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Letter to editor

# The pitfalls of an invasive non-neuroendocrine GATA3- and TTF1+ urothelial carcinoma

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Dear Editor,
in February 2020 a 58-year-old man was referred to the Urology Department for dysuria and hematuria. He had a history of smoking, high blood pressure and hypercholesterolemia. A urinary cytologic test showed atypical urothelial cells and he therefore underwent cystoscopy with trans-urethral resection of the bladder (TURB). Histological assessment without immunohistochemical (IHC) support revealed the presence of a high-grade papillary urothelial carcinoma (UCC) with foci of UCC in situ. He was then treated with intra-vesical Bacillus Calmette-Guérin (BCG). A follow-up TURB was performed in September 2020, without evidence of disease. The patient presented again with gross hematuria in December 2021. Cystoscopy revealed a lesion in the left vesical wall. Pathological investigation of the new TURB specimen showed highgrade infiltrative UCC with evidence of muscularis propria involvement. Imaging studies did not show any sign of other lesions in the body. In February 2022 a radical cystoprostatectomy, combined with the removal of pelvic and obturator lymph nodes, was performed. The surgical specimen featured a neoplastic mass that was also involving a vesical diverticulum, together with UCC in situ and with both gross and microscopic peri-vesical adipose tissue infiltration (Fig. 1A and 1B). Histologically, the lesion had a solid growth, with necrotic foci and focal myxoid areas. At high-power, tumoral cells had an epithelioid phenotype, with evident nucleoli and slightly granular cytoplasm. Metastatic disease was present in a regional lymph node (Fig. 1C).
While no clear areas of divergent differentiation were identified, the neoplastic population was reminiscent of a large cell neuroendocrine carcinoma (NEC) [1]. Hence, the proliferation was tested with IHC reactions in order to investigate a neuroendocrine differentiation. The neoplasm turned out to be diffusely positive for CK AE1/AE3 and CK Cam5.2, with focal areas expressing HMWCK (CK34bE12 clone). Unexpectedly, not only neuroendocrine markers (synaptophysin, chromogranin, INSM1 and CD56) but also urothelial makers were negative (GATA3, uroplakin III and p63; Fig. 1D), with the exception of GATA3-positive UCC in situ. While these results ruled out a neuroendocrine differentiation, they also

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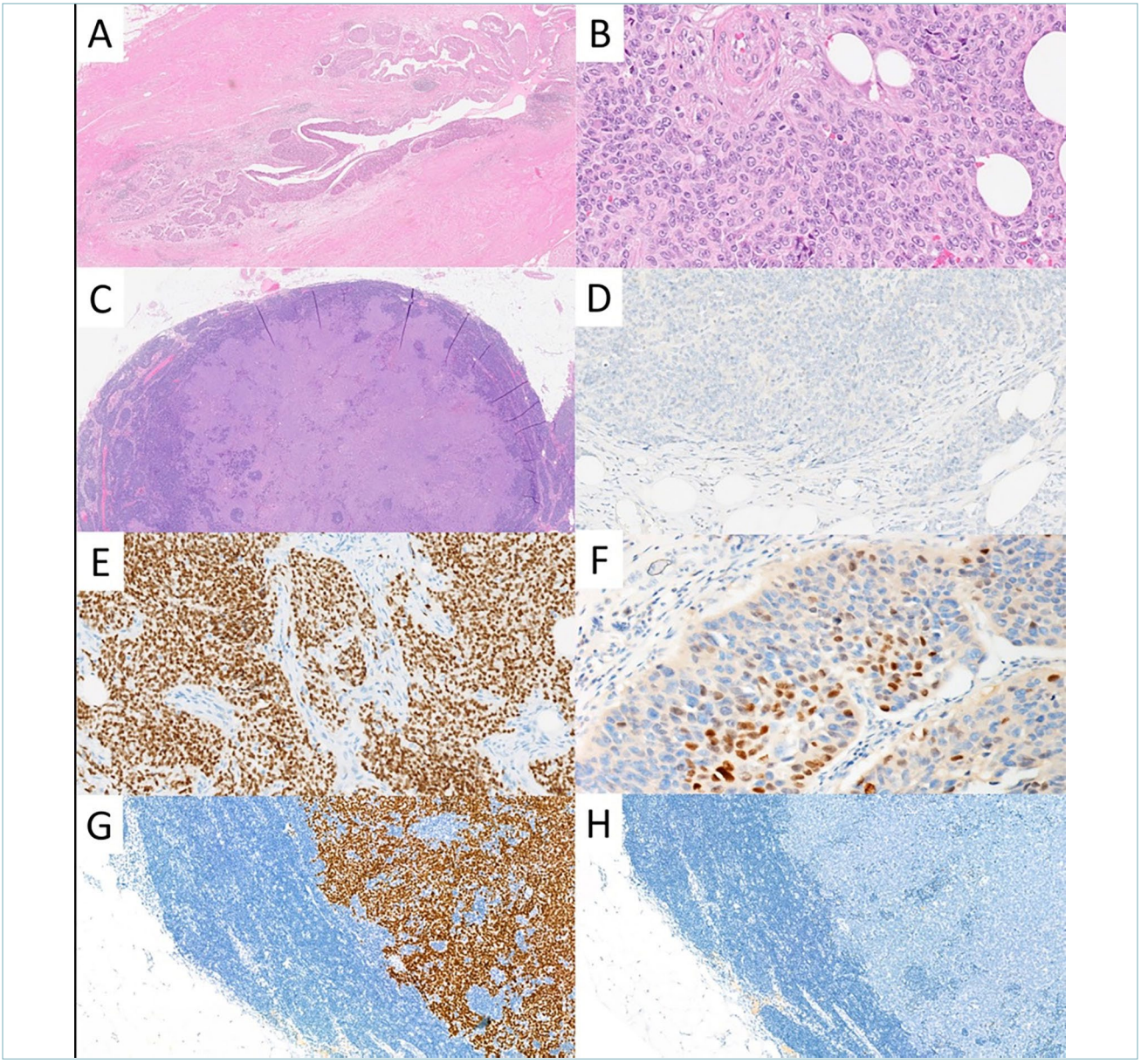


**Figure 1.** A) Vesical-diverticulum-derived urothelial cell carcinoma (UCC) in surgical specimen; B) Tumoral cells with an epithelioid phenotype, with evident nucleoli and slightly granular cytoplasm, C) Metastatic UCC to a regional lymphnode; D) GATA3 in infiltrative UCC; E) TTF1 (SPT24 clone); F) TTF1 (8G7G3/1 clone) in UCC in situ; E) TTF1 (SPT24 clone) in metastatic cells; F) GATA3 in metastatic cells.

brought to fear the possibility of a vesical metastasis from a different organ (with concomitant UCC in situ). Therefore, further site-specific markers were tested. The neoplasm was NKX3.1-negative, but diffusely positive for TTF1 (SPT24 clone) (Fig. 1E). Following these results, the neoplasm was also tested with TTF1 8G7G3/1 clone, which retained some expression, mainly present in the most superficial areas of the tumor (Fig. 1F). Metastatic cells to the lymph node showed the same TTF1+ GATA3- pattern of expression (Fig. 1G, H).

Putting together clinical, morphological and IHC information, despite the unusual IHC phenotype, a diagnosis of high-grade invasive UCC of the bladder was dismissed. Following surgery, three doses of gemcitabine+cisplatin were administered. Further cycles

were hindered by declining renal function. A positron emission tomography (PET) scan in July 2022 showed only minimally increased signal in iliac and abdominal lymph nodes. In December 2022 the patient was hospitalized for acute kidney injury. A new PET scan identified pathologic tissue involving the pelvic fossa, together with nodular areas on the abdominal wall and with thoracic and abdominal pathological lymphnodes. In January 2023, two cycles of pembrolizumab were administered as second-line therapy, but the patient died of multiorgan failure.

We believe our case highlights how, even if the aid of IHC markers has become of paramount importance to define tumor type and assign site of origin in modern pathology [2], clinical information and morphological data acquired with hematoxylin and eosin staining are still key factors in diagnosis [3]. The atypical GATA3- TTF1+ IHC expression pattern of UCC was present also in a metastatic regional lymph node. This could have led to a misdiagnosis, especially if the initial presentation had been at a distant metastatic site from an unknown primary neoplasm or IHC results had been put above morphological evaluation.

TTF1 is a transcription factor (TF) widely employed as a marker of pulmonary and thyroid tumors [4]. In the lung, it is mostly used to differentiate adenocarcinoma from squamous cell carcinoma, mesothelioma and metastases[4]. Different authors agreed upon different performance based on the antibody clone of choice. While 8G7G3/1 is more specific, SPT24 is more sentitive [4]. As NECs are entities with a frequent promiscuous expression of site-specific antigens, TTF1 presence has also been repeatedly described in both small- and large-cell vesical NECs, along with common general neuroendocrine markers (i.e. CD56, synaptophysin, chromogranin, INSM1) [5]. Conversely, TTF1 expression in non-neuroendocrine bladder urothelial carcinoma has received little attention in the literature [6].

GATA3 is also a TF that can be used to confirm urothelial origin, alongside uroplakin, p63/p40, high-molecular-weight cytokeratin (HMWCK) and CK5/6 [7]. Interestingly, GATA3-negative UCCs are considered to have a non-luminal differentiation [8]. The latter includes: basal phenotype, with CK5/6 positivity; mesenchymal-like phenotype, with sarcomatoid differentiation; neuroendocrine-like phenotype, with neuroendocrine areas and synaptophysin positivity [8].

In conclusion, this case draws attention to the possibility of promiscuous expression of site-specific antigens even in non-NECs and that it is still of paramount importance to gather of clinical and morphological data, alongside IHC and molecular results, to get to the final diagnosis.

### Conflicts of interest

Authors have no conflicts of interest to declare.

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None.

### Authors' contributions

Report concept and design: CP, GMP. Acquisition of clinical and pathological data: CP, MG, GMP. Drafting of the manuscript: GMP. Critical revision of the manuscript for important intellectual content and supervision: CP, MG, MC, GMP.

### Ethical consideration

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

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