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Rare late mandibular recurrence of uterine leiomyosarcoma: a case report

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Summary

Sarcomas represent 1–2% of all uterine malignancies and leiomyosarcomas (LMSs) are the most common histological subtype, accounting for nearly 30% of all uterine sarcomas. The diagnosis is incidental following routine hysterectomy, and the disease exhibits a high rate of relapse and distant metastases. The most common location for metastasis is the lung, while the finding of bone metastasis in the oral region is exceedingly rare. Here the authors report the case of an exceedingly rare mandibular disease recurrence from a previously uterine LMS refractory to multiple treatments, which was beneficially managed by systemic trabectedin administration. The authors also discuss the features connected with the diagnosis and management of such an uncommon presentation of the metastatic disease.

Key words: Leiomyosarcoma; Mandibular; Recurrence; Trabectedin.

Introduction

Sarcomas represent 1–2% of all uterine malignancies [1]. Leiomyosarcoma (LMS), the most common histological subtype, accounting for nearly 30% of all uterine sarcomas [2], is often discovered incidentally following routine hysterectomy, and exhibits a high rate of relapse and distant metastases. The most common location for metastasis is the lung, while the finding of bone metastasis in the oral region is exceedingly rare [3]. Although the occurrence of metastatic disease is usually associated with extremely poor prognosis, early and correct recognition of such lesions seems to be important for selecting the most rational and optimal warranted treatment strategy. The management of recurrent uterine LMS is very difficult and often requires flexibility and an individualized approach with integration of different therapeutic modalities [4]. Despite the availability of systemic chemotherapy and local therapies, the prognosis of advanced uterine LMS remains almost uniformly fatal [5, 6]. Since the early 1970s, anthracycline–based chemotherapy has been the backbone of treatment for advanced disease, but it offers only marginal benefit [7]; moreover, its clinical use is limited by the occurrence of associated toxicities such as myelosuppression, chemotherapy-induced nausea and vomiting (CINV), alopecia, stomatitis and most importantly, cumulative dose-related cardiotoxicity [8]. Doxorubicin, ifosfamide docetaxel, gemcitabine alone or in combination are nowadays the most common drugs used for treating advanced disease with response rates ranging from 27–36%, whereas other agents such as trabectedin are still investigational [2].

Here the authors report the case of an exceedingly rare mandibular disease recurrence from a previous uterine LMS refractory to multiple treatments, which was beneficially managed by systemic trabectedin administration. Together with the clinical case description, considering the rarity of the event, the authors also discuss the features connected with the diagnosis and management of such an uncommon presentation of the metastatic disease.

Case Report

In March 2009 a 41–year–old woman, otherwise healthy, underwent hysterectomy for fibroids in another institution. Twenty months later she complained of the onset of a painful left mandibular swelling. Ultrasonography and MRI revealed the presence of an expansive solid mass in the left mandibular region with bone fracture and thickening of surrounding soft tissues (Figures 1- 3).

A mandibular biopsy was performed revealing a malignant mesenchymal tumor with smooth muscle differentiation consistent with metastatic LMS. In addition, a subsequent revision of previous pathology specimens from hysterectomy confirmed the diagnosis of LMS. A total body staging CT scan was negative for other distant metastases.

A surgical excision of the mandibular mass was performed in January 2011 and gross examination revealed a LMS of 4.8 cm in diameter invading the surrounding soft tissues. Surgical interven-

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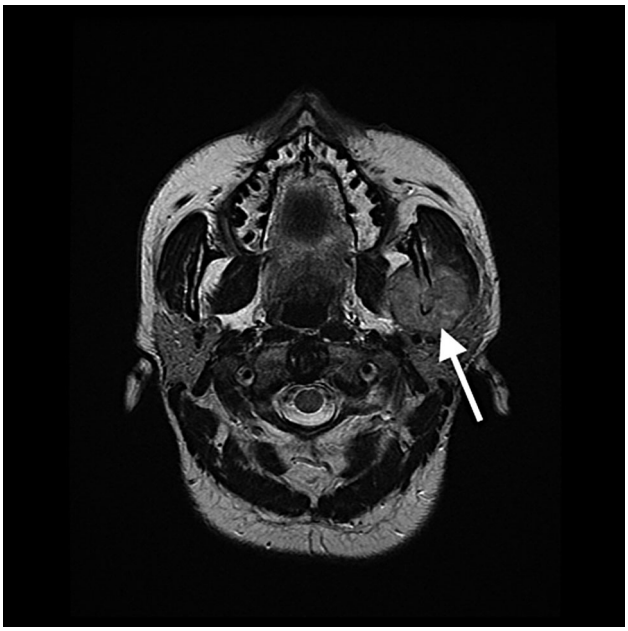

Figure 1. — Axial MRI scan showing the left mandibular metastasis (white arrow).

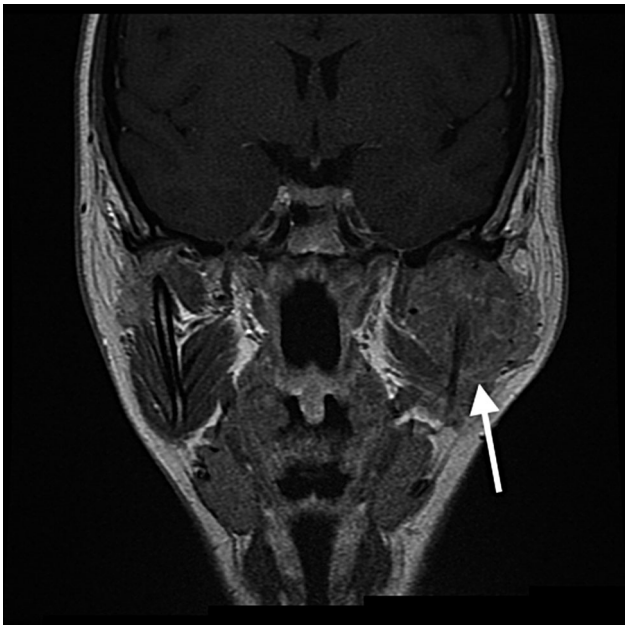

Figure 2. — Coronal MRI scan showing the left mandibular metastasis (white arrow).

tion was considered not radical because of microscopic margin involvement recognition therefore the patient underwent radiotherapy (4050 Gy/18 fractions in the left mandibular region) with adjuvant intent.

In July 2011 a total body CT scan documented lung (lingula) and bone (parietal bone, humeral head) disease progression. First-line palliative chemotherapy with gemcitabine–docetaxel combination was begun. After two cycles, a further bone disease progression (pelvis) was detected by a further CT scan. The patient was then treated with epirubicin plus ifosfamide concomitant with palliative pelvic radiotherapy, leading to disease stabilization and symptom control. In March 2012, after completion of the planned six cycles of chemotherapy, the patient underwent consolidation cryotherapy on right-sided iliac and ischiatic lesions [9].

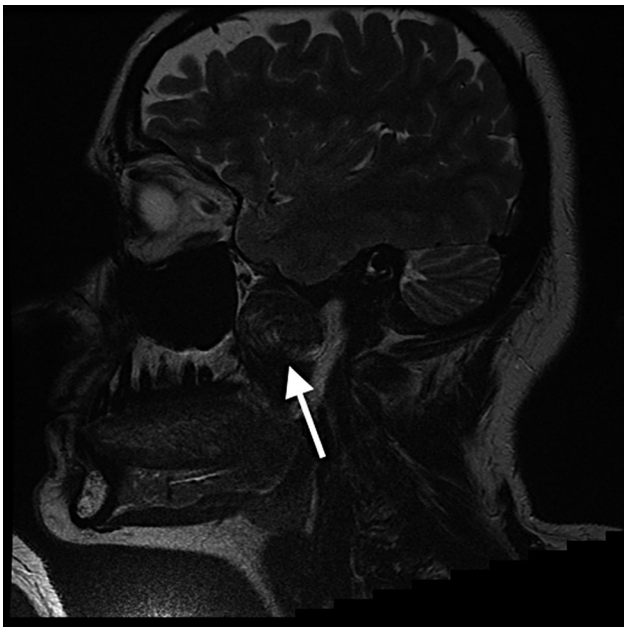

Figure 3. — Sagittal MRI scan showing the left mandibular metastasis (white arrow).

In April 2012, a significant worsening in the patient's clinical conditions was found, with CT-documented further lung and bone disease progression. A third-line treatment with trabectedin was therefore begun at a 75% dose because of the heavy pretreatments. Given the good tolerance observed in the initial two cycles, from the third cycle the treatment was increased to the full dose (trabectedin 1.3 mg/mq 24-hour endovenous infusion) without any further relevant toxicity.

The only one-week delay occurred for the finding of grade 2 neutropenia in day 1 of the programmed fourth cycle. The overall clinical picture improved and hepatic function remained stable, except for the occasional finding of grade 2 transaminase increase and grade 1 fatigue and nausea. Furthermore, CT scan performed after the ninth cycle of treatment with trabectedin revealed stable disease. The treatment was stopped in February 2013 because of further progression of the disease.

Discussion

Uterine LMS has a high propensity to metastasize to the lungs, peritoneum, vagina, liver and bone, whereas metastases to brain, adrenal glands, lymph nodes, kidneys, breast, heart, soft tissue, skin, thyroid gland, and pancreas are far less common [3]. The finding of bone metastasis in the oral region is an exceedingly rare event [3, 10]; in fact, to the best of the present authors' knowledge, this is the first case reporting a uterine LMS metastatic to the mandible.

In the case described, the detection of a late bone metastasis in the left branch of mandible was the first sign of recurrence from a previously unrecognized uterine LMS. Histology was important to distinguish between a primary bone tumor and a metastatic lesion, with obvious consequences on the authors' further medical decision-making.

Cases of advanced or recurrent uterine LMS have a grim (poor) prognosis and chemotherapy is the mainstay of treatment. Moreover, many patients undergo multiple treatment lines that entail considerable, cumulative toxic side effects which may adversely affect their future quality of life [11]. In addition, there are still concerns about the optimal drug choice, and the precise treatment algorithm is not yet well established [12].

Doxorubicin alone or in combination with ifosfamide is a widely adopted regimen for uterine LMS, with objective response observed in nearly 30% of patients [12]. Gemcitabine and the combination of gemcitabine and docetaxel are additional alternatives [13]. Other agents, used alone or in combination, that have shown to possess moderate activity include dacarbazine, temozolomide, ifosfamide, and liposomal doxorubicin [14], whereas other agents such as trabectedin seems to be promising [2]. Trabectedin, an alkaloid extracted from Ecteinascidia turbinate, binds to the N2 position of guanine in the minor groove of DNA, causing structural changes that lead to double-strand DNA breaks, as well as to the inhibition of transcription in a promoter and gene–dependent fashion. The homologous recombination (HR) pathway seems to be essential for the genesis of this drug's cytotoxicity and cells that lack this pathway are extremely sensitive to the drug [15]. Although the overall response rate to trabectedin is rather low, this agent demonstrated to provide an encouraging disease control, with a rate exceeding 50% and major benefits [12, 16], especially in liposarcoma and leiomyosarcoma compared to other sarcomas. Moreover, safety profile of trabectedin seems to be better than other chemotherapeutic agents and enables patients to receive anthracyclines and ifosfamide [12, 16].

The reported case is an uncommon site of disease recurrence and also supports the potential clinical efficacy and safety of trabectedin even in a heavily pre–treated LMS patient. Trabectedin, in fact, was administered as a third-line treatment and the patient obtained a progression-free survival of nearly ten months without appreciable toxicity. This is quite remarkable in view of the palliative intent of the medical treatment.

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References

[1] Brooks S.E., Zhan M., Cote T., Baquet C.R.: "Surveillance, epidemiology and end results analysis of 2677 cases of uterine sarcoma 1989-1999". *Gynecol. Oncol.,* 2004, *93*, 204.
[2] Prat J., Mbatani N.: "Uterine sarcomas". *International Journal of Gynecol.Obstet.,* 2015, *131*, S105.
[3] Ferreira M., Malpica A.: "Metastatic uterine leiomyosarcoma to the submandibular gland". *Ann. Diagn. Pathol*., 2009, *13*, 208.
[4] Dizon D.S., Birrer M.J.: "Advances in the diagnosis and treatment of uterine sarcomas". *Discov. Med.,* 2014, *17*, 339.
[5] Kapp D.S., Shin J.Y., Chan J.K.: "Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy". *Cancer,* 2008, *112*, 820.
[6] Oláh K.S., Dunn J.A., Gee H: "Leiomyosarcomas have a poorer prognosis than mixed mesodermal tumours when adjusting for known prognostic factors: the result of a re.trospective study of 423 cases of uterine sarcoma". *Br. J. Obstet. Gynaecol.*, 1992, *99*, 590.
[7] Berchuck A., Rubin S.C., Hoskins W.J., Saigo P.E., Pierce V.K., Lewis J.L. Jr.: "Treatment of uterine leiomyosarcoma". *Obstet. Gynecol.*, 1988, *71*, 845.
[8] Sutton G., Blessing J.A., Malfetano J.H.: "Ifosfamide and doxorubicin in the treatment of advanced leiomyosarcomas of the uterus: a Gynecologic Oncology Group study". *Gynecol. Oncol.*, 1996, 62, 226.
[9] Pusceddu C., Capobianco G., Valle E., Dessole S., Cherchi P.L., Meloni G.B.: "Computed tomography-guided cryoablation of pelvic metastasis from uterine leiomyosarcoma". *Int J Gynaecol Obstet*, 2011, *114*, 87.
[10] Cassoni A., Terenzi V., Bartoli D., Zadeh O.R., Battisti A., Pagnoni M., *et al.*: "Metastatic uterine leiomyosarcoma in the upper buccal gingiva misdiagnosed as an epulis". *Case Rep. Oncol. Med.*, 2014, 2014, 402342.
[11] El-Khalfaoui K., du Bois A., Heitz F., Kurzeder C., Sehouli J., Harter P.: "Current and future options in the management and treatment of uterine sarcoma". *Ther. Adv. Med. Oncol.*, 2014, *6*, 21.
[12] Amant F., Lorusso D., Mustea A., Duffaud F., Pautier P.: "Management Strategies in Advanced Uterine Leiomyosarcoma: Focus on Trabectedin". *Sarcoma*, 2015, 2015, 704124.
[13] Maki R., Wathen K., Patel S., Priebat D., Okuno S., Samuels B., *et al.*: "Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: result of sarcoa Allianace for Research Through Collaboration Study 002". *J. Clin. Oncol.*, 2007, *25*, 2755.
[14] Anderson S., Aghajanian C.: "Temozolomide in uterine leiomyosarcomas". *Gynecol Oncol*, 2005, *98*, 99.
[15] Miolo G., Viel A., Canzonieri V., Baresic T., Buonadonna A., Santeufemia D.A., Lara D.P., Corona G.: "Association of the germline BRCA2 missense variation Glu2663Lys with high sensitivity to trabectedin-based treatment in soft tissue sarcoma". *Cancer Biol. Ther.*, 2016, *17*, 1017.
[16] Monk B.J., Blessing J.A., Street D.G., Muller C.Y., Burke J.J., Hensley M.L.: "A phase II evaluation of trabectedin in the treatment of advanced, persistent, or recurrent uterine leiomyosarcoma: A gynecologic oncology group study". Gynecol. Oncol., 2012, *124*, 48.

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