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THE EVOLUTION OF PRIMARY URETERAL LEIOMYOSARCOMA: CASE STUDY

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Abstract: *The most common primary neoplasm of obstructive reno-ureteral pathology is transitional cell carcinoma, while soft tissue sarcomas, in our case primary leiomyosarcoma, have a very low frequency in this anatomical location. The diagnosis of certainty is provided by histopathological examination following the nephroureterectomy.(1) Due to the aggressiveness of this sarcoma, chemotherapeutic treatments become ineffective, with a poor prognosis, given the short survival of reported cases.(2,7) The gold standard in treating leiomyosarcomas is performing nephroureterectomy with en bloc excision of the tumor.(3,4) We introduce the case of a 65-year-old patient who presented to our department with a diagnosis of primary ureteral leiomyosarcoma. Subsequent to the polychemotherapy treatments, the aggressiveness of this pathology led to the unfavourable evolution of the case.*

INTRODUCTION

Primary ureteral leiomyosarcoma is a rare soft tissue tumour that accounts for about 20% of all soft tissue tumours. This type of tumour is generally found in middle-aged patients, and those with retroperitoneal location or associated with blood vessels are more common in females.(1,2,5) The 10% metastasis rate varies according to location, with about 30% in the extremities, over 55% intra-abdominally and between 50-70% in the uterus.(3)

It is a very aggressive and with an extremely poor prognosis tumour that originates from smooth muscle cells or precursor mesenchymal cells which eventually differentiate into smooth muscle cells. Histopathologic analysis shows the presence of spindle cells with abundant eosinophilic cytoplasm, while from an immunohistochemically point of view smooth muscle actin is present.(1,3,4)

Preoperatively, the diagnosis of certainty of this tumour is rarely evident. The abdominal-pelvic computer tomography, abdominal ultrasonography or nuclear magnetic resonance are essential in the detection of tumour formation, and ureteroscopy with biopsy is indicated before surgery, in order to know exactly the benign or malignant nature of the tumour and to consider the preservation of renal function. Histopathological examination remains the key to diagnosis and future therapeutic options.(1,6)

CASE REPORT

The 65-year-old female patient was diagnosed in 2018 with ureteral leiomyosarcoma, p T3 p N0 p Mx, after a CT scan of the chest, abdomen, and pelvis, for which a radical left laparoscopic nephroureterectomy with perimeatric cystectomy and left adnexectomy with extended left lateroaortic and iliac-obturator lymph node dissection was performed. She subsequently underwent adjuvant treatment in another centre with 3 series of Dacarbazine with Doxorubicin, with the disease in remission. She presented to the oncology department of the Elias Emergency University Hospital in Bucharest with pain and functional impotence in the left lower limb, moderate edema and frank haematuria.

The objective examination at the time of admission revealed a suffering facies, pale skin and mucous membranes, intense pain in the left lower limb with left buttock irradiation with functional impotence, moderate edema at this level and macroscopic haematuria, the patient being hemodynamically and respiratory balanced with normal biological samples, except for the presence of hematomas in the urine sample.

Abdominal and pelvic computed tomography was performed, which confirmed local recurrence, respectively a heterogeneous tissue mass of approximately 7/2/6.9 cm, with diffusely delimited necrosis area delimited, loss of cleavage plane to the left external iliac artery and to the descending colon, located retroperitoneally on the projection area of the left pelvic ureter.

On May 26th, 2021, surgery was performed again, and exploratory laparotomy was carried out with biopsy of the retroperitoneal tumour formation. A tumour nodule at the level of the great omentum was excised together with several tumour nodules of the wall of the first jejunal loop (possibly peritoneal metastases). Postoperative imaging was re-evaluated by abdominal and pelvic computed tomography and an expansive process was confirmed in the left iliac and psoas areas that had encased the iliac vessels, with nonuniform structure, the lesion being located adjacent to the left paravertebral intestinal ansae (L4-L5-S1-S2). Histopathological examination confirmed the diagnosis of ureteral leiomyosarcoma.

Given the ongoing symptomatology, in particular the intense algic syndrome rated 9/10 which has not subsided in intensity after opioid treatment, a neurological consultation is requested, due to a possible sensory origin of the pain. Following neurological consultation, the diagnosis of left

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femoral or left lumbosacral neuropathy was established and systemic corticosteroid, myorelaxant, neuropathic analgesic and opioid analgesic were administered and proved effective.

An interdisciplinary committee decided that due to the loco-regional, intraperitoneal tumour extension and areas of necrosis adjacent to the tumour, radiotherapeutic treatment in this case is not indicated as it would not provide benefits. Instead, chemotherapeutic treatment with doxorubicin and Ifosfamide with prophylactic urinary tract protection was considered.

Imaging reassessment was performed, and an expansive process was revealed in the iliac and left psoas muscle that encased the iliac ansae with inhomogeneous structure. The lesion focused adjacently to the intestinal ansae (descending colon), paravertebral L4-L5-SA-S2 left.

In June 2021, the first series of doxorubicin with ifosfamide and prophylactic protection was administered, and subsequently the patient developed significant myelosuppression with the onset of grade IV febrile neutropenia. This led to the activation of varicella-zoster virus with the appearance of herpetic lesions on the lips, reason for which it was decided to stop chemotherapeutic treatment.

After remission of symptoms and normalization of biological evidence, it was decided to continue the adjuvant regimen with doxorubicin and ifosfamide.

Due to significant myelosuppression, it was decided to reduce chemotherapeutic doses to 75% to allow tolerability. Tumour markers gradually decreased, which is why we reserved a favourable prognosis and treatment response.

On September 14th, 2021, the 4th round of chemotherapy was administered. Subsequently, treatment was discontinued after the 3rd day of treatment (the treatment regimen was administered for a period of 4 days, and on the 5th day hydroelectrolytic balancing treatment was administered), due to the fact that she presented with confusional state, visual disturbances, dizziness, postural instability, and temporo-spatial disorientation.

Following this, brain MRI was performed, which detected a microangiopathic appearance, without oncological substrate or other damage that could explain the patient's condition.

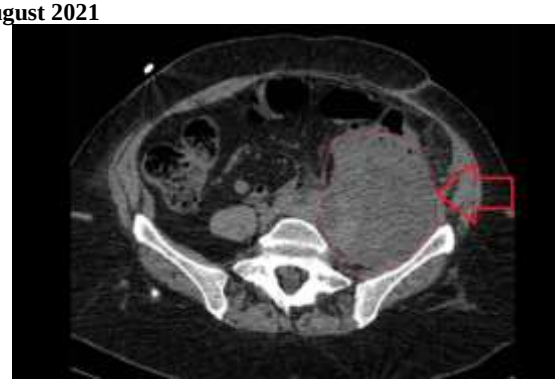
Biologically, severe anemia (hemoglobin approximately 7g/dl) was detected in the hemo-leukogram. From a biochemical point of view, it was found significant hepatic cytolysis (aspartate aminotransferase 110, alanine aminotransferase 170), thus the patient's condition being explained by a possible encephalopathy after the administration of ifosfamide. It was decided to delay treatment, and the patient remained hospitalized for correction of anemia and hepatic cytolysis, administering hepatoprotective, erythrocyte concentrate, thrombocyte mass and granulocyte stimulating factors. The patient's condition improved, she was discharged with the recommendation to administer corticosteroid at home, to allow her to restore marrow cellularity.

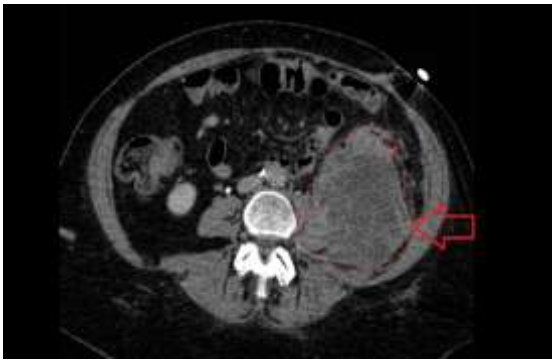
In August 2021, imagistic re-evaluation was performed and a tissular of 10.5/10 cm was revealed, with retroperitoneal and abdominal necrosis areas, with loss of cleavage plane to the iliac arteries, colon, ileal ansae, psoas and iliac muscles without paravertebral involvement. The investigation showed three hepatic cystic lesions, normal spleen, right adrenal gland, and pancreas, normal right kidney, normal right ureter, uterus with fibromatous appearance, lung parenchyma without localized processes, thin sludge of perilesional fluid and in the pelvis (possibly haemorrhagic fluid).

After a few days, the patient's condition deteriorated and she was taken to the emergency department in another hospital unit close to her home, presenting fever of approximately 38 degrees Celsius, diffuse abdominal pain with left buttock irradiation, altered mental status, anxiety, depression, with worsening anemia, despite the administration of erythrocyte, thrombocyte, and erythropoietin products, which could not be completely corrected.

Brain CT/MRI examination showed no evidence of space-replacing formations at this level. The inflammatory samples were altered, so that although antibiotic treatment was administered, according to the antibiogram, the patient's condition gradually deteriorated with septic state and disseminated intravascular coagulation. Despite resuscitation manoeuvres, death was declared.

Figures no. 1,2. Tumour formation image on CT scan August 2021





DISCUSSIONS

Leiomyosarcoma is one of the most common soft tissue tumours, accounting for about 20% of sarcomas, affecting the middle age, with retroperitoneal or vessel-associated location predominantly in females. Most patients are detected between the ages of 50-60.(1,3,7)

The following may be considered possible risk factors: history of radiotherapy, Li-Fraumeni sdr, hereditary retinoblastoma, Tamoxifen (in case of uterine leiomyosarcoma), immunocompromised patients (organ transplant, congenital mutations), Epstein Barr virus etc.(1)

Differentiation of leiomyosarcoma from rhabdomyosarcoma, spinal neoplasms, sarcomatoid carcinoma, melanoma should be considered by immunohistochemical testing which may suggest the presence of desmin and smooth muscle actin (SMA) and the absence of cytokeratin, S-100 marker, myoglobin, and detectable epithelial membrane antigens.(1,4,2)

According to the studies, female subjects presented macroscopic/microscopic haematuria as a frequent symptom.(7) In other patients diagnosed with this tumour type, hydronephrosis and ureterolithiasis were associated.(8) The symptomatology presented by our patient was macroscopic

haematuria, excluding hydronephrosis and ureterolithiasis.

In rare cases, the ureteral leiomyosarcoma is asymptomatic at onset, so the diagnosis is established after investigations, imaging, performed by chance.

Laparoscopic nephroureterectomy was performed without a definite diagnosis, in which 8 similar patients were investigated. This intervention should be considered in young patients with suspected benign tumours, with the preservation of renal function by performing ureteroscopy with biopsy before nephroureterectomy.(2,9)

Adjuvant chemotherapy has been tested on patients with soft tissue sarcomas located in the extremities/trunk. It has been shown to be beneficial in children but remains controversial in adults.(1)

Concomitant use of cytostatic drugs, doxorubicin with ifosfamide, has been shown to reduce the risk by approximately 11% compared to the use of doxorubicin alone.(7)

Administration of Ifosfamide in a dose less than or equal to 5 g/m2, could produce minimal results 13, perhaps in our case as well, but adverse reactions forced us to reduce the dose. In uterine leiomyosarcomas, ifosfamide alone has not been shown to be effective in studies.(1)

Adverse reactions, such as thromboembolism, disseminated intravascular coagulation or haemolytic uraemic syndrome, may occur with increased frequency with chemotherapy regimens that include ifosfamide. Another common adverse reaction following ifosfamide administration is encephalopathy, manifested by: memory impairment, depressive psychosis, disorientation, anxiety, dizziness, confusion, hallucinations. According to the literature, methylene blue has been shown to improve these symptoms, but this treatment has only been instituted in severe encephalopathy following a risk-benefit analysis.(10)

According to the NCCN 2022 guidelines (10), doxorubicin administration with ifosfamide in tumours larger than 5 cm is a viable option, since the leiomyosarcomas located in the extremities have a better response compared to retroperitoneal locations.(5)

The complications of leiomyosarcomas are specific and include external compression due to the mass effect and early metastases, which determine tumour aggressiveness.2 In our case, tumour compression caused intense pain, distant thrombosis, lower limb edema on the tumour side and macroscopic haematuria. Surgical resection with negative margins offers better chances of survival.(1,4,11)

CONCLUSIONS

Due to the rare occurrence of this type of tumour, diagnosed patients should be encouraged to participate in clinical trials in order to establish the clinic-biological features and to administer a more effective therapeutic management.

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