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Case Report
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Unusual Metastatic Localizations of Urothelial Carcinoma of Ureter in Young Male Patient

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Abstract

Renal pelvis and ureter's tumors constitute upper urinary tract tumors, whose histological subtype is urothelial carcinoma, that occurs more frequently in bladder. The pattern of metastases is similar between upper urinary tract and bladder urothelial carcinoma: Lymph nodes, liver, bone and lung. Here we describe a case report where a 43-years-old man affected by urothelial carcinoma of ureter underwent right nephroureterectomy and retroperitoneal lymph nodes dissection and then it was administered adjuvant chemotherapy (4 cycles of cisplatin/gemcitabine). Then, during his clinical and radiological follow-up, some uncommon sites of metastases were found, such as stomach, peritoneum, left axillary, right and left supraclavicular lymph node. At the end of five cycles of first-line chemotherapy, he developed symptoms connected to Leptomeningeal Carcinomatosis (LMC), which is absolutely an atypical site of relapse for this kind of tumor. Patient was treated with intrathecal methotrexate 12 mg once weekly and second-line therapy with Pembrolizumab 200 mg flat dose for four cycles. In literature we have found only other two case reports which describe LMC in urothelial carcinoma of upper urinary tract and no patient affected by this tumor treated with systemic immunotherapy and intrathecal chemotherapy for LMC. Our patient died three months after the LMC diagnosis, supporting the fact that the prognosis for this site of metastasis is poor.

Keywords: Urothelial carcinoma; Leptomeningeal carcinomatosis; Metastatic

Introduction

Leptomeningeal Carcinomatosis (LMC) is a very unusual metastatic localization for urothelial carcinoma of ureter. In this case report we describe a 43-years-old man affected by this kind of tumor with atypical sites of relapse: Stomach, peritoneum, left axillary, right and left supraclavicular lymph node and finally LMC. The treatment for LMC from solid tumors is not established, but Intrathecal Therapy (IT), radiotherapy and systemic chemotherapy according to primary tumor are usually administered [1,2]. In literature there are not many metastatic presentations like this, as well as few descriptions of treatment based on systemic immunotherapy and IT for LMC.

Case Presentation

In February 2019, a 43-years-old Caucasian man, presented hematuria. He had no concomitant diseases. His familiar history was positive for breast cancer (grandmother and sister). An abdominal ultrasound scan identified right hydronephrosis of grade II-III and pelvic expansion of right ureter. A contrast-enhanced Computed Tomography (CT) of chest and abdomen confirmed the presence of right hydronephrosis and a mass of 2 cm of ureter, the bladder had irregular walls, retroperitoneal lymph nodes were enlarged, the major of them of 2 cm × 1.2 cm. A Cystoscopy revealed normal mucous membrane without macroscopic alterations with thickening of the right walls. In March 2019, a right nephroureterectomy and retroperitoneal lymph nodes dissection were performed. A macroscopic examination showed 5 cm mass of right ureter. Histological examination found a papillary and not papillary urothelial carcinoma of right ureter, G3, and metastatic involvement of only one of three lymph nodes. According to the American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC) Tumor-Node-Metastasis (TMN) staging system, 8th edition (2017) [3] tumor staging was pT3 pN1 cM0, stage IV.

The patient had good clinical conditions; Eastern Cooperative Oncology Group (ECOG) performance status score was 0. His blood examination was normal, in particular serum creatinine was 1.24 mg/dl with estimation Glomerular Filtration Rate (eGFR) >60 ml/min. He was fit for cisplatin-based chemotherapy; in particular he had no cardiovascular, audiometric and neurological

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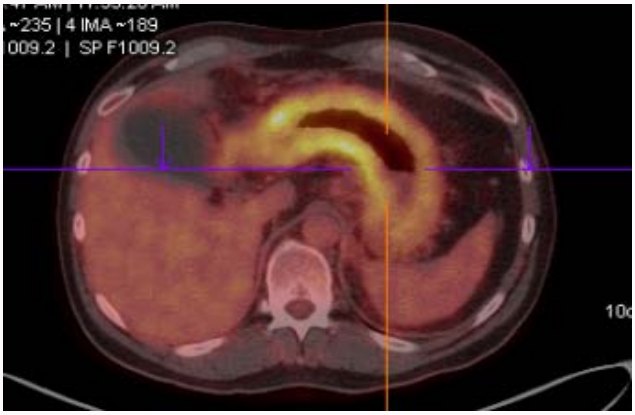

Figure 1: PET-CT showed elevated uptake of stomach (SUVmax 10.9).

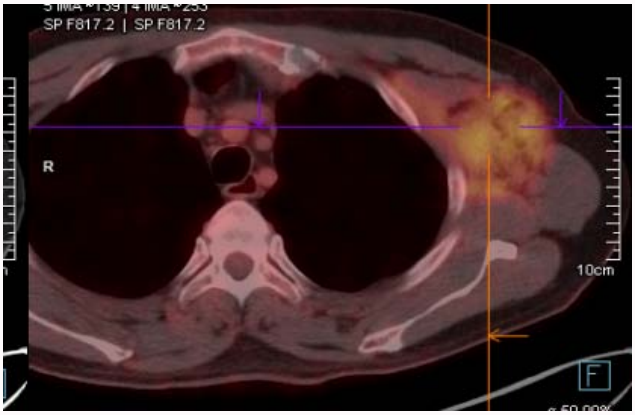

Figure 2: PET-CT showed elevated uptake of left armpit (SUVmax 6.4).

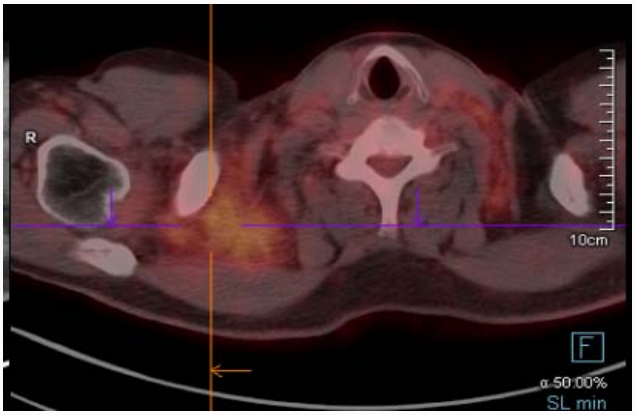

Figure 3: PET-CT showed elevated uptake of right and left superclavear lymph nodes (SUVmax 5.5 and 5.6, respectively).

alterations. From April to July 2019, our patients received 4 cycles of first line intravenous chemotherapy with gemcitabine 1000 mg/m^2 on days 1-8 q21 plus cisplatin 70 mg/m^2 on day 1-q21 without significant adverse events, except Grade (G) 1 nausea from day 1 to day 3 of chemotherapy and G1 fatigue according to the National Cancer Institute Common Terminology Criteria for Adverse Event version 5.0 (CTCAE v5.0). There was no relapse of disease at abdominal Magnetic Resonance Imaging (MRI) and a chest CT scan performed in August 2019. He underwent observation with blood examination, urinary cytology, abdominal ultrasound/MRI and chest CT scan, all of these were negative.

Thirteen months later (September 2020), patient complained G1 left armpit pain, G2 abdominal pain, G2 nausea and G2 vomit. ECOG performance status score was 0. He showed weight loss of 7% in last 6 months and reduced oral intake (50%) in past 7 days. An axillary ultrasound showed 5 cm × 1.7 cm × 3 cm mass of left armpit. Urinary cytology was negative for atypical cells. Abdomen ultrasound revealed 6 mm mass of posterior portion of bladder. For gastrointestinal symptoms, patient received Total Parenteral Nutrition (TPN) and underwent Esophageal-Gastro-Duodenoscopy (EGDS) with biopsy that found diffusely edematous, hyperemic and hypertrophic mucosa from fundus to antral region of stomach; duodenal mucosa was edematous and hyperemic with some superficial erosions. Histological examination revealed neoplastic cells positive for GATA3, CK7, p63 at Immunohistochemistry analysis, with a possible urothelial origin. There was no alteration of mismatch repair proteins (MLH1, PMS2, MSH2, MSH6).

A (18F) Fluoro-Deoxy-Glucose (FDG) Positron Emission Tomography (PET) in Combination with CT (PET-CT) showed elevated uptake of stomach (SUVmax 10.9) (Figure 1), left armpit (SUVmax 6.4) (Figure 2), right and left superclavear lymph nodes (SUVmax 5.5 and 5.6, respectively) (Figure 3) and peritoneum (SUVmax 3.8). Based on the long progression free survival after first line chemotherapy treatment, the good tolerance of first line of chemotherapy, the good clinical condition and young age of patient, between October and December 2020, were administered 4 cycles of intravenous chemotherapy with gemcitabine 1000 mg/m^2 on days 1-8 q21 plus cisplatin 70 mg/m^2 on day 1-q21. Then, FDG-PET-CT revealed a partial metabolic response, in particular, there were no uptake in stomach and peritoneum and there was uptake reduction of left armpit (SUVmax 2.5), right and left superclavear lymph nodes (both with SUVmax 3). A Cystoscopy of control was negative. For the disappearance of abdominal symptoms and the recovery of normal weight (/increase of weight), TPN was interrupted with a gradually intake of oral food. On January 20th, 2021 was administered, the patient was in good clinical conditions, he accused only G1 nausea and G1 vomiting from day 1 to day 3 of chemotherapy and G1 fatigue.

Ten days later after the fifth cycle of chemotherapy, for the onset of frontal headache, diplopia and visual blurring, the patient underwent ophthalmological evaluation showing bilateral hyperemic and edematous papillae with flame hemorrhages and peripapillary exudates. A brain CT scan described intracranial hypertension without brain metastatic lesions. There was mild tortuosity of the optic nerves and mild ectasia of perioptic sheaths, and a slight appearance detected of both optic papillae. There were no neurological alterations at clinical examination. So, he was admitted in the Neurology department. Neurological evaluation found diplopia with a deficit of left VI cranial nerve, mild anisocoria major on the left than right. A brain MRI confirmed intracranial hypertension and contrast enhancement involving of leptomeninges. A lumbar puncture was performed. Cerebrospinal Fluid (CSF) was colorless, transparent, glucose and protein levels were normal (57 mg/dl and 46 mg/dl, respectively), chloride was 131 mEq/l; cells count was increased (50 cells/µL) with lymphocytes and atypic cells. Cytological CSF examination revealed atypic cells positive for GATA 3 and negative for p63 and TTF1, with a possible metastatic localization of urothelial carcinoma. Microbiological examination and CSF antibodies research

were negative.

Frontal headache was stopped after pharmacological treatment with acetazolamide but there was no benefit in left visual loss and appeared vomiting. The patient was transferred to the Oncology Department, for other evaluation and treatment. He received steroid, anti-emesis and anti-edema therapy. For leptomeningeal carcinomatosis, we decided to administer Intrathecal (IT) methotrexate 12 mg weekly and concomitant second line of systemic treatment with the checkpoint inhibitor pembrolizumab at flat dose of 200 mg intravenous on day 1 q21n (a total of four cycles were administered). Next Generation Sequencing (NGS) evaluation of DNA and RNA was performed in CSF of the first IT infusion, identifying uncommon alteration of exon 11 of *BRAF* gene (G466V) (missense) and of exon 3 of *AKT1* gene (E17K) (missense), did not found alteration of *BRCA1* gene. NGS examination performed to the following IT infusion did not identify gene alterations.

After 4 doses of IT chemotherapy, CSF was colorless, transparent, glucose level was normal (54 mg/dl), protein was 68 mg/dl (elevated), chloride was 123 mEq/l (normal), cells count was decreased (1 cells/μL) but cytological CSF examination was still positive for atypical cells, so this treatment was interrupted after five IT methotrexate infusions.

At the beginning of April, he was admitted in the Oncology department because of sepsis from *Pseudomonas aeruginosa*; during the hospitalization he underwent a brain RMI which showed stable intracranial hypertension without contrast enhancement in leptomeninges. From the middle of April, his clinical condition became worse and worse because of the onset of epileptic seizures and progressive postural instability. He passed away at the beginning of May, three months after the diagnosis of LMC.

Discussion

Urothelial carcinoma of ureter and renal pelvis is rare, representing respectively 1% and 5% of all urothelial cancers. On the contrary, the most common histology of Bladder Cancer (BC) is urothelial one. More often these tumors metastasize to lymph nodes, liver, bone and lung [1]. Our patient showed atypical sites of metastasis, such as stomach, peritoneum, left axillary, right and left supraclavicular lymph nodes. Moreover, he had Leptomeningeal Carcinomatosis (LMC), which is absolutely an atypical site of metastasis of this kind of tumor.

Leptomeningeal Carcinomatosis (LMC) consists in cancer cell localization in pia mater, arachnoid and in the space between them, called subarachnoid space. It is also called leptomeningeal disease and leptomeningeal metastasis. The percentage of solid tumors and hematologic malignancies that metastasize to leptomeninges is about 5% to 8% and 5% to 15%. More often, lung cancer (9% to 25%), breast cancer (5% to 8%) and melanoma (6% to 18%) could show this particular metastatic site, with major incidence in some histological subtypes such as lobular histology and triple-negative molecular subtype for breast cancer and Non-Small Cell Lung Cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR)-mutant disease.

In general, the incidence of LMC has increased because of new detection instruments for diagnosis. Most therapeutic arms are developing to control this kind of disease.

About 1.2 to 2 years occur from diagnosis of systemic solid cancer to LMC [4]. Specifically, our patient developed LMC after 2 years. Onset symptoms were headache and blurred vision. When LMC started, FDG PET/TC showed partial response of the other metastasis sites. To our best knowledge, only two cases of metastatic urothelial cancer of upper urinary tract and LMC were reported in literature. Imamura et al. describe a case report where otologic symptoms (facial nerve paralysis and bilateral hearing loss) were the first clinical presentation of LMC from transitional carcinoma of renal pelvis: these symptoms were connected to the infiltration of malignant cells in temporal bone [5]. In Matsushita et al. case report it is described a transitional carcinoma of bladder and ureter, where LMC symptoms developed sixteenth month after radical cystectomy and right nephroureterectomy, and then patient died six days after LMC diagnosis [6].

Actually LMC therapy consists in Intrathecal Therapy (IT), systemic chemotherapy and radiotherapy [2]. Our patient was treated with five administrations of intrathecal methotrexate 12 mg once weekly. Moreover, in February 2021 he started second-line therapy with Pembrolizumab 200 mg flat dose every three weeks for four cycles.

Umezawa et al. [2] collected 33 cases of LMC and metastatic BC; the majority of them were urothelial carcinoma, except for two cases with different histologies (adenocarcinoma and small cell neuroendocrine carcinoma).

As in most cases described in this review, our patient has developed LMC during the first-line chemotherapy, after the histological diagnosis of gastric relapse. Umezawa et al. [2] reported that twenty-four patients were treated, while nine patients did not receive any treatment because their clinical conditions quickly became worse. 14 of 24 treated patients (58.3%) received IT chemotherapy (methotrexate alone in 13 pts, unknown in 1 pt). Seven patients (29.2%) underwent a radiotherapy treatment (in 1 craniospinal radiotherapy, spinal radiotherapy in 1, and whole-brain radiotherapy in 5). Finally, two patients (8.3%) received systemic medical treatment, based on MVAC or Gemcitabina [2].

In the present case, it was administered a combined treatment (IT and systemic immune-checkpoint inhibitor). If we analyze the review just mentioned, we can observe that seven patients, who underwent IT, received another therapy: Six patients also radiotherapy and one also systemic chemotherapy.

A recent case report describes LMC in a bladder cancer and its treatment: After the clinical and radiological manifestation of LMC, patient received whole-brain radiotherapy (30 Gy) and then immunotherapy, Pembrolizumab 200 mg, but he died of bladder cancer one month after the diagnosis of LMC [7].

Therefore in literature there is not a description of a treatment similar to our case: IT with MTX 12 mg weekly and Pembrolizumab 200 mg q21.

According to the prognosis, our patients passed away 3 months after the diagnosis of LMC. Umezawa et al. [2] confirm the poor prognosis: 35 days (interquartile range: 16 to 134 days) was the median survival time from the diagnosis of LMC, except for rare cases.

In conclusion, advanced urothelial cancer of upper urinary tract has low survival rates [8]; if we add LMC's median survival time, the final prognosis becomes really adverse, like in our case report.

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