Somatically derived Yolk Sac tumor of the urinary bladder: A case report and differential diagnosis

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Abstract
Background: Yolk sac tumor is a germ cell neoplasm that arises predominantly in the gonads, but can also derive from somatic neoplasms in extragonadal locations. These cases have been denominated recently as “somatically derived Yolk sac tumors”, and have been documented in several locations, although reports from the urinary tract are scarce. To our knowledge, this is the first report of a Yolk sac tumor derived from urothelial carcinoma.

Case presentation: We present a unique case of a 76-year-old man with a recurrent urinary bladder tumor, initially interpreted as a high grade urothelial carcinoma with glandular differentiation. In the recurrent tumor, diverse histological patterns were identified, including glandular, hepatoid and sarcomatoid. This tumor showed positivity for AFP, GLP3 and SALL4, and negativity for CK7 and EMA. Fluorescent in situ hybridization study showed a polysomic pattern of chromosome 12. All these findings led to the final diagnosis of a Yolk sac tumor derived from urothelial carcinoma.

Conclusions: Somatically derived Yolk Sac tumors should be considered in the differential diagnosis of a high grade urothelial carcinoma, particularly when glandular and other unusual patterns are observed. Key words: Yolk sac tumor, somatically derived, urothelial carcinoma, urinary bladder, case report.

Background
Yolk sac tumor (YST) is a germ cell neoplasm that arises predominantly within the gonads, but a significant minority of cases can be found in extragonadal midline locations, such as sacrococcygeal region, mediastinum, retroperitoneum and brain [1]. YSTs may also derive from somatic neoplasms. This group of YSTs has been denominated recently as somatically derived YSTs (SD-YSTs), and several cases have been reported, mainly from gastrointestinal and gynecologic sites [2]. However, published cases from urinary tract are scarce [3]. Herein, we present a case of a recurrent urinary bladder neoplasm, initially diagnosed as an urothelial carcinoma with glandular differentiation, which showed multiple unusual histological patterns, and raised the diagnostic possibility of a SD-YST. This report aims to increase the limited literature for YSTs derived from urothelial neoplasms.

Case Presentation
A 76-year-old man with previous history of smoking, type 2 diabetes mellitus, dyslipidemia, high
blood pressure and alkaptonuria with achronotic arthropathy, was referred to our hospital by edema in lower extremities and renal dysfunction. Image studies showed a papillary proliferation in the distal portion of the right ureter. The biopsy of this lesion revealed a high grade urothelial carcinoma (Fig. 1), and the patient was treated with a right nephroureterectomy. One year later, the tumor relapsed and the patient underwent a transurethral resection (TUR) of a lesion located in the right wall of the bladder. This sample was diagnosed as a high grade urothelial carcinoma with extensive glandular differentiation. During the subsequent year, a positron emission tomography ($^{18}$F-FDG PET/CT) showed areas of intense uptake in the urinary bladder, in multiple pelvic lymph nodes and in a mass located in the right thoracic wall, where a surgical trocar was placed during the previous nephroureterectomy. The patient was submitted to radical cystectomy, pelvic lymphadenectomy and excision of the thoracic mass.

The specimen of cystectomy showed a polypoid tumor of 10 cm diameter filling the lumen of the bladder. The tumor was implanted on the right wall, involved the right ureteral meatus and grossly extended into the paravesical adipose tissue. Macroscopically, the lesion was heterogeneous, with extensive necrotic and hemorrhagic areas. Solid areas with white-tan color were also identified (Fig. 2A). Microscopically, the tumor exhibited several components and patterns. First, an epithelial component, organized in papillary and glandular structures with tall columnar cells. These cells had clear cytoplasm and showed infra and supranuclear vacuoles, resembling endometrium or primitive intestinal epithelium. Second, an epithelial component organized in trabecular and solid patterns composed of polygonal cells with wide eosinophilic cytoplasm, central nuclei and nucleoli, similar to hepatocytes. Third, an undifferentiated stromal component with densely cellular areas composed of round, blue and small cells, intermingled with less cellular areas with myxoid stroma and nodules of chondroid tissue with atypical features. Fourth, an epithelial component with reticular and microcystic patterns, composed of atypical cells exhibiting intra and extracellular hyaline globules (Fig. 2B-F). All these components were admixed.

Immunohistochemistry results are listed in Table 1 and illustrated in Fig. 3. Fluorescent in situ hybridization (FISH) showed a polysomic pattern, but an isochromosome 12 (i12p) was not identified.
The thoracic mass showed a pure glandular proliferation with morphological and immunohistochemical features similar to those observed in the bladder tumor, and it was considered as a tumoral seeding along the surgical trocar path.

After surgery, the patient received chemotherapy cycles with poor response and several systemic complications. Pulmonary and brain metastasis were identified nine months after cystectomy. The patient died eleven months after diagnosis, and an autopsy was not performed.

| Antibody      | Observation                                                                 |
|---------------|-----------------------------------------------------------------------------|
| CK AE1/AE3    | Diffusely positive, except in chondroid nodules                               |
| CDX2          | Positive in glandular areas                                                  |
| Hep Par 1     | Positive in hepatoid areas                                                   |
| AFP           | Diffusely positive, more intense in glandular and hepatoid areas             |
| GLP3          | Diffusely positive, more intense in glandular and hepatoid areas             |
| SALL 4        | Diffusely positive, more intense in glandular and hepatoid areas             |
| GATA 3        | Negative (positive in the initial urothelial component)                      |
| VIM           | Positive in small undifferentiated cells                                    |
| OCT ¾         | Negative                                                                    |
| EMA           | Negative                                                                    |
| CK7           | Negative                                                                    |
| SYN           | Negative                                                                    |

Discussion And Conclusions

In this report we present a unique case of an YST arising from a recurrent urothelial carcinoma in a 76-year-old man. This tumor showed a mixture of several histologic patterns, including a sarcomatoid component, which is extremely infrequent.

The YSTs originated from a somatic neoplasm have been defined recently as somatically derived YSTs (SD-YSTs). These tumors may arise from benign and malignant lesions in several organs. For example, it is well documented the transformation of benign or malignant ovarian and endometrial tumors into YST [4]. SD-YSTs have also been observed in the sinonasal region, where they have been denominated teratocarcinosarcomes [5], in the stomach, colon, lung, and renal pelvis [6; 7]. To our knowledge, this is the first report of a SD-YST derived from a bladder urothelial carcinoma that was completely replaced by the germ cell tumor overgrowth in the recurrent lesion.

SD-YSTs are more frequently diagnosed in adults of 63 years-old on average, thus differing from primary extragonadal YST that are more common in young patients. High serum Alphafetoprotein
(AFP) levels may be evidenced among these patients. Regarding our case, AFP serum levels were not determined, because this enzyme is not routinely measured in post-surgical controls of adult patients with a bladder carcinoma. The elevation of serum AFP levels supports the diagnosis of SD-YST, when this determination is available.

Histologically, our case showed a mixture of diverse patterns, ranging from classical reticular-microcystic to sarcomatoid pattern with chondroid differentiation. Indeed, the most relevant histological characteristic of SD-YSTs is the identification of several patterns, which can be grouped in two categories: the classical ones, which comprise reticular-microcystic, polyvesicular, vitelline, solid and parietal patterns, and the special ones, which comprise glandular, hepatoid and sarcomatoid patterns [1]. The glandular pattern is the most frequently observed among SD-YSTs, while sarcomatoid pattern is extremely uncommon [8]. In addition to the morphologic features, the diagnosis of a SD-YST requires confirmation with a characteristic immunohistochemistry profile. A majority of SD-YST shows positivity for AFP, SALL4, and negativity for differentiated epithelial markers, such as CK7 and EMA [2]. CDX2 is usually positive in areas with glandular pattern, while hepatic differentiation markers, such as HepPar 1, may be positive in hepatoid areas. Our case showed the described immunohistochemistry profile, in agreement with the diagnosis of SD-YST. Moreover, immunohistochemistry performed in previous biopsy specimens, showed similar results in the areas of glandular differentiation (Fig. 1).

We identified genetic alterations in the short arm of chromosome 12, which showed a polysomic pattern, but an isochromosome 12 (i12p) was not identified. This pattern of 12p abnormality has been described previously in germ cell tumors of the central nervous system, although it is of unknown significance [9]. Chromosome 12 abnormalities, either as an i12p or as 12p overrepresentation, are the hallmark cytogenetic alteration of germ cell tumors. These alterations are identified in the majority of gonadal germ cell tumors, with few exceptions [10], and in somatic type malignancies, derived from germ cell tumors. However, the occurrence of chromosome 12 abnormalities is not well established in SD-YSTs. Some authors reported SD-YSTs cases without i12p, arguing that their results supported the possible somatic origin of these neoplasms [8]. However, other authors identified i12p
and other genetic alterations of chromosome 12 in tumors diagnosed as SD-YSTs [11]. The contradictory results may be due to problems in interpretation of the FISH, which is a common assay to identify i12p, but can be difficult to evaluate and lacks of ideal sensitivity and specificity [12]. Also, the results may be explained by uncertainties regarding the actual origin of the neoplastic cells in SD-YSTs, which may derive from somatic neoplastic cells through a process of retrodifferentiation or neometaplasia, or from a pluripotential embryonic stem/germ cell [2]. Currently, further investigation is required to better characterize genetic alterations in SD-YSTs, and to elucidate the actual histogenesis of these neoplasms.

Differential diagnosis included primary extragonadal YST, sarcomatoid urothelial carcinoma, chordoid urothelial carcinoma [13], and carcinoma with enteroblastic or hepatoid differentiation. Primary extragonadal YST of the bladder is extremely infrequent, and was ruled out after the revision of previous biopsies, which showed conventional urothelial carcinoma admixed with areas of glandular differentiation (Fig. 1). These areas were morphologically and histochemically similar to the glandular component of the cystectomy specimen, supporting the diagnosis of SD-YST. Sarcomatoid and chordoid urothelial carcinoma were excluded after the identification of areas with classical YST pattern and immunohistochemistry results. Carcinoma with enteroblastic differentiation has been reported in several organs (gastrointestinal, lung, etc) [14], while carcinoma with hepatoid differentiation has been mainly reported in gynecologic tumors [15]. These neoplasms show similar histologic and immunohistochemical features to those identified in our case, and according to some authors [2], enteroblastic and hepatoid tumors should be considered part of the wide spectrum of SD-YSTs.

In summary, this is a unique case of SD-YST derived from an urothelial carcinoma, showing multiple and complex histological patterns. SD-YST should be suspected in adult patients with extragonadal somatic tumors, also urothelial carcinoma, exhibiting diverse histological patterns, particularly glandular and hepatoid. The diagnosis of SD-YST requires confirmation with immunohistochemistry results, which necessarily include positivity for AFP, GLP3 and SALL4, and negativity for epithelial markers like CK7 and EMA. Elevated AFP serum levels may support the diagnosis, when this
determination is available.

Abbreviations
SD-YST
Somatically derived Yolk sac tumor
18F-FDG PET/CT
2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography
CK AE1/AE3
Cytokeratin AE1-AE3
CDX2
Caudal type homeobox 2
Hep Par 1
Hepatocyte Paraffin 1
AFP
Alpha fetoprotein
GLP3
Glypican 3
SALL4
Sal-like protein 4
VIM
Vimentin
OCT ¾
Octamer-binding transcription factor ¾
EMA
Epithelial Membrane Antigen
CK7
Cytokeratin 7
SYN
Synaptophysin
i12p
isochromosome 12
Declarations
Ethics approval and consent to participate
This case was reviewed for its publication by the Research Ethics Committee of the Hospital
Universitari de Bellvitge. Informed consent was waived in accordance with the exceptions established by legal regulations. Personal data were protected according to National and European regulations on information privacy.

Consent for publication
All authors consent to the publication of the manuscript in Diagnostic Pathology.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

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Figures
Surgical specimen of previous nephroureterectomy exhibiting a high grade urothelial carcinoma (HE10X) (a). CK7 staining was positive (20X) (b). CDX2 (c). AFP (d). GLP3 (e). SALL4 in areas with glandular differentiation (f).
Figure 2

Surgical specimen of cystectomy showing a macroscopically heterogeneous tumor. Solid areas are marked with *(a). Microscopically the tumor exhibited an area of glandular pattern with supra and infranuclear vacuoles (b). Area with hepatoid pattern (c). Area with an undifferentiated sarcomatoid component and focus of chondroid differentiation (HE20X) (d). Areas with reticular-microcystic pattern exhibiting hyaline globules (HE20X and 25X) (e-f).
Figure 3

Immunohistochemistry results. CK A1/A3 (a). EMA (b). CK7 (c). CDX2 (d). HepPar1 (e). AFP (f). GLP3 (g). SALL4 (h). GLP3 and SALL4 in sarcomatoid areas with chondroid differentiation (i-j).

Supplementary Files

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