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RESEARCH ARTICLE

CLINICAL PRESENTATION AND LITERATURE REVIEW: MUSCLE METASTASIS IN UPPER TRACT UROTHELIAL CARCINOMA

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Abstract

Urothelial carcinoma often metastasizes by lymphatic pathways to locations including lymph nodes, bone, and liver. Similar to other cancers, muscle metastasis is uncommon. M.M., a 68-year-old with a history of hypertension, dyslipidemia, and thyroidectomy, has been suffering from lumbar discomfort since April 2023. CT scans revealed secondary lesions and infiltrating urothelial neoplasia in the kidney, renal pelvis, and abdomen. An FDG PET scan confirmed right renal neoplasia. The patient was treated with platinum-based chemotherapy, followed by avelumab. In the sixth cycle, the patient experienced severe pain in the left thigh and a painful mass. MRI of the left thigh confirmed the suspicious origin of the mass, located in the adductor muscle compartment. A PET scan showed clear morphometabolic progression in the right (para)renal locoregion, likely including invasion of the peritoneum, muscles, and right adrenal gland. Pathology confirmed the metastatic origin of the muscle mass.We decided to give enfortumab vedotin based on the ECOG performance scale (PS) and radiotherapy for the painful metastasis in the left thigh. The patient's condition worsened during hospitalization, causing intermittent bewilderment. An brain MRI showed asymmetric pachymeningeal enhancement of the right convexity, indicating meningoencephalitis. A lumbar puncture confirmed the diagnosis, and acyclovir was administered. However, the patient succumbed five days after antibiotic therapy. The literature research revealed 18 documented instances of urothelial cell carcinoma with muscle metastases, all of which were male and involved the bladder. This instance underscores the need to meticulously assess all muscular discomfort in patients with a history of malignancy, as it may indicate skeletal muscle metastases, which correlates with heightened morbidity and death.We present the following case by the CARE reporting checklist.

Introduction:-

Urothelial carcinoma is a significant public health issue worldwide, with varying incidence rates depending on geographic region(1).Urothelial cancer, especially bladder cancer, has a notable incidence in Belgium. Data on urothelial cancer in the country have been systematically collected by national cancer registries, particularly by

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Belgium's Belgian Cancer Registry (BCR)(2). According to available data, the incidence rates of urothelial cancer in Belgium are comparable to other Western European countries.

UTUC often metastasizes to lymph nodes, lungs, liver, bones, and peritoneum.Metastasis to skeletal muscle is an uncommon oncological occurrence across all cancer types, attributed to muscle-protective mechanisms including contractility, pH regulation, and lactic acid clearance(3). We provide the second documented instance of solitary upper tract urothelial carcinoma with skeletal muscle metastases(4).

Medical Observation:
Patient M.M., 68 years old, has a medical history of hypertension, dyslipidaemia, and a complete thyroidectomy for thyroid nodules exhibiting grade 1 and 2 follicular proliferation, chronic depression treated with Sipralexa, and has been an ardent smoker, consuming 3–5 cigarettes daily since 1993.

The onset of his ailment began in April 2023 with the manifestation of lumbar discomfort, leading the patient to seek consultation. A CT scan showed nodules on the left inferior diaphragm (LID) and left supraglottic (LSG) in the thorax that looked like secondary lesions. The scan also showed infiltrating urothelial neoplasia in the upper segment of the right kidney, the renal pelvis, and the proximal section of the right ureter in the abdomen, along with several lymph nodes in the retro-caval and inter-aortic-caval areas. A supplementary FDG PET scan revealed metabolic evidence supporting right renal neoplasia, characterized by semi-solid nodular abnormalities in the lower right and upper left lobes, which exhibited metabolic activity. The case was reviewed at the oncourological-CMO following anatomopathological confirmation, leading to the decision to initiate platinum-based chemotherapy.

The patient had three courses of first-line chemotherapy of gemcitabine and carboplatin from October 8, 2023, to September 20, 2023. Subsequent to clinical and radiological advancement, a second-line therapy with Avelumab was initiated in October 2023. In the sixth cycle of Avelumab, the patient arrived to the emergency room with marked decline in general health, requiring hospitalization. The patient described intense, unmitigated pain in the left thigh. A physical examination revealed a painful mass in the left thigh. The blood tests revealed no indications of infection, whereas the individual had moderate hypercalcemia, hyperleukocytosis, a normal microbiological test, and acute renal failure against a backdrop of chronic conditions. The patient had intravenous hydration and modifications to pain management medication.

A soft-tissue ultrasound scan was ordered for the mass in the left thigh (Figure 1-2), showing a suspicious-looking muscle mass.

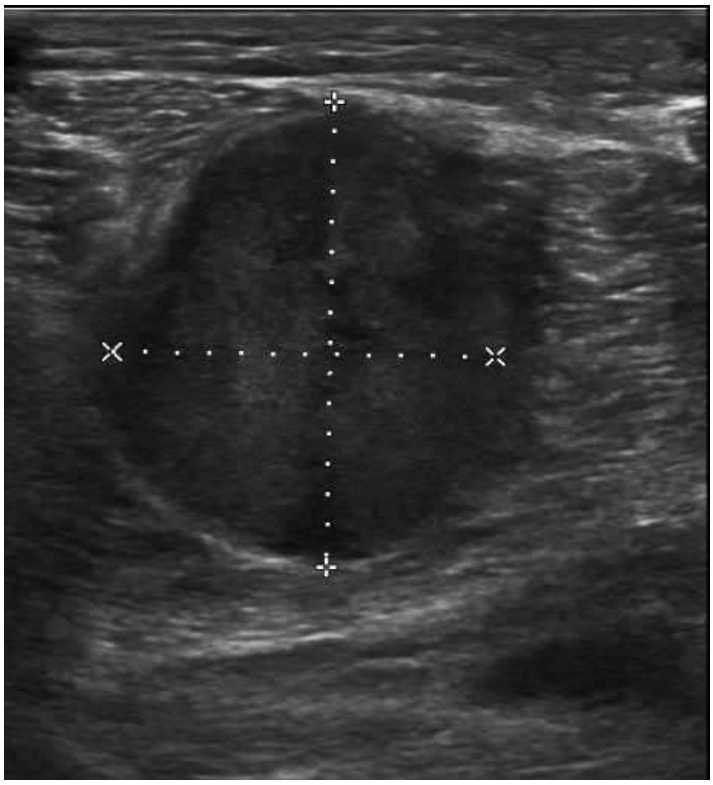
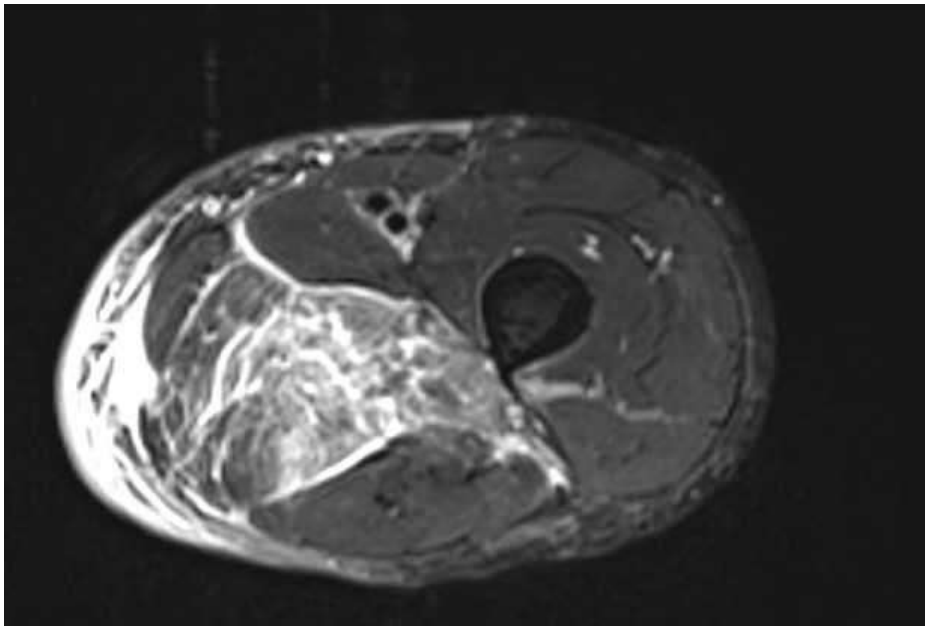


Figure 1-2:- Ultrasound image of a hypoechoic mass in the semitendinosus muscle; must be compared with MRI data.

MRI of the left thigh confirmed the suspicious origin of the mass, located in the adductor muscle compartment (Figure 3-4).



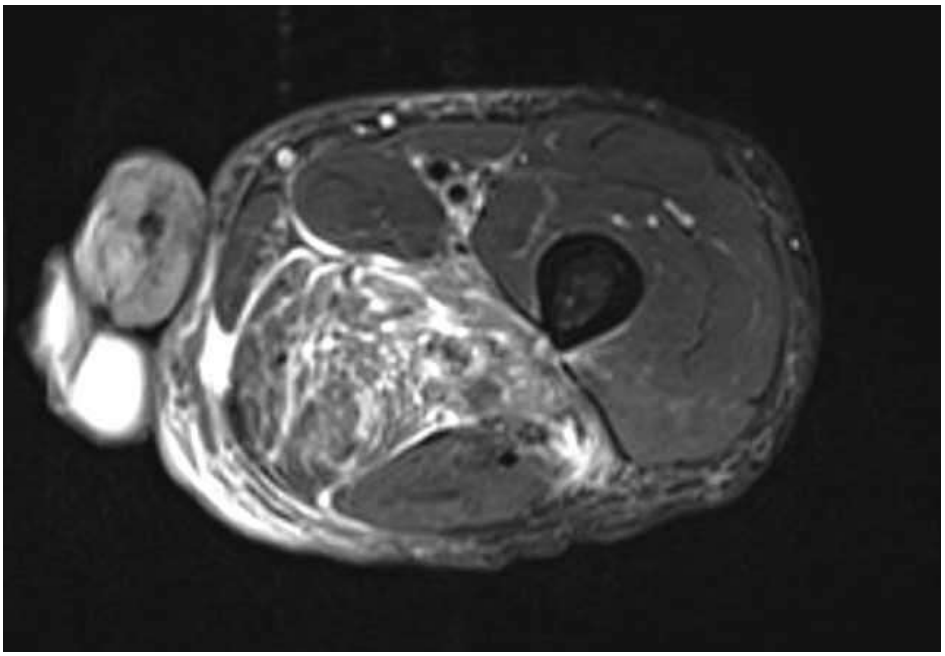


Figure 3-4:- A mass located in the adductor muscle compartment, with a maximum diameter of 43 mm, a heterogeneous appearance, restricted diffusion and intense, homogeneous enhancement, with rapid wash-in/wash-out in dynamic analysis.

A PET scan showed clear morphometabolic progression in the right (para)renal locoregion, likely including invasion of the peritoneum, muscles, and right adrenal gland. The scan also showed many metastases in the pleuropulmonary region, lymph nodes, and muscles.

Pathology confirmed the metastatic origin of urothelial carcinoma after biopsying the muscle mass: CKAE1AE3 positive, CK7 positive, CK20 positive, and GATA3 positive.

The onco-urological CMO talked about the case and decided to give enfortumab vedotin based on the ECOG performance scale (PS) and radiotherapy for the painful metastasis in the left thigh. This was done because of the progress in the clinico-radiological tests, the appearance of a neoplastic syndrome, and the confirmation that the left thigh muscle mass was metastasized.

Throughout the hospitalization, the patient's overall condition progressively worsened, and he exhibited intermittent bewilderment. An MRI of the brain (Figure 5) showed asymmetric pachymeningeal enhancement of the right convexity, which is a sign of meningoencephalitis but no signs of the disease spreading to other parts of the body. A lumbar puncture confirmed the diagnosis of varicella meningoencephalitis, and the patient was administered intravenous acyclovir ; nonetheless, he succumbed five days after the initiation of antibiotic therapy.

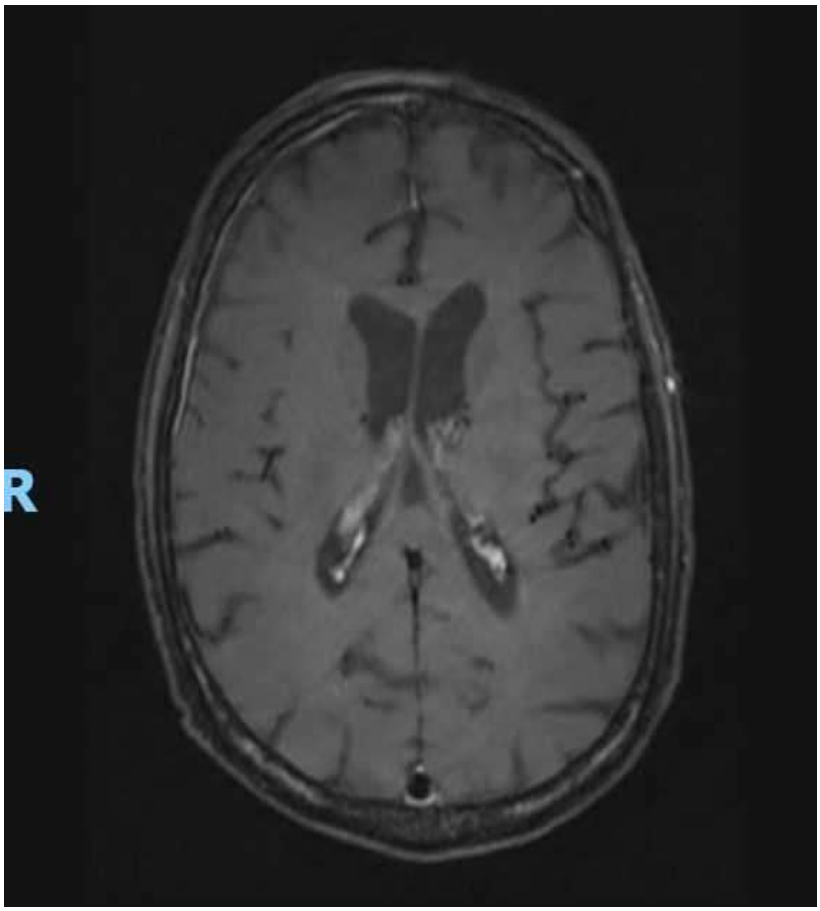


Figure 5:- Brain MRI showing asymetric pachymeningeal enhancement of the right convexity: related to meningoencephalitis? Intraparenchymal punctiform enhancement on the right frontobasal: to be continued. No obvious parenchymal or meningealmeningeal metastasis.

Discussion:-

Urothelial carcinoma (UC) is a malignancy that affects the lining of the urinary tract, from the renal pelvis to the distal urethra. Urothelial carcinoma is seldom observed in the upper urinary system (renal pelvis and ureter), accounting for 5-10%, and is much more uncommon in the urethra, at under 1%(5).

Urothelial cancer of the excretory tract is influenced by a combination of environmental, lifestyle, and genetic risk factors. The most significant and well-established risk factors are smoking, age, occupational exposures, and chronic inflammation(6). As the incidence of urothelial cancer continues to rise in aging populations, especially in developed countries, understanding and mitigating these risk factors will be critical in reducing the disease burden. Public health efforts focusing on smoking cessation, reducing occupational exposures, and improving early detection could potentially lower the incidence of urothelial carcinoma, particularly in high-risk populations(7).

Upper tract urothelial carcinoma (UTUC), which includes cancers of the renal pelvis and ureters, tends to present with a range of nonspecific symptoms. Symptoms can vary depending on the location, tumor size, and stage of the cancer(8) . Hematuria, flank pain, urinary obstruction, recurrent infection, and systemic symptoms like weight loss for the upper tract(9).Many of these symptoms overlap with those of urinary tract infections or stones, so the diagnosis of urothelial cancer often requires careful clinical evaluation and imaging to confirm.
CT Urography is the gold standard for imaging of the upper urinary tract (renal pelvis and ureters) and the bladder. It helps visualize the entire urinary system, detect tumors, and assess the extent of disease with high sensitivity (87%) and specificity (96%)(10). Magnetic Resonance Urography is an alternative to CT for visualizing the upper urinary tract, especially in patients who have contraindications to contrast (e.g., renal insufficiency) or who are at

high risk for radiation exposure(11).Early detection is crucial for improving outcomes, especially for upper tract urothelial carcinoma, which tends to be more aggressive and harder to diagnose early compared to bladder cancer.

A biopsy for upper urinary tract urothelial carcinoma (UTUC) is crucial for diagnostic confirmation and therapy planning. The selection of biopsy technique is contingent upon the tumor's location, dimensions, and accessibility.Percutaneous biopsy is efficacious for malignancies located in the renal pelvis and proximal ureter; nonetheless, it entails concerns such as tumor seeding and sample inaccuracies, necessitating precautions and sterilization protocols.Ureteroscopic biopsy is regarded as the gold standard for accessible tumors in the distal ureter and renal pelvis, with a high diagnostic yield(12). Cytology has lower sensitivity for upper tract urothelial carcinoma (UTUC) compared to bladder tumors and should be conducted preferentially in the afflicted upper urinary tract. One research indicated that barbotage cytology identified up to 91% of malignancies; however, barbotage cytology obtained from renal cavities and ureteral lumina is favored before the administration of a contrast agent for retrograde ureteropyelography(13,14).

Metastatic urothelial carcinoma (UC) of the upper urinary tract refers to the spread of cancer cells from a primary site (often the bladder) to the renal pelvis, ureter, or other parts of the upper urinary tract. Although urothelial carcinoma primarily affects the bladder, it can metastasize to the upper urinary tract, either by direct extension or via hematogenous or lymphatic routes. Metastasis via the lymphatic system occurs when cancer cells spread to regional lymph nodes, and may later involve distant lymphatic chains or the upper urinary tract.

Urothelial carcinoma can spread via the bloodstream to distant organs such as the lungs, liver, or bones(15). Muscle metastases from urothelial cancer is exceedingly uncommon, with less than 21 occurrences documented. Less than 0.3% of urothelial malignancies are known to spread to skeletal muscle(4). The usual manifestation of muscle metastases is localized discomfort and edema. These symptoms are often enduring despite focused efforts at pain control(16).

This case is the second documented instance of muscle metastases in urothelial carcinoma without concurrent bladder involvement, contrasting with all previously described instances that had bladder involvement(4). The treatment of muscle lesions is generally palliative; options such as excision, chemotherapy, and radiation may be contemplated, however evidence supporting these methods is limited. Chemotherapy is the most often preferred treatment due to the prevalence of extensive metastatic disease in individuals with skeletal muscle metastases(17). The prognosis for urothelial carcinoma with skeletal muscle metastases is very unfavorable, with a mean survival of just 9 months(18).

Among the 18 documented instances in litterature, eight succumbed within a year, four were living at the time of the case report's composition, and the outcomes for six cases were not disclosed(4).

Conclusion:-

We present the second documented instance of skeletal muscle metastases associated with upper tract urothelial carcinoma (UTUC) without bladder involvement. The report's strengths include heightened awareness of an uncommon and severe oncologic consequence, while its drawbacks are characterized by a scarcity of preceding data on the subject. Skeletal muscle metastases is a very uncommon consequence of urothelial carcinoma, linked to advanced disease and a worse prognosis. Consequently, it is essential to assess muscle discomfort in any patient with a history of urothelial carcinoma.

Highlights :

We emphasize the need of thoroughly assessing all chronic muscle pain in patients with current or past cancer, especially when accompanied by soft tissue edema. Imaging and biopsy should be used as necessary to assess painful muscle lesions in this demographic. Skeletal muscle has many features that safeguard against neoplastic invasion, including pH, contractility, and lactic acid clearance mechanisms. Skeletal muscle metastases, albeit infrequent, may be underrecognized and are often linked to extensive metastatic illness and a graver prognosis, necessitating immediate commencement of therapy.

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Conflict Of Interest
The authors declare that they do not have any conflict ofinterest.

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