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*Łukasz Światłowski, Michał Górnik, Tomasz Roman, Ewa Kuklik, Małgorzata Szczerbo-Trojanowska

Chemoembolization in the treatment of metastasis from uterine sarcoma to the spine

Zastosowanie chemoembolizacji w leczeniu przerzutu mięsaka macicy do kości

Department of Interventional Radiology and Neuroradiology, Medical University in Lublin
Head of Department: Professor Małgorzata Szczerbo-Trojanowska, MD, PhD

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Address/adres:

*Łukasz Światłowski
Department of Interventional Radiology and Neuroradiology
Medical University in Lublin
ul. K. Jaczewskiego 8, 20-954 Lublin
tel. +48 (81) 724-41-54
fax +48 (81) 724-48-00
lukasz.swiatlowski@umlub.pl

S u m m a r y

Uterine sarcomas are a rare heterogeneous group of tumors of mesenchymal origin. They are responsible for approximately 8% of uterine malignancies. The most common histological type of uterine sarcoma is leiomyosarcoma. This tumor is associated with poor prognosis. Most of them occur in women over 40 years of age (mean age – 60 years). The etiology has not been fully understood. Leiomyosarcoma can give metastatic lesions. The most frequent place for metastases are surrounding soft tissues and retroperitoneal space. Spinal metastases occur very rarely. The treatment of spinal metastases depends mainly on the location of the metastatic change on the spine and on the symptoms reported by the patient. The standard procedure is the surgical removal of the metastases and systemic chemotherapy. The basic drug used in chemotherapy in all lines is doxorubicin. In our case, the recurrence of metastatic change to the spine occurred in a patient with leiomyosarcomas of the uterus and metastatic lesion to the spine which had been previously treated surgically. Due to the lack of proposals from surgery treatment and because of very painful symptoms that prevent the normal functioning of the patient, it was decided to perform transarterial chemoembolization using drug eluting particles soaked with doxorubicin. In available literature we did not find the description of a similar case, where chemoembolization was used to treat metastatic change to the spine.

S t r e s z c z e n i e

Mięsaki macicy są rzadką heterogenną grupą nowotworów biorących swój początek z tkanki mezenchymalnej. Są odpowiedzialne za około 8% złośliwych zmian w macicy. Najczęstszym typem histologicznym mięsaków macicy jest mięsak gładkokomórkowy (LMS), który charakteryzuje się agresywnym przebiegiem. Większość mięsaków gładkokomórkowych macicy występuje u kobiet powyżej 40. roku życia (średnia wieku – 60 lat). Etiologia nie jest do końca poznana. Mięsaki gładkokomórkowe macicy mogą dawać przerzuty, a miejscem ognisk przerzutowych najczęściej są okolice tkanek miękkich z zajęciem przestrzeni zaotrzewnowej. Przerzuty do kręgosłupa występują bardzo rzadko. Leczenie zmian przerzutowych do kręgosłupa zależy głównie od rozległości zajęcia kręgosłupa oraz od objawów podmiotowych zgłaszanych przez pacjentkę. Standardem postępowania jest chirurgiczne usunięcie przerzutów i chemioterapia systemowa. Podstawowym lekiem stosowanym w chemioterapii we wszystkich liniach jest doksorubicyna. W naszym przypadku, u chorej z mięsakiem gładkokomórkowym macicy i przerzutem do kręgosłupa leczonym uprzednio operacyjnie, nastąpiła wznowa zmiany przerzutowej do kręgosłupa. Ze względu na brak propozycji leczenia chirurgicznego i w związku z silnymi dolegliwościami bólowymi uniemożliwiającymi normalne funkcjonowanie chorej, podjęto decyzję o zabiegu przetętnicznej chemoembolizacji przerzutu z użyciem cząstek nasączonych doksorubicyną. Po zapoznaniu się z dostępną nam literaturą, nie odnaleźliśmy opisu podobnego przypadku, gdzie zastosowano chemoembolizację przerzutu do kręgosłupa.

INTRODUCTION

Uterine sarcomas are a heterogeneous group of rare tumors taking its origin from mesenchymal tissue. They are responsible for about 8% of malignant

changes in the uterus (1). Depending on the tissue from which it can develop, sarcoma of the uterus can be divided into leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), undifferentiated endometrial

sarcoma (UES) and adenosarcoma (2). Gynecologic Oncology Group (GOG) implemented an additional division of uterine sarcomas on nonepithelial and mixed epithelial-nonepithelial (3).

The most common histological type of uterine sarcoma is leiomyosarcoma. Most of these tumors take its origin *de novo*, only about 0.2% of the lesions develop in the process of benign uterine myoma malignant transformation (4). These are characterized by an aggressive process (even if the change is located only in the uterus) of 5-year survival rates fluctuating from 18.8 to 68%. The risk of relapse ranges between 45 and 73% (1, 5, 6).

Most leiomyosarcomas occurs in women over 40 years of age (mean age 60 years). While the etiology is not fully understood, it is supposed that factors which can be associated with the development of the tumor is long-term taking of tamoxifen and the exposure to radiation of the pelvis in the past (3).

The symptoms of sarcomas may be similar to the symptoms resulting from benign fibroid and include abnormal vaginal bleeding (56%), palpable tumor in the pelvis (54%) and can lead to pelvic pain (22%). Bleeding from the tumor into the peritoneal cavity, due to the rupture of the tumor mass, occurs less frequently. As a result of the uterine sarcoma metastases the first symptom can appear in a completely different place (6). Although the rapid growth of the fibroid is suspicious, diagnosis of a sarcoma on the basis of this feature is controversial. Therefore, preoperative differentiation of benign uterine fibroids from the leiomyosarcoma is very difficult (if not impossible) and is based only on clinical symptoms and remains a challenge for clinicians (1, 6).

Leiomyosarcomas can metastasize usually to the surrounding soft tissues with involvement of retroperitoneal, internal organs (e.g. lung, liver), and skin. Spinal metastasis occurs very rarely, although it is the most common site of leiomyosarcoma bone metastases (6). Most common site of metastatic lesions in the spine is the upper part of the thoracic segment, which is a problem in finding a suitable method for the treatment of these lesions, especially if typical surgery treatment is chosen (7, 8). Nowadays, the procedure depends mainly on the extent of lesions in the spine and the symptoms reported by patient, which results from the extent of lesions in the spine. In most cases, interdisciplinary approach is necessary. In the early stage of non-metastatic uterine sarcoma radical hysterectomy is performed. In those cases, the role of adjuvant chemotherapy or local radiation therapy is still controversial (6, 9, 10).

In sarcomas of the uterus with the occurrence of metastasis in the management standards surgical removal of metastases, chemotherapy, hormone therapy and targeted therapy is performed. The primary drug used in all lines in chemotherapy is doxorubicin (6-12). In the literature there are cases of long-term response to chemotherapy in advanced stages of leiomyosarcoma.

This is a case report of the patient with leiomyosarcoma of the uterus and recurrence of the spine metastasis pre-treated previously with surgery. Disqualification of the patient from a surgery treatment, concomitant severe pain, which prevents the normal functioning of the patient, was a reason to perform transarterial chemoembolization of spinal metastases using particles soaked with doxorubicin (DEM-TACE).

CASE REPORT

The patient aged 44 with sarcoma of the uterus diagnosed in 2005, originally regarded as benign uterine leiomyoma. Subsequent biopsies with a histopathological evaluation found no malignancy. In 2009 due to the sudden increase in the tumor size and changes seen in the magnetic resonance images another biopsy was done for histopathological examination. Biopsy result – leiomyosarcoma of the uterus. In 2009 the radical surgery was performed to remove the entire uterus. There was no preoperative and postoperative chemotherapy. In 2012 PET-CT examination was performed and there were no active changes. In 2014 a strong pain in the spine occurred, assessed on visual analogue scale (VAS) on 10 points. Pain radiated to both lower extremities, causing a difficulty in walking rated on Nurick scale on 3 points (tab. 1). In MRI metastases were found that included a part of the L3 vertebral body. In addition a few metastases in the lungs were detected in CT. The patient underwent an embolization of the arteries supplying metastases in the spine. In the next step, the surgical removal a part of the L3 vertebral was performed. Intraoperatively collected tissue subjected to histopathological examination confirmed that metastasis comes from uterine sarcoma. After the operation, the pain decreased significantly. The patient estimated it at 3 pts according to VAS and at 2 points according to Nurick scale. The patient also received 2 courses of chemotherapy with doxorubicin and had the cardiothoracic surgery to remove the individual metastatic lesions in the lungs. In 2016 the pain in the spine returned, defined by the patient at 10 point according VAS. Severe pain caused that the patient was unable to work or perform activities of daily living. According to the Nurick scale the patient had a 4/5 points. MRI revealed a recurrence of spinal metastases occupying the rest of the L3 and all L4 vertebra in the spine. This lesions caused the compression and narrowing of the spinal canal, resulting in very severe clinical symptoms. Due to the lack of proposals of surgery treatment, the patient was qualified for transarterial chemoembolization of metastases in the spine using drug eluting particles soak with doxorubicin. The intervention was performed under local anaesthesia (10 ml 2% lignocaine subcutaneously) by puncturing right common femoral artery using Seldinger method. Then, using a Simmonds catheter arteries on the right side, supplying the metastases in the spine were catheterized (fig. 1). Chemoembolization was performed using particles soaked with cytostatic

Tab. 1. Nurick clinical scale

Grade 0	Signs of symptoms of root involvement but without evidence of spinal cord disease
Grade 1.	Signs of spinal cord disease but no difficulty walking
Grade 2.	Slight difficulty in walking which does not prevent full-time employment
Grade 3.	Extreme difficulty in walking that requires assistance and prevents full-time employment and occupation
Grade 4.	Able to walk only with someone else's help with the aid of a walker
Grade 5.	Chairbound or bedridden

– 100 mg of doxorubicin. 2 ml of particles size 75 μ m in diameter were used. Control angiography demonstrated almost complete closure of the vessels supplying the lesions (fig. 2). During the procedure the pain occurred and was alleviated by administration of 100 mg of ketonal. The day after embolization a petechiae appeared on the skin – probably a local allergic reaction caused by doxorubicin (fig. 3). After a few days without any treatment ecchymosis disappeared. 2.5 months later the second embolization was performed. Remaining arteries supplying the lesions in the spine on the L3 and L4 level were closed. The intercostal arteries supplying metastases were selectively catheterized and embolized using particles Embozene 500 and 700 μ m in diameter. Control angiography showed complete closure of the vessels. After a period of four months control MRI with contrast was done. The examination was compared to the MRI performed before embolization (fig. 4, 5). Tumor mass was decreased. In the upper-lower dimension from 92 to 80 mm, the anterior-posterior dimension from 84 to 66 mm and right-left dimension from 140 to 113 mm. Part of the tumor mass pressing the spinal cord (causing a 12-millimeter in-

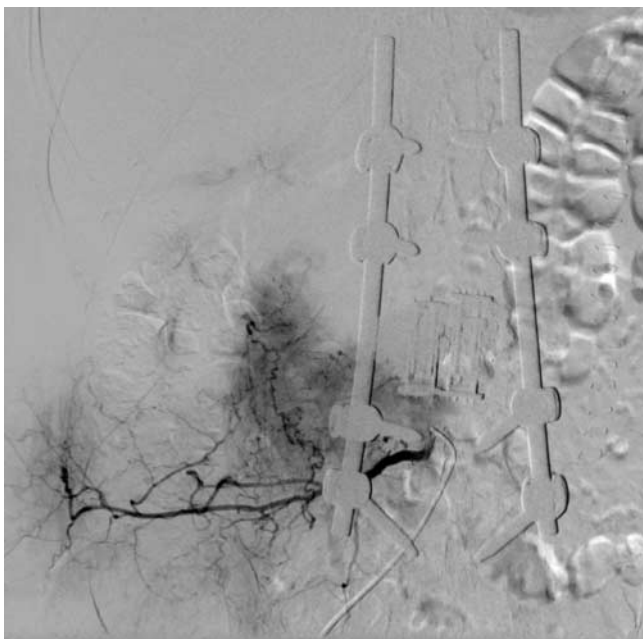


Fig. 1. Selective angiography of the artery supplying the metastatic lesion located on the right part of the L4 vertebra

tussusception) undergone complete regression, what explained the almost complete disappearance of the symptoms. The impression on the vessels – the aorta and inferior vena cava was significantly lower. Metastases have changed also in terms of morphology – there was more fibrosis in the metastasis (more on the side which was chemoembolized – right) and contrast enhancement was significantly lower (fig. 4, 5).

DISCUSSION

Leiomyosarcoma of the uterus is a rare malignant tumor, occurring in 0.6 to 1.7 per 100,000 women (13). Bone metastases are extremely rare, and usually they are the late manifestation of the natural progression (14). Spinal metastases are the most common



Fig. 2. Selective angiography of the artery performed after the chemoembolization. Lack of branches supplying metastasis in the right part of the L4 vertebra

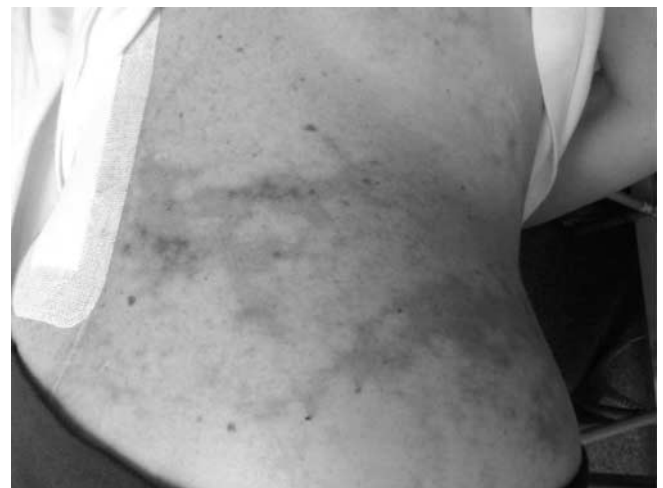


Fig. 3. Allergic rash on the skin appeared one day after the chemoembolised side (right). After a few days changes resolved without any treatment and complications

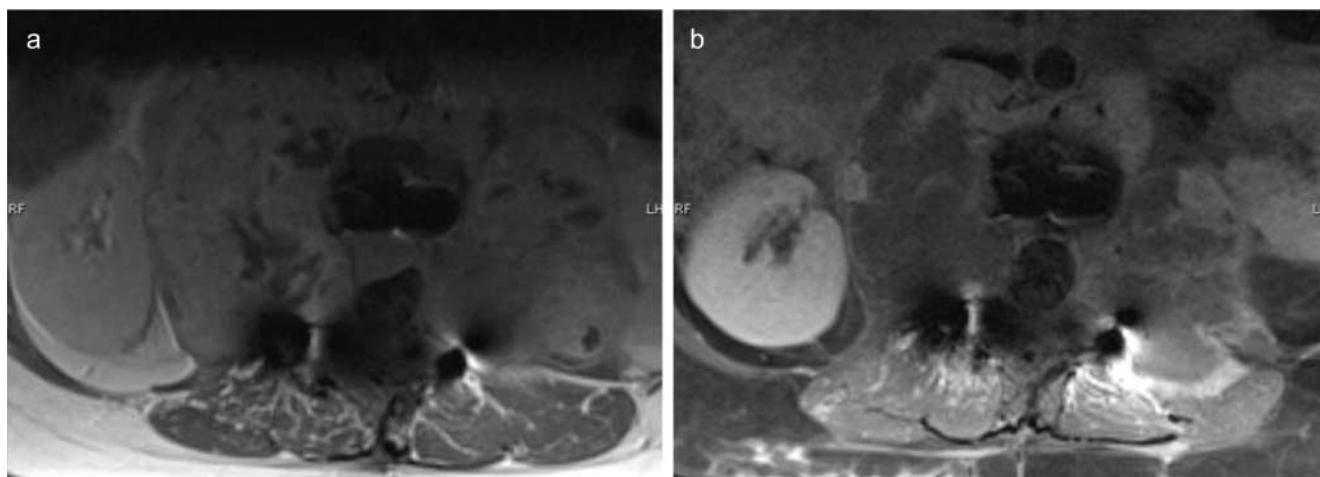


Fig. 4a, b. Comparison of two MRI examinations performed before (a) and after chemoembolization (b). On fig. a extensive lesion compressing the spinal cord. On fig. b – the visible part of the tumor mass which compressed the spinal cord has regressed completely

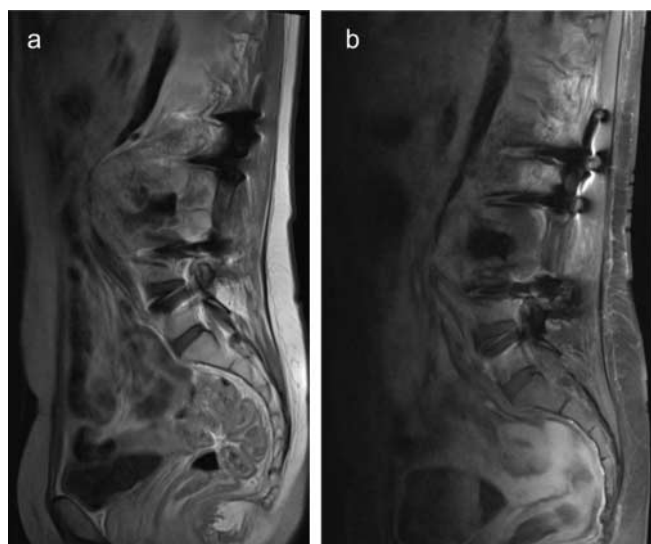


Fig. 5a, b. Comparison of sagittal images before (a) and after the procedure (b). There is a noticeable decrease of the lesion size, a significant reduction in vessel pressure, and a change in morphology as well as the decrease in postoperative contrast enhancement of the lesion

bone location (15, 16) and generally occupy thoracic spine (17, 18). The origin of this tumor is controversial. Chromosomal aberrations may be responsible for the occurrence of milder forms of this cancer (19). On the other hand, one hypothesis says that this cancer may be derived from blood vessels (20) or pluripotential mesenchymal cells (21). On MRI metastases are visible as a hypointense areas on T1 sequences and hyperintense areas on T2 sequences (22). The differential diagnosis includes neurofibromatosis, schwannomas, meningiomas, lymphomas, fibrous tumors, ependymomas, and other metastatic tumors. Histologically, sarcomas represent a wide range of cellular atypia, starting from well differentiated cells to an anaplastic cells, which are the most aggressive forms. Cell morphology is quite similar to benign fibroids, consisting of spindle-shaped bundles containing smooth muscle cells with oval nucleus and elongated cytoplasmic appendages. Atypia in the cell nucleus, high mitotic index with the zone of necrosis, confirm the malignant nature of the tumour (23, 24).

It is worth highlighting that the distinction between primary and metastatic changes is not an easy task. Basic differential diagnosis taking into consideration the benign type of uterine fibroids called leiomyoma is very difficult and which (in rare cases) can be a starting point for malignancy. It can lead to incorrect diagnosis (e.g. determine the change as benign), or cause the primary tumor to be detected at the site of the metastatic tumor, which can lead to wrong selection of the treatment and improper observation. The appearance of metastases usually indicates a poor prognosis, as Abeler et al. showed in a study on 400 patients with a primary malignant lesion derived from the uterus. In their study, the mean survival in patients with the metastases from leiomyosarcoma outside the uterus was less than 1 year (25). Other authors report about better results with respect to the time of disease development. These differences may be due to the unstable clinical course of this sarcoma, which depends on the location of the primary tumor, the extent of the occupied spine and clinical condition of the patient.

Based on the literature review, we found leiomyosarcoma originally occurring in the spine and in paraspinous muscles only in 14 reported cases, what proves the very rare occurrence of this malignant tumor as a primary lesion in the spine (16, 21, 22, 26-29). A similar situation occurs in the case of the metastases to the spine from LMS – these changes are very rare with only a few cases described in the literature (15-18, 30-35), constituting the first manifestation of a tumor or a secondary relapse of primary disease (36, 37). In most cases, spinal metastases occurred as a tumor occupying bone or epidural space (38).

In our study, we analyzed the available literature to find information about the treatment taking into account the surgical treatment in cases with metastases to the spine derived from leiomyosarcoma.

Due to the rarity of the occurrence of this cancer, we have found only a few reported cases of treatment and two publications describing several patients who underwent surgical resection for metastatic lesions from

leiomyosarcoma to the spine. Available cases were collected and described by Maimone et al. In their analysis the average age for the total collected 20 patients (16 women and 4 men) with this disease was 51 years (25-83). As expected, the most common primary tumor localization was uterine muscle (13/20 patients – 65%). The most common symptoms resulting from the occurrence of metastases in the spine were pain in the back and lower limbs, which occurred in 80% of cases (16/20 patients). The next symptoms were of paraplegia – 50% of cases (10/20 patients) and severe sensory disorders – 40% of the cases (8/20 patients). Radiological examinations shown that the most common occurrence of metastases in the spine was thoracic (in 70% of cases, 14/20 patients) and lumbar (30%, 6/20 patients) section. Surgical therapy in these cases include both laminectomy, vertebrectomy, segment stabilization depending on the extent of metastases and their location. The results show a general improvement in the neurological symptoms, and especially abolish the pain and symptoms resulting from the spinal myelopathy (39). Ziewacz et al. reported a general improvement in reducing symptoms in movement to one or two points according to the Nurick scale and reduced the symptoms of pain to 5 points of the VAS scale (18). Although median survival does not seem to be associated with adjuvant therapy, chemotherapy was regularly administered in 82% of documented cases, while only 47% of patients received radiotherapy. Median survival has quite significant differences in the described situations. Elhammady et al. in their publication based on 5 patients showed an average survival time of nearly nine years (17). If we compare these results with the publication of Ziewacz et al. and other authors we will see significantly shorter survival time which amounted about 10.7 months (15, 18, 30, 34). Significant differences in the length of survival may be due to more aggressive tumor growth occurring in patients described by Ziewacz et al., in comparison with patients described by Elhammady et al., what has been confirmed in the incidence of tumor recurrence (62% Ziewacz et al., 40% Elhammady et al.) or as a result of delayed treatment implementation resulting from an incorrect primary diagnosis and classify the changes as a benign tumor – leiomyoma.

In our case, the patient has been living seven years from diagnosis of the lesion in the uterus. Three years

passed from the spinal metastases was diagnosed. Despite radical surgery, after 2 years the recurrence of metastases occurred and occupied the remaining part of the operated vertebrae. Due to the lack of proposals for treatment of metastases in the spine and because of clinical symptoms that prevent normal functioning of the patient (even caused patient disability), the patient has been qualified for the chemoembolization. In the literature, we did not find a case in whom chemoembolization was used in the treatment of metastases to the spine. According to the guidelines of the American Cancer Society from 2016, there are no standards of conduct in the case of metastases of uterus sarcoma to the bone. While according to the National Comprehensive Cancer Network (NCCN), a standard procedure in the 4th stage of the disease in relation to disseminated malignancy, apart from typical palliative care (palliative surgery, palliative chemotherapy, palliative radiotherapy, stereotactic radiosurgery and ablation) is also embolization, but there is no information about chemoembolization. After numerous consultations with neurosurgeons and after receiving informed consent from the patient, the chemoembolization was performed. An important factor in favor of performing this treatment, using particles soaked with doxorubicin, was the fact, that this patient had the chemotherapy with this drug in the past and responded well. Basic method of treating advanced metastatic leiomyosarcoma of the uterus are cycles of chemotherapy based on doxorubicin (39, 40).

Three months after treatment the patient returned to normal life – started to move independently, returned to work, and even began to drive a car. Previously, none of these activities was possible. Now, according to VAS scale the pain is evaluated by the patient at 1-2 points. By the scale Nurick patient has 1 point. MRI examination performed 4 months after the intervention showed a significant reduction of the metastases in the spine compared to the MRI performed before chemoembolization.

CONCLUSIONS

Chemoembolization of the spine metastases derived from leiomyosarcoma brought a favorable result in the form of reducing the tumor mass, reduction of pain and significant improvement in quality of life of the patient.

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