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CASE REPORT

Synchronous bilateral testicular metastases of malignant melanoma: a case report and literature review

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Abstract

Background: Metastatic melanoma to the testis is rare and is often identified incidentally at autopsy. Its presence at diagnosis typically indicates widespread disease. This report presents a case of testicular metastasis from malignant melanoma and a literature review to evaluate its clinical presentation, diagnostic approach and prognostic implications. **Case**: The case of a 56-year-old male diagnosed with testicular metastasis from melanoma was assessed, and a review of literature was conducted to identify similar cases using PubMed, Cochrane, Embase and Google Scholar databases until 16 July 2024, with the search terms: (Testis OR Testicular OR Testicle) AND (Metastases OR Metastatic OR Metastasis). A total of 15 articles were identified for the analysis. Metastatic melanoma to the testis is typically diagnosed at a median age of 60 years (range: 28 to 83 years). While some patients remain asymptomatic, others present with a palpable mass, testicular enlargement or pain. The size of testicular lesions varies widely, ranging from 1 to 9 cm. Ultrasonography typically reveals hypoechoic nodules, while computed tomography (CT) often demonstrates heterogeneous nodules with vascularization. The distribution of testicular metastases is reported as follows: right testicle in 43% of cases, left testicle in 47% and bilateral involvement in 10%. Inguinal orchiectomy was performed both for diagnostic and therapeutic purposes. The primary melanoma may originate from various anatomical sites. Reported Breslow thickness values range from 1.5 to 11 mm, and the Clark levels vary between II–IV. Metastases frequently affect the lungs, lymph nodes, retroperitoneal adenopathies and brain. The prognosis remains poor, with a median survival of 11 months. **Conclusions**: Testicular metastasis from melanoma represents an aggressive manifestation of the disease, typically indicating advanced-stage malignancy. Early diagnosis, inguinal orchiectomy and systemic therapies remain essential. Further research is needed to explore individualized treatment strategies and their impact on survival and quality of life.

Keywords

Testicular; Metastasis; Melanoma; Orchiectomy; Metastatic melanoma

Metástases testiculares bilaterais sincrónicas de melanoma maligno: relato de caso e revisión da literatura

Resumen

Antecedentes: El melanoma metastásico testicular es una entidad sumamente rara, frecuentemente identificada de forma incidental durante la autopsia. Su detección al momento del diagnóstico suele reflejar una enfermedad diseminada. En este informe se presenta un caso de metástasis testicular por melanoma maligno, acompañado de una revisión de la literatura para analizar su presentación clínica, abordaje diagnóstico y repercusiones pronósticas. **Caso**: Se analizó el caso de un paciente de 56 años con metástasis testicular de melanoma, acompañado de una revisión de la literatura en PubMed, Cochrane, Embase y Google Scholar hasta el 16 de julio de 2024, utilizando los términos: (Testis OR Testicular OR Testicle) AND (Metastases OR Metastatic OR Metastasis). Se identificaron 15 artículos para el análisis. El melanoma testicular metastásico se diagnostica, en promedio, a los 60 años (rango: 28–83). Algunos pacientes son asintomáticos; otros presentan masa palpable, aumento testicular o dolor. El tamaño de las lesiones varía entre 1 y 9 cm. La ecografía suele mostrar nódulos hipoecoicos, y la tomografía computarizada revela nódulos heterogéneos con vascularización. Las metástasis afectan el testículo derecho en el 43 % de los casos, el izquierdo en el 47 % y son bilaterales en el 10 %. Se realizó orquiectomía inguinal con fines diagnósticos y terapéuticos. El melanoma primario puede originarse en múltiples localizaciones. El grosor de Breslow varía entre 1,5 y 11 mm, y los niveles de Clark entre II y IV. Las metástasis suelen extenderse a pulmones, ganglios linfáticos, retroperitoneo y cerebro. El pronóstico es desfavorable, con una mediana de supervivencia de 11 meses tras el diagnóstico. **Conclusiones**: La metástasis testicular de melanoma representa una manifestación agresiva con mal pronóstico. Las tasas de supervivencia siguen siendo limitadas. La orquiectomía inguinal y las terapias sistémicas son fundamentales. Se necesita mayor evidencia sobre enfoques personalizados y su impacto en la calidad de vida.

Palabras Clave

Testicular; Metástasis; Melanoma; Orquiectomía; Melanoma metastásico

1. Introduction

Testicular metastases are a rare manifestation of metastatic melanoma and are often diagnosed post-mortem. With autopsy studies indicating that melanoma accounts for 2% to 41% of testicular metastases [1–3]. In clinical settings, metastatic involvement of the testes is rarely identified, with only 0.8% of cases diagnosed during orchiectomy performed for suspected primary testicular tumors [3]. Among malignancies that metastasize to the testes, prostate cancer is the most common, comprising 35% of cases, followed by lung cancer (19%), melanoma (9%), colorectal cancer (9%) and kidney cancer (7%) [4].

When evaluating a testicular mass, germ cell tumors represent the primary diagnostic consideration. However, secondary testicular involvement should also be considered, particularly in older patients with a history of malignancy [5].

After inguinal orchiectomy, the histological features of metastatic melanoma can be highly variable, posing a diagnostic challenge and potentially leading to misclassification as a primary testicular tumor [5]. Thus, accurate diagnosis is of great clinical importance, as testicular metastases, regardless of patient age, are associated with a poor prognosis, as the disease is characterized by rapid progression, with most patients surviving less than one year after diagnosis [6].

This study presents a case report of metastatic melanoma to the testes and includes a literature review to further characterize its clinical presentation, diagnostic challenges and prognostic implications.

2. Methods

A literature review was conducted using the PubMed, Cochrane and Embase databases on 16 July 2024, using the following search terms: (Testis) OR (Testicular) AND (Metastatic) AND (Melanoma). Based on the inclusion criteria, 15 articles were selected for analysis, comprising a total of 16 cases included in the case series.

3. Results

The case report describes a 56-year-old male with a prior history of cutaneous malignant melanoma diagnosed three years earlier and a family history of melanoma in his sister. He presented with a palpable, painful, and stony-hard nodule in his left testicle, while the right testicle appeared normal. Scrotal ultrasonography (US) revealed a 3.2 cm intratesticular, hypoechoic, solid nodule in the left testicle, and a similar 1.1 cm nodule in the right testicle. A staging thorax-abdomen-pelvis (TAP) computed tomography CT scan showed no abnormalities apart from the bilateral testicular nodules (Fig. 1). Laboratory tests, including tumor markers (lactate dehydrogenase (LDH), α-fetoprotein and β-human chorionic gonadotropin (β-HCG)), were within normal limits.

Given the bilateral involvement, an exploratory inguinal surgical approach was performed. Intraoperative fresh smear and frozen section analysis revealed a malignant neoplasm requiring further characterization. Consequently, a left inguinal orchiectomy was performed, and a testicular prosthesis was inserted. Histopathological examination (Fig. 2) of the resected testis, measuring $59 \times 35 \times 33$ mm, revealed a well-defined, solid, yellow tumor measuring $33 \times 32 \times 30$ mm. The tumor was composed predominantly of highly pleomorphic

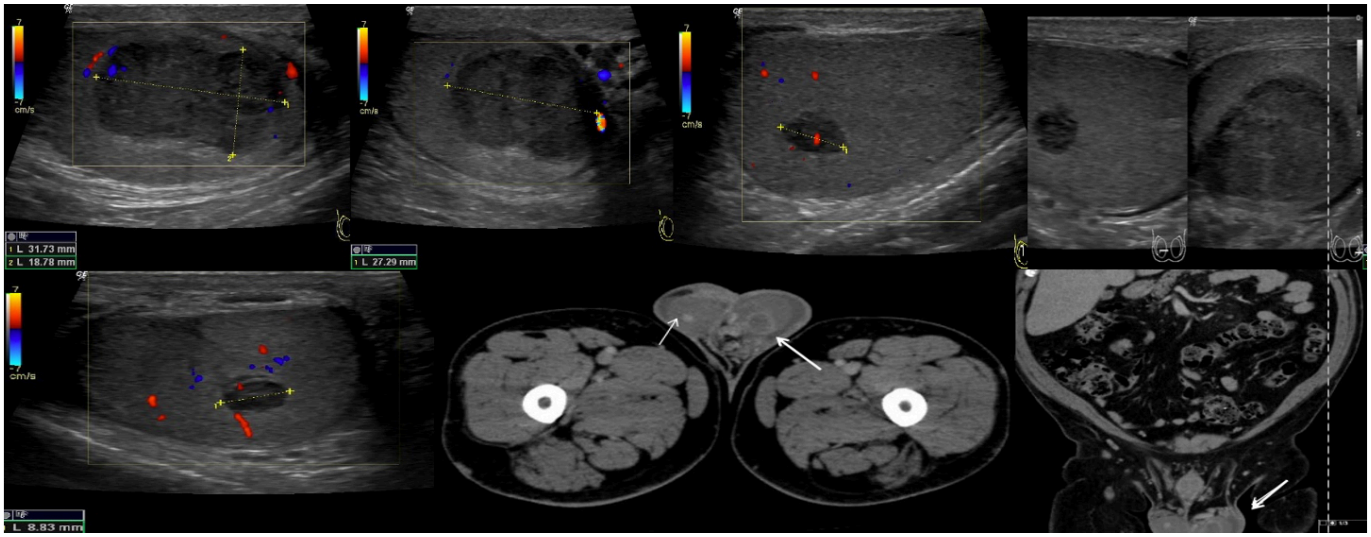

FIGURE 1. Ultrasound images demonstrating bilateral hypoechoic nodules, while axial and coronal CT scans reveal bilateral testicular nodules.

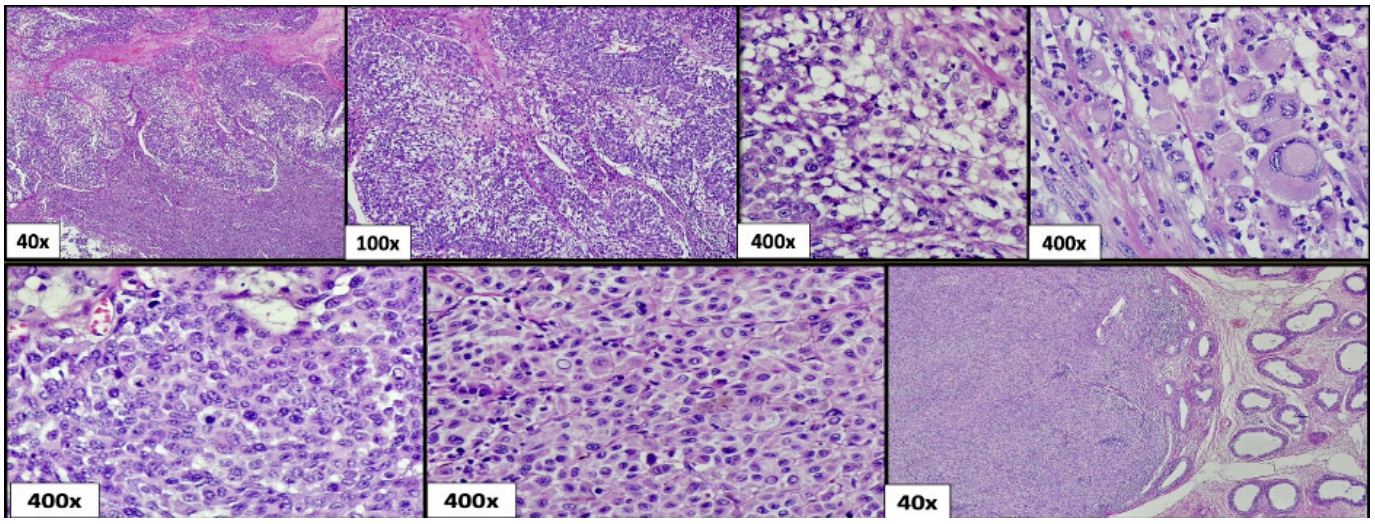

FIGURE 2. Histopathological analysis.

neoplastic cells with eosinophilic or amphophilic cytoplasm, irregular nuclei, granular chromatin, and prominent nucleoli. In addition, a high mitotic rate was observed, along with extensive necrosis and invasion of the epididymis.

Immunohistochemical analysis (Fig. 3) demonstrated strong positivity for Human Melanoma Black-45 (HMB-45), Melan A and S-100 protein, confirming the diagnosis of metastatic malignant melanoma. After the surgery, the patient underwent a positron emission tomography (PET) scan with fluorodeoxyglucose (FDG), which revealed a single hypermetabolic focus in the right testicle. Consequently, a right inguinal orchiectomy was performed, confirming the presence of bilateral testicular metastases of malignant melanoma. Three years later the patient experienced disease recurrence with brain metastasis, underwent whole-brain radiotherapy, and was treated with dexamethasone, trametinib and drabafenid. Despite these treatments, he succumbed to the disease one year after recurrence.

The Immunohistochemical analysis showed strong positivity for HMB-45, Microphthalmia-associated transcription factor (MiTF), Melan A, S-100 protein (S-100), Vimentin, Alpha 1 Antitrypsin, Alpha-fetoprotein, Neuron-Specific Enolase (NSE), focal positivity for Actin (muscle) Monoclonal Antibody (HHF-35). We also observed negative staining for pan-cytokeratins, Cytokeratin Pan Monoclonal Antibody (MNF-116), Epithelial membrane antigen (EMA), Leukocyte Common Antigen (LCA), Myeloperoxidase, Placental alkaline phosphatase (PLAP), c-Kit (CD117), CD30, Alpha-inhibin, CD57, Renal cell carcinoma marker (RCCM), CD34, Caldesmon, Desmin, MyoD1 and Calretinin. Together, these findings confirm the diagnosis was testicular involvement by melanoma.

In addition to the present case, sixteen other instances of testicular metastases originating from cutaneous melanoma have been documented in the literature. The clinical presentation, imaging characteristics, and outcomes of these cases were reviewed and compared. A summary of these findings is presented in **Supplementary Table 1**.

The average age of patients diagnosed with testicular metastases from cutaneous melanoma was 60 years, with an age

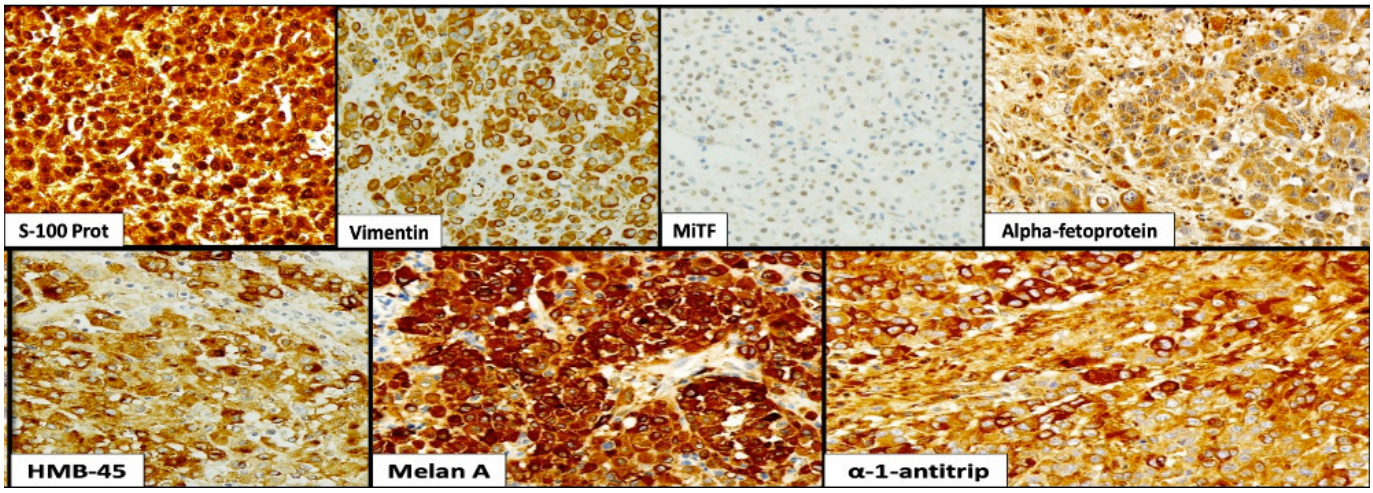

FIGURE 3. Immunohistochemical analysis (400×). MiTF: Microphthalmia-associated transcription factor; HMB-45: Human Melanoma Black-45.

range of 28 to 83 years. Metastatic involvement occurred in the right testis in 43% of cases, the left testis in 47% and bilaterally in 10%. The most common clinical presentations included asymptomatic cases, palpable masses, testicular enlargement and pain. Ultrasonography typically revealed hypoechoic nodules, while contrast-enhanced CT scans described the lesions as hypervascular. The size of the testicular metastatic lesions varied from 1 to 9 cm in diameter.

Among the reported cases, inguinal orchiectomy was performed in fourteen patients. Macroscopically, the excised tumors often exhibited black pigmentation, while microscopic analysis revealed diverse growth patterns, including diffuse, nested, follicular and fascicular arrangements. The seminiferous tubules remained intact, and intracytoplasmic melanin pigment was frequently observed [5]. Immunohistochemical staining confirmed the diagnosis in all cases, demonstrating positivity for S-100, HMB-45 and Melan-A. In literature, the primary melanoma lesions have been reported to be located on the face, neck, thorax, abdomen, back and extremities. Prognostic histopathological assessments conducted included the Breslow scale, which measures tumor thickness, and the Clark scale, which evaluates the depth of tumor invasion into the dermal and hypodermal layers [2]. The reported Breslow thickness ranged from 1.5 to 11 mm, while the Clark level varied from II/III to IV.

Testicular metastases were identified either concurrently with the primary melanoma or up to 16 years later, with a mean interval of 6.7 years between the initial melanoma diagnosis and testicular involvement [5].

Apart from the testes, metastatic spread has been frequently reported in several other organs, including the lungs, lymph nodes, retroperitoneal adenopathies, brain, cervical region, bones, abdominal nodules, liver, adrenal glands, pelvic cavity and peritoneum [1–3, 5–12].

The prognosis remained poor, with overall survival following the diagnosis of testicular metastasis ranging from 1 to 44 months, and a mean survival duration of 11 months [6].

4. Discussion

Melanoma is a malignant tumor originating from melanocytes, with its incidence increasing globally [4]. Despite advances in understanding melanoma pathophysiology, no definitive mechanism for melanoma testicular metastasis has been established [7]. However, Dusaud proposes several potential routes of dissemination including retrograde venous reflux, arterial embolism, lymphatic invasion, direct extension from a primary lesion and systemic dissemination [2].

When a testicular mass is detected, the initial clinical suspicion typically favors a germ cell tumor. Given the overlapping clinical presentations of testicular masses, distinguishing between metastatic and primary tumors remains challenging often delaying diagnosis. The rare occurrence of bilateral testicular involvement underscores the necessity of comprehensive bilateral evaluation in melanoma patients presenting with scrotal abnormalities [4]. In cases of bilateral lesions, particularly in older patients, the differential diagnosis should include synchronous germ cell tumors or lymphoma [11]. The findings also highlight the importance of multimodal imaging, particularly ultrasonography and CT, in establishing an accurate diagnosis. However, the differentiation between metastatic lesions and primary testicular neoplasms remains a diagnostic challenge. Even after inguinal orchiectomy, histopathological evaluation may lead to misclassification due to histological patterns that mimic primary testicular tumors [5]. If a diffuse pattern is observed, seminoma is the most likely diagnosis; a nested pattern suggests a Sertoli cell tumor, while a diffuse pattern with foamy cytoplasm may indicate a Leydig cell tumor [5]. Additionally, extensive intratubular involvement may mislead the pathologist into diagnosing intratubular germ cell neoplasia [2].

The evidence observed from immunohistochemical staining demonstrates positivity for melanocytic differentiation markers, including S-100, Melan A and HMB-45, while showing negativity for alpha-inhibin. These findings support the utility of these markers in distinguishing metastatic melanoma from other malignancies [2, 5, 9, 11]. Patnana reported cases in which metastatic melanoma lesions exhibited a significant loss

of immunohistochemical expression for melanocytic markers, such as Melan-A, HMB-45 antigen and MiTF [4], thereby underscoring the need for cautious interpretation of immunohistochemical results and reinforces the importance of integrating histopathological, clinical, and imaging findings to achieve an accurate diagnosis findings to achieve an accurate diagnosis. Regarding melanoma progression, the results indicate that even a Breslow depth of 1.5 mm may be associated with a substantial risk of metastasis [13]. The interval between the initial diagnosis and the detection of testicular metastases varies considerably. While some patients are promptly referred from Dermatology to Urology following their initial diagnosis, others develop testicular metastases up to sixteen years later [5] which highlights the necessity for maintaining a comprehensive and detailed patient history to facilitate early recognition and appropriate management of metastatic disease.

Patients diagnosed with testicular metastases from cutaneous malignant melanoma (CMM), frequently present with metastatic disease at other sites [14]. As observed in the present case and reported in the literature, the most commonly affected organs include the lungs, retroperitoneum, lymph nodes and brain. This widespread dissemination correlates with a poor prognosis, with an average survival of 10 months, following the diagnosis, consistent with previously documented findings [2, 7, 10].

The findings from our present case and the literature review indicate that inguinal orchiectomy remains the primary surgical approach for testicular metastases. However, its impact on overall survival appears minimal given the aggressive nature of the disease, the high likelihood of concurrent metastatic spread and the limited life expectancy. A multimodal treatment strategy is essential, such as integrating surgical intervention with systemic therapies, highlighting the need for early involvement of Oncology specialists in the management of these patients [7].

Beyond the clinical and diagnostic challenges, testicular metastases from melanoma pose significant concerns regarding patient quality of life, particularly in younger individuals. The psychosocial impact of such a diagnosis necessitates comprehensive support to address emotional and psychological distress. Clinicians must maintain a high level of suspicion when evaluating patients with a history of melanoma who present with new testicular symptoms, and early recognition and timely intervention remain essential for optimizing patient outcomes and improving overall disease management.

The literature review identified only 16 additional reported cases, yielding a limited sample size which precludes robust statistical analysis. Additionally, the included cases were drawn from reports spanning several decades, during which diagnostic imaging, immunohistochemical markers, and systemic therapies for melanoma have evolved. This heterogeneity introduces variability in diagnostic criteria, reporting quality, and management strategies, making direct comparison across cases challenging. Also, given the rarity of testicular melanoma metastases, findings from this study may not be generalizable to the broader melanoma population.

5. Conclusions

In conclusion, testicular metastasis from cutaneous malignant melanoma is a rare but aggressive manifestation of the disease, characterized by a poor prognosis. A history of melanoma in patients presenting with testicular masses should raise immediate clinical suspicion and warrant thorough evaluation. Despite inguinal orchiectomy being the primary local treatment, survival outcomes remain poor, supporting the need for potential systemic therapeutic strategies. Further research should focus on identifying factors that facilitate early detection of metastatic spread and developing comprehensive treatment approaches aimed at improving both survival and quality of life in affected patients.

AVAILABILITY OF DATA AND MATERIALS

The data are available in the Supplementary material.

AUTHOR CONTRIBUTIONS

MC—was involved in drafting the manuscript and revising it critically for important intellectual content. MC, ACa, CT, ASA, LP, ACo, AMF and JCR—contributed to the manuscript with the acquisition of data; research study; conception and design. JCR—was directly involved in the patients care and gave final approval of the version to be published. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study is in full compliance with the data protection legal framework as established by the Ethics Department of Braga Hospital-Braga Local Health Unit (ULS). The reference number for ethical approval is: 20250032. Informed consent was obtained from the patient's wife.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://files.intandro.com/files/article/1972837100007899136/attachment/Supplementary%20material.docx.

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