Urothelial carcinoma masquerading as retroperitoneal fibrosis: A case report

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Abstract. Retroperitoneal fibrosis, a rare and often idiopathic condition, poses significant diagnostic challenges. While most cases are considered idiopathic or immune-mediated, a small but important proportion are associated with malignant neoplasms, with implications for prognosis and management. The present study describes the case of a 69-year-old man who presented to the emergency department of the Virgen de las Nieves University Hospital (Granada, Spain), with a 2-week history of epigastric pain, vomiting and altered bowel habits. Laboratory investigations revealed previously undiagnosed renal insufficiency. An abdominal computed tomography (CT) scan showed extensive diffuse retroperitoneal infiltration extending from the periduodenal region to the pubic bone, resulting in gastric dilatation and hydronephrosis. A CT-guided retroperitoneal biopsy was performed and pathology confirmed the presence of urothelial carcinoma. This diagnosis led to the initiation of a chemotherapy regimen consisting of carboplatin and gemcitabine specifically designed for urothelial carcinoma. A follow-up 18F-FDG PET scan performed 6 months later showed a partial functional response. This case illustrates a rare presentation of urothelial carcinoma masked by extensive retroperitoneal fibrosis, and highlights the importance of accurate diagnosis in reducing tumor burden and improving the clinical status of patients.

Introduction

Retroperitoneal fibrosis (RF) is a group of conditions characterized by abnormal growth of fibroinflammatory tissue around the abdominal aorta, inferior vena cava, and iliac vessels. This proliferation can affect nearby structures, often compressing the ureters and ultimately leading to renal damage (1).

Most cases of RF are idiopathic and associated with IgG4; other non-malignant causes include radiation, medications, inflammation, or trauma. The pathogenesis of RF is still unknown, but immune responses may play an important role. Clinical symptoms are nonspecific and may include constitutional symptoms. Laboratory tests may show elevated erythrocyte sedimentation rate and C-reactive protein and variable renal insufficiency as nonspecific findings (1).

However, 10% of cases may be associated with neoplasms, such as metastases from carcinomas, sarcomas, or lymphomas (2,3). The distinction is clinically crucial, as malignant RF has a poor prognosis, with a median survival of only 3 to 6 months (4). Imaging studies are therefore of paramount importance in this context, as they can both detect and characterize the lesion and possible complications and suggest the most plausible diagnosis.

We describe a case of urothelial carcinoma (UC) with atypical radiological features resembling RF and presenting with upper gastrointestinal symptoms. Diagnosis required image-guided biopsy and histopathology, which allowed tailored treatment resulting in reduced tumor burden.

Urothelial tumors are rarely associated with RF, and only a few cases have been described in the literature (5,6), none of which showed such extensive retroperitoneal involvement or have demonstrated response to treatment.

Case report

A 69-year-old man, with a history of smoking and alcoholism, presented to the Emergency Department of the University Hospital Virgen de las Nieves in May 2023 with epigastric pain, vomiting, and altered bowel habits of 2 weeks' evolution.

Laboratory tests revealed an elevated C-reactive protein level of 279 mg/dl (normal range <3 mg/dl) a serum creatinine level of 2.8 mg/dl (normal range 0.7-1.2 mg/dl), significantly elevated from his normal baseline, and a serum urea level of 73 mg/dl (normal range 12-54 mg/dl). Diuresis was preserved without pollakiuria or dysuria. These findings were consistent with acute renal failure. Urinalysis showed no significant changes, raising doubts about the underlying nature of the

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renal failure. Physical examination revealed pitting edema of both lower extremities. The patient reported no fever or night sweats.

An initial abdominal ultrasound showed bilateral hydronephrosis, gastric dilation, and thickening of the duodenal wall. A subsequent abdominal computed tomography (CT) scan was performed and showed extensive diffuse retroperitoneal infiltration from the periduodenal region to the pubis, causing gastric dilation and hydronephrosis (Fig. 1).

Urological evaluation by endoscopy was unsatisfactory due to the inability to visualize the ureteral orifice due to the bladder floor mass and the extrinsic compression of the lesion which prevented placement of the double J catheter. Upper gastrointestinal endoscopy revealed congested gastric folds and gastric biopsy was negative for neoplasia (Fig. 2).

A CT-guided core-needle biopsy of the right perirenal infiltrative lesion showed a diffuse infiltration of neoplastic cells amidst retroperitoneal adipose fibrosis. Immunohistochemical analysis firmly established the diagnosis of UC and excluded differential diagnoses. Specific markers such as TTF1, NKX3.1, CDX2, SATB2 and Hepar1 were negative, excluding pulmonary, prostatic, intestinal, and hepatic origin. The urothelial origin of the neoplasm was confirmed by positive staining for keratin 7, keratin 20, p40 and especially GATA-3, together with strong positivity for uroplakin II and absence of carcinoembryonic antigen (CEA) expression. This profile also effectively excluded lymphoid neoplasms due to keratin positivity, neoplasms of biliary origin due to CEA negativity, and various types of renal cell carcinoma due to the absence of PAX-8 (Fig. 3).

Positron emission tomography with 18F-fluorodeoxyglucose (18F-FDG PET) demonstrated moderate metabolic activity in the described retroperitoneal mass without evidence of other lesions or adenopathy consistent with metastasis elsewhere (Fig. 4A). The case was discussed in a multidisciplinary tumor board. There was a small nodule in the bladder that was disproportionate to the retroperitoneal infiltration and did not allow identification of the bladder as the primary site (Fig. 1D). The inaccessibility of the lesion during cystoscopy due to pelvic compression secondary to the retroperitoneal disease led to the decision not to consider transurethral resection of the bladder (TURB) in the diagnostic process.

The lesion was diagnosed as stage IV advanced metastatic UC based on histopathologic biopsy findings in the perirenal retroperitoneum. Periduodenal, periureteral, lateral pelvic, and perirectal infiltrates observed on radiologic studies were also diagnosed as retroperitoneal metastases (Fig. 1C-E).

Due to his renal insufficiency, the patient could not receive cisplatin, so he received an individualized chemotherapy regimen of carboplatin and gemcitabine. This regimen consisted of a series of four 21-day cycles. Carboplatin was administered on the first day of each cycle and the dose was calculated to achieve an area under the curve (AUC) of 4.5. This calculation was individualized for each cycle, taking into account the patient's renal function according to the Calvert formula (7). At the same time, gemcitabine was administered on the first and eighth day of each cycle at a dose of 1,000 mg/m^2. This dose was carefully determined according to the patient's body surface area.

A follow-up 18F-FDG PET scan performed 6 months later showed a significant reduction in the extent of the retroperitoneal lesion, consistent with a partial functional response (Fig. 4B). At the most recent follow-up visit in January 2024, the patient reported improvement in digestive symptoms and improvement in lower extremity edema. Creatinine improved to 2 mg/dl. The patient is currently receiving maintenance immunotherapy with Avelumab.

Discussion

RF is a rare condition of unclear pathogenesis characterized by the formation of a soft tissue mass around the prevertebral area, encircling the aorta and iliac arteries. The ureters may also be involved leading to entrapment and hydronephrosis, as in the case presented. The signs and symptoms of RF are variable and are not helpful in the differential diagnosis of other conditions, such as non-specific abdominal pain or lower extremity edema, leading to delayed diagnosis (1).

Metastatic spread of urothelial carcinoma to the gastrointestinal tract is rare and tends to involve the rectum in bladder cancer (8). Upper gastrointestinal symptoms, such as vomiting and epigastric pain due to duodenal obstruction in our specific case, are rare because extrinsic malignancy of the duodenum in urothelial cancers of the upper urinary tract and bladder is uncommon, with few documented cases (9-11). Tokunaga *et al* (9) reported two cases of bladder cancer in which abnormal perirectal tissue was initially identified and classified as stage M0. Subsequently, both cases evolved with the development of RF adjacent to the duodenal wall, although less pronounced than in our study. On the other hand, Andersen *et al* (11) described a case of UC of the renal pelvis with retroperitoneal extension leading to duodenal obstruction. Similarly, Iwamoto *et al* (10) documented a case in which periduodenal tissue was detected and reported as inflammatory changes unrelated to the primary tumor, with the final diagnosis made postmortem. These reports suggest that the presence of fibrosis or retroperitoneal inflammatory changes associated with UC, although less obvious on imaging than in our case, deserves detailed evaluation for its potential impact on the evolution and clinical management of patients.

The existing literature has demonstrated the association of RF with malignancy in tumors in a variety of sites, including the prostate, rectum, colon, stomach, or lung, although it is difficult to diagnose and differentiate from other secondary conditions coexisting in the same anatomic location (12,13). Lymphomas, sarcomas, or irregular lymph node metastases can look very similar to RF on a CT scan (14). They are difficult to detect on CT, and the signs that have been described to suggest a neoplastic cause are often non-specific. These signs include anterior displacement of the abdominal aorta and inferior vena cava or extension into the renal hilum with lateral displacement of the ureters (2). Idiopathic RF tends to present as a plaque-like density, whereas neoplasms show nodularity and peripheral lobulation (15). Some studies have highlighted the tendency of lymphomas to have a more cranial distribution, often involving the posterior mediastinum, whereas benign RF occurs predominantly caudal to the renal hilum (14). We suggest that the extensive involvement observed in our case, particularly the concentrated involvement of the perirectal and perivesical fat

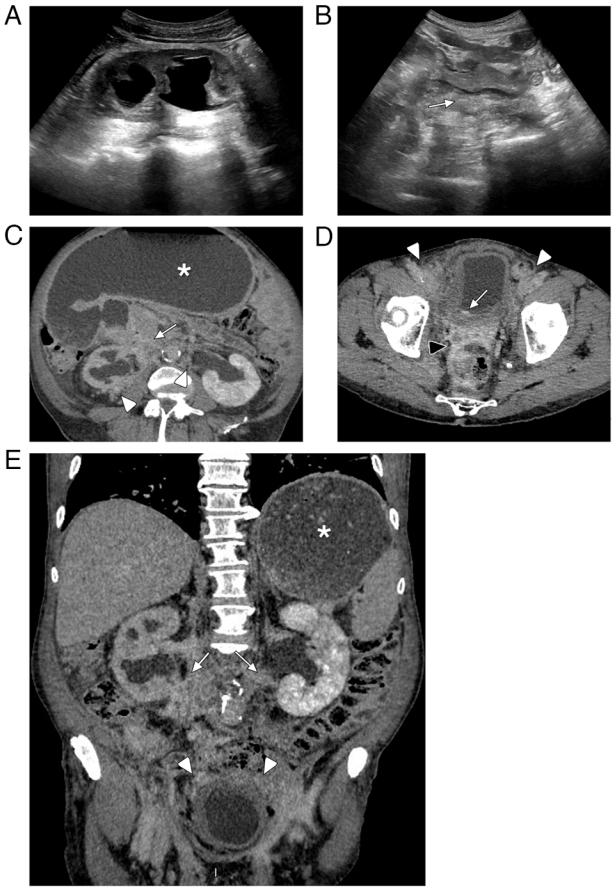

Figure 1. Ultrasound and CT findings of the lesions. (A) Abdominal ultrasound shows right hydronephrosis with decreased cortical thickness. (B) Ultrasound slice shows thickening of a duodenal segment with increased echogenicity of its posterior wall (arrow). (C) Late phase contrast-enhanced CT shows an enhancing infiltrative lesion in the retroperitoneum. The lesion surrounds the aorta and inferior vena cava, extends to the duodenal wall (arrow), and causes gastric dilatation (*). It involves both perirenal spaces (arrowheads) and causes bilateral hydronephrosis with right renal atrophy. (D) CT of the pelvis scan shows a diffuse pelvic infiltrative lesion involving both inguinal ducts and pelvic sidewalls (white arrowheads) and perirectal fat (black arrowhead). Note the thickening of the bladder wall and the small enhancing nodule adjacent to the right ureterovesical junction (arrow). (E) Coronal section showing enhancing tissue in the bilateral proximal periureteral (arrows) and perivesical (arrowheads) areas. CT, computed tomography.

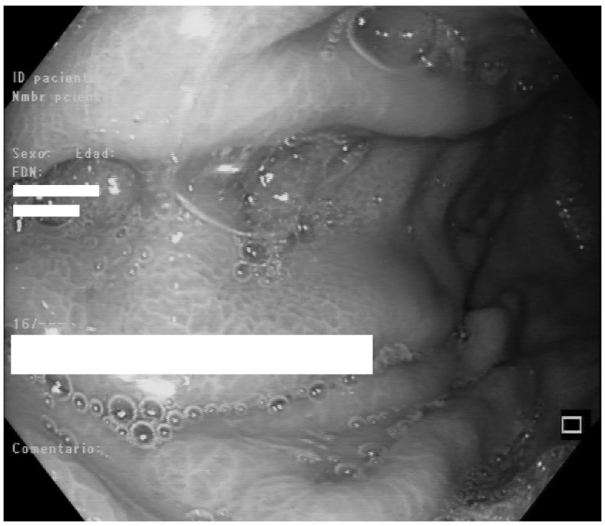

Figure 2. Gastroscopic image visualized at the level of the gastric body showing gastric folds with a congested and edematous appearance with good distensibility.

and the inguinal canals, serves as a strong impetus to investigate the possibility of a secondary neoplasm. This is exemplified by our patient's condition, where such an extensive pattern of disease was a key indicator that prompted further investigation.

Cases of RF associated with urothelial carcinoma are rare, but present unique diagnostic challenges and insights. For example, Murray and Woo-Ming (6) reported a case characterized by normal cystoscopy and inability to catheterize the ureters along with duodenal obstruction in its third portion caused by fibrotic plaque. A biopsy from the right fossa showed only RF and the definitive diagnosis was made post mortem. Conversely, the case documented by Reiner *et al* (5) involved a patient whose cystoscopic biopsy failed to identify tumor cells. The suspicion was raised by urography and subsequently confirmed by surgery.

The underlying mechanism driving the development of RF in carcinoma is unknown. The ability to disseminate from the original site and migrate into the surrounding stroma could be explained by the loss of E-cadherin expression via the epithelial-mesenchymal transition (EMT). Fibrosis may be facilitated by an intense desmoplastic reaction that, when occurring in the retroperitoneum, may encapsulate abdominal organs and major blood vessels. Spread through the retromesenteric and interfascial planes connecting the retroperitoneum from the duodenum to the inguinal region would explain the findings seen in this case (1,3,16).

Malignant RF is refractory to pharmacologic treatment with immunosuppressants. Therefore, the focus should be on the diagnosis and treatment of the underlying neoplasm (17). Because recognition of a neoplastic cause alters the therapeutic approach, management algorithms for the diagnosis of secondary RF have been proposed, emphasizing the need for PET to detect active fibrosis or cancer and to guide biopsy (18,19). An optimal diagnostic strategy for the effective detection of this type of RF should include a CT scan to define the extent of the disease. In addition, it is essential to perform a PET scan to identify the most hypermetabolic areas, followed by a targeted biopsy of the most suspicious or accessible areas for the procedure.

In this case report, the diagnosis of UC was primarily suggested by histopathology, but the lack of a clear origin in the bladder or ureter added complexity. What makes this case novel is the unusually extensive RF seen on CT imaging involving both genitourinary systems, the bladder, and beyond. This extensive involvement, coupled with a small nodule in the bladder that appears disproportionate to the retroperitoneal infiltration, obscures the bladder as the primary site. In addition, the behavior of the lesion, involving the upper urinary tract and retroperitoneum without presenting as an expansile lesion or showing adenopathy metastasis, mimics RF on imaging. These peculiar and novel features make this case exceptional and demonstrate an atypical presentation of UC.

According to the European Association of Urology guidelines, both upper urinary tract and bladder urothelial cancer respond to platinum-based systemic chemotherapy, with

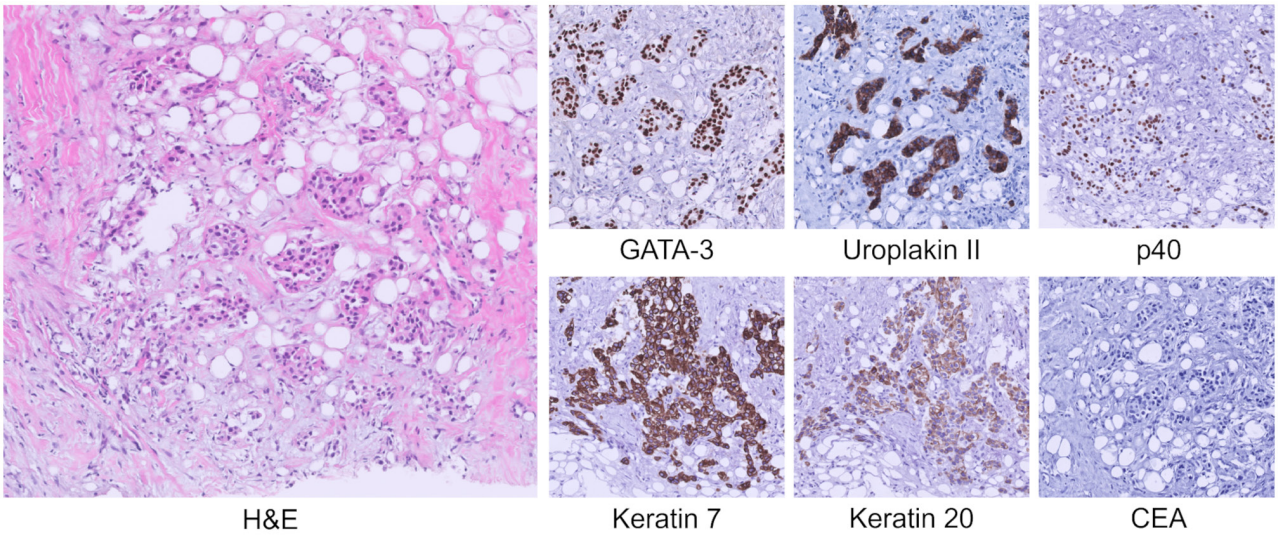

Figure 3. Pathologic diagnosis of urothelial carcinoma: Hematoxylin and eosin staining shows cohesive cell clusters with differentiated eosinophilic cytoplasm and nuclei that are mildly to moderately basophilic. These are arranged within a fibrous stroma infiltrating the retroperitoneal fat. Immunohistochemical analysis at 20x magnification shows strong positivity for uroplakin II and GATA-3. This together with the expression of keratin 7, keratin 20 and p40 and the absence of CEA supports a urothelial origin of the neoplasm.

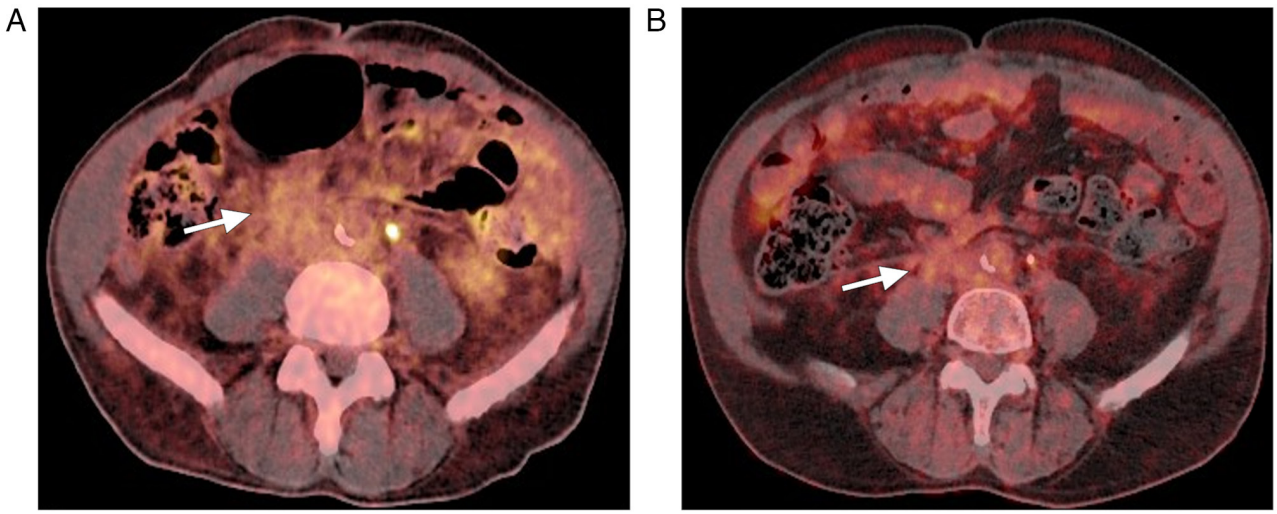

Figure 4. (A) Initial PET-computed tomography scan showing hypermetabolism over a retroperitoneal abdominal tumor including the para-aortic region (arrow) and the pelvis. (B) Control at 6 months showing a significant decrease in size of the retroperitoneal lesion consistent with a partial functional response (arrow), with no other new hypermetabolic lesions.

cisplatin-based combination chemotherapy being the standard of care for advanced or metastatic urothelial cancer. The use of cisplatin-based chemotherapy is widely considered for patients with an estimated GFR >45 ml/min. In patients ineligible for cisplatin, the combination of carboplatin and gemcitabine is recommended, as in our patient (20,21). Maintenance immunotherapy with avelumab is the recommended standard of care for patients whose disease has stabilized after first-line platinum-based chemotherapy (22).

The treatment of advanced UC and malignant RF is a major challenge in oncology due to the aggressiveness of these diseases and the lack of effective therapeutic options. RF-associated cancers are often diagnosed at advanced stages, which limits the chances of successful treatment, with a median survival of only 3 to 6 months (4). The lack of treatment options that provide durable remissions and prolonged survival is an ongoing unmet need for urothelial cancer patients (23). Treatment of advanced urothelial cancer with gemcitabine and carboplatin has shown a limited median overall survival of approximately 9.8 months (24). No data have been found in the literature regarding the treatment and prognosis of cases of UC with this unusual presentation.

Future lines of research should be directed at further exploring the association between RF and malignancy, improving the understanding of the biology of UC, and including the development of treatments that specifically target molecular pathways involved in disease progression and the development of malignant RF. In addition, research in immunotherapy and targeted therapy offers hope for improved

outcomes in this patient population. A multidisciplinary approach to the management of these patients is essential.

In conclusion, the unusually extensive retroperitoneal infiltration documented on CT in this patient underscores the need for a comprehensive evaluation to identify the underlying cause. Furthermore, the positive response to chemotherapy with carboplatin and gemcitabine, as demonstrated by PET/CT follow-up, emphasizes the importance of early diagnosis and appropriate management of these unusual clinical presentations.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AM was responsible for the initial diagnosis and the study design. DL and AS performed the biopsy and contributed substantially to the conception, design and writing of the manuscript. JP and MC performed the histopathological examination and participated in the imaging process. DL and JP confirm the authenticity of all the raw data All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the case information and images to be published in this case report.

Competing interests

The authors declare that they have no competing interests.

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