, sagittal T1 (arrow)-weighted images show a hypointense lesion affecting the vertebral pedicle of L2 that is enhanced after the administration of gadolinium (b). (c) A coronal PET/CT reconstruction that shows the lesions' ^{18}FDG uptake (arrow). (d) The biopsy of the lesion that affects the right vertebral pedicle of L2 shows an osseous metastasis of a primary skin melanoma, which infiltrates spongy bone in a $\times 20$ and has positivity for S-100. ^{18}FDG, fludeoxyglucose F 18; CT, computed tomography; PET, positron emission tomography.

through lymphatics and the blood stream. Skeletal muscle or solitary bone metastases are more frequently found in patients with advanced-stage melanoma, being evidence of systemic spread. Treatment of these patients is challenging, and it should be based on the clinical guidelines for metastatic melanoma according to the clinical condition of the patient.

The metastatic behavior of malignant melanoma is uncommon because the sites of metastases are widespread compared with other tumors. Melanoma mainly spreads in the following organs: skin (other areas), subcutaneous tissue and lymph node (50–75%), liver (54–77%), brain (36–54%), bone (23–49%), gastrointestinal tract (26–58%), heart (40–45%), adrenal glands (36–54%), kidneys (35–48%), spleen (30%), and others [10–13]. Although bone metastases and the direct invasion of muscle by carcinoma are well recognized, the incidence is low [13].

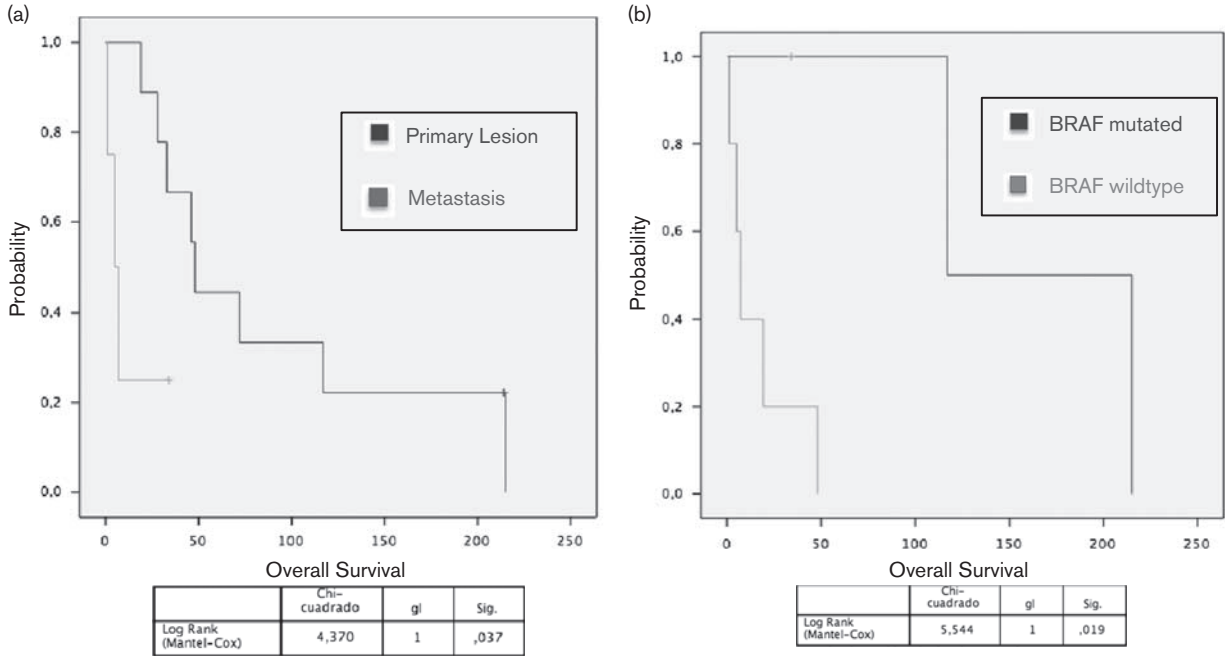
Imaging modalities including CT, MRI, and FDG PET/CT play an important role in the evaluation of the primary tumor, assessment of metastatic disease, and monitoring response to treatment. Imaging specialists who diagnose skeletal muscle and solitary bone lesions in patients with a history of melanoma find that the most likely diagnosis is a lesion arising from melanoma. Nevertheless, there is no pathognomonic image test for the metastatic lesions arising from melanoma, only the presence of melanin in the MRI, which, however, is not detected in most of our cases. Because the clinical diagnosis of skeletal muscle and solitary bone metastasis is rare, little information has been published on the natural history, and the laboratory and imaging features. Thus, there

Fig. 4



Analyzing this PET/CT, a small 6 mm nodule was observed with elevated FDG-18 uptake (SUV_{max} 7, 6) in the left longissimus thoracis muscle, marked by arrows on PET image (a), fused PET/CT (b) and corresponding axial CT (c) and fused PET/CT (d), interpreted as metastatic in origin. ^{18}FDG, fludeoxyglucose F 18; CT, computed tomography; PET, positron emission tomography.

Fig. 5



(a) Overall survival according to type of bone or muscle lesion (primary lesion or metastatic lesion. (b) Overall survival according to BRAF status (mutated vs. wild type).

is no consensus on how many single lesions observed on imaging are metastatic and what proportion are melanoma. In our experience, if there are suspicious image findings or new lesions arising from muscle or bone, a biopsy is essential because we cannot rule out other concomitant solitary tumors by imaging.

In our experience, the method of choice is the PET/CT technique for suspected single bone involvement and MRI in case of muscle involvement. However, sometimes, both imaging tests are necessary. Radiologists should be aware of the typical imaging manifestations of extracutaneous melanoma, the different patterns of metastatic involvement as well as treatment response and toxicities associated with treatment [14]. In routine clinical practice for initial staging and re-evaluation of metastatic malignant melanoma, we recommend the PET/CT technique. Nevertheless, in the case of solitary bone or skeletal muscle metastasis, CT and/or MRI can be used for characterization. However, as we have observed in our patients, the biopsy of the lesion is essential because the image findings are not definitive for making a diagnosis.

Skeletal muscle metastases of malignant melanoma

Skeletal muscle metastases from malignant tumors are rare [4]. The factors for this low incidence can probably be attributed to a hostile environment: contractile activity, local changes in pH, oxygenation, the accumulation of lactic acid and other metabolites, blood flow per weight, intramuscular blood pressure, and local temperature [11]. Solitary muscle metastases are less common than multiple muscle metastases on ^{18}F-FDG PET/CT imaging. They are usually associated with other metastases and do not affect tumor staging. Isolated cases are very rare. Nevertheless, in patients with a diagnosis of malignant disease, a solitary, ^{18}F-FDG-avid intramuscular focus should be considered to represent metastasis [15]. Biopsy is essential in such cases. On MRI, the lesion had a signal intensity similar to that of muscle on T1-weighted images and a heterogeneous increase in signal intensity on T2-weighted images.

The most common tumors metastasizing skeletal muscle are lung, kidney, and colon carcinoma [16], leukemias, and lymphomas [17]. Direct invasion of muscles by primary growth is more common than metastatic involvement [13]. Most publications on muscle metastasis from melanoma are small series or single case reports [5, 18–22]. Herring *et al.* [18] reported on a series of 15 patients with skeletal muscle metastasis, of which only two of the primary tumors were melanoma. Gomez Portilla *et al.* [19] reported an isolated rectus abdominis metastasis from melanoma. Calvert and Pigg [20] and Goforth [21] reported metastatic melanoma in skeletal muscle in postmortem reports on patients with disseminated melanoma. Moss and Rees [22] reported a case of a metastatic melanoma directly infiltrating sartrious muscle. Autopsy observations suggest that the phenomenon may be common, but that it occurs as a late event in the progression of the disease [17]. Autopsy series suggest an incidence of skeletal muscle metastases from malignant neoplasms ranging from 0.8 to 16%, but there are no specific figures for melanoma [4].

Our study is consistent with the literature, the lower extremity being the most common site, followed by the trunk musculature and the upper extremity [18]. In our case series, the four patients with skeletal muscle metastases of melanoma were not by direct invasion, so they can be classified as distant metastasis. To our knowledge, this is the largest case series to date of skeletal muscle metastases arising from malignant melanoma that has been confirmed pathologically.

Solitary bone metastases of melanoma

Bone is a common site of melanoma metastatic spread, but usually occurs in patients who already have widespread metastases; thus, it is a late site of metastasis. In most clinical series, bone metastases from malignant melanoma are less frequent than liver or brain metastases, ranging from 11 to 17% [23]. Nevertheless, the autopsy series have shown that skeletal involvement is more common than it has been published in most clinical series (23–49%) [24–26]. In the literature, it has been reported that only in 3.7% of patients bone was found to be the first and only site of disease and there is limited literature on solitary bone metastasis arising from malignant melanoma that has been confirmed pathologically, as in our study. Studies have shown that 80% of bone metastases from malignant melanoma are found in the axial skeleton (skull, ribs, vertebral column, and pelvis) [27]. When a lesion of malignant melanoma is encountered within bone, two possibilities are considered for its origin: skeletal metastasis of malignant melanoma or direct bone invasion of malignant melanoma of soft parts. However, in a small subset of patients, it can represent the first site of metastatic recurrence [27,28].

Brountzos *et al.* [29] reported, in a series of 28 patients with bone metastases from melanoma, that only 3.7% of their patients had bone metastases as the first and only site of recurrence, which is in agreement with the literature [30]. In our case series, all patients diagnosed with bone involvement had a solitary bone lesion and two of these patients who underwent curative surgery have not experienced relapse. There were no significant differences in BRAF status among the different locations. OS was longer than reported in the literature, probably because solitary bone lesions have a better prognosis and are underdiagnosed [22]. The improvement in the quality and availability of imaging modalities, particularly the increase in the utilization of ^{18}F-FDG PET/CT in routine staging and follow-up of patients with different tumors, has increased the number of patients diagnosed.

For our knowledge, this is the largest case series of solitary bone metastases arising from malignant melanoma that has been confirmed pathologically.

This study is not free from limitations: (a) the limitations of the patient population include problems in the inclusion of patients because of the fact that it was a retrospective study; (b) there may have been underestimation in the evaluation of the clinical images.

Conclusion

The choice of a correct therapeutical approach for melanoma requires accurate localization of the site, number, and size of metastases as well as their depth. Skeletal muscle and solitary bone metastases of malignant melanoma are rare and CT, MRI, and PET/CT are useful for the evaluation of musculoskeletal findings. In our experience, the method of choice is the PET/CT technique for suspected single bone involvement and the MRI in skeletal muscle involvement. Image findings are not definitive for making a diagnosis; thus, when a solitary lesion is encountered within bone or skeletal muscle, a pathologic confirmation with a biopsy specimen is recommended to rule out malignancy.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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