Primary yolk sac tumour of the prostate mimicking small round blue cell tumour

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ABSTRACT

Prostatic yolk sac tumour is a germ cell tumour with a wide range of age of occurrence, unusual anatomic locations, diverse morphologic patterns, and aggressive biologic behavior, posing challenges both to diagnosis and clinical management.

We report a rare case of primary yolk sac tumour of the prostate with extensive local and liver metastasis, the latter of which exhibited sheets of small blue cells expressing CD99 and focal SALL4 on biopsy. Positivity for CD99 and GATA3 in the initial biopsy raised the differential diagnosis of Ewing sarcoma and poorly differentiated carcinoma. The primary tumour demonstrated an admixture of solid and glandular growth patterns and occasional Schiller–Duval bodies. A panel of immunohistochemical stains showing positivity for AE1/3, SALL4, CDX2, and focal alpha-fetoprotein, and negativity for OCT-4, facilitated the diagnosis.

A thorough review of the literature and our current report indicate that a large tumour load, incomplete tumour resection, limited response to preoperative neoadjuvant chemotherapy, and late stage of the disease are predictive factors for a poor clinical outcome.

Key Words Yolk sac tumours, germ cell tumours, prostate

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INTRODUCTION

Extragenadal germ cell tumours are much less common than their gonadal counterparts, comprising 1%–5% of all germ cell tumours¹. Extragenadal yolk sac tumours (YSTs), like other extragenadal germ cell tumours, are rare malignant neoplasms that typically arise in the sacrococcygeal, mediastinal, retroperitoneal, and head-and-neck regions². Only 8 cases of primary prostatic YSTs have been reported in the literature^{3–10}. Because of their extreme rarity, low index of clinical suspicion, and broad spectrum of morphologic patterns, prostatic YSTs pose a diagnostic pitfall. In addition, prostatic YSTs carry a poor prognosis, even with the advent of aggressive management with combined preoperative neoadjuvant therapy and radical prostatectomy. Here, we report a case of prostatic YST in a young adult, with a review of the literature to determine clinicopathologic features that might help to predict clinical outcomes.

CASE DESCRIPTION

A 26-year-old man with a history of urinary urgency for 6 months was treated for prostatitis. He was subsequently

admitted for worsening urinary symptoms, hematochezia, and pelvic pain. Upon admission, abdominal and pelvic computed tomography and magnetic resonance imaging showed a 12.2×11.0×9.1 cm prostatic mass [Figure 1(A)] locally invading the rectum and bladder neck, with pelvic lymphadenopathy and hepatic metastases [Figure 1(B)].

FIGURE 1 (A) Pelvic computed tomography (CT) imaging showed a 12.2×11.0×9.1 cm prostatic mass locally invading the rectum and bladder neck, with lymphadenopathy. (B) Abdominal CT imaging showed hepatic metastases measuring 1.8 cm.

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No testicular lesion was identified by physical exam or sonography.

An initial biopsy of liver showed sheets and nests of small round blue cells with hyperchromatic nuclei and small-to-moderate amounts of eosinophilic cytoplasm [Figure 2(A)]. No glandular differentiation or other characteristic morphologies were identified. Numerous apoptotic bodies and mitotic figures were noted. Immunohistochemical studies showed that tumour cells were positive for pan-cytokeratin and CD99, partially positive for SALL4 [Figure 2(B–D)] and GATA3 (not shown), but negative for OCT-3/4, Nkx-3.1, and WT1. Expression of INI1 was retained in tumour cells.

Because the liver biopsy was inconclusive, a transrectal ultrasound-guided prostatic biopsy was subsequently performed for definitive evaluation. This second biopsy exhibited an admixture of glandular, cord-like, solid, and papillary architectures [Figure 3(A)]. Schiller–Duval bodies were occasionally present [Figure 3(B)]. Immunohistochemical stains were positive for cytokeratin AE1/3, SALL4, CDX2, and alpha-fetoprotein [AFP (focal), Figure 4(D)], and negative for OCT-3/4 [Figure 4(C)], CD30, C-kit, inhibin, human chorionic gonadotropin, cytokeratin 7, keratin 20, placental alkaline phosphatase, prostate-specific acid phosphatase, and Nkx-3.1. The histologic and immunohistochemical findings were diagnostic for extragonadal yolk sac tumour.

Combined neoadjuvant chemotherapy was given, and the patient initially responded well to 4 courses of etoposide, iphosphamide, and cisplatin. Serum AFP dropped from a pre-treatment baseline of 7207 IU/mL to 7 IU/mL (Figure 5). However, the tumour progressed 5 months after completion of chemotherapy, with serum AFP rebounding

FIGURE 2 (A) The liver metastasis showed nests and sheets of small blue cells with brisk mitosis and apoptosis. The tumour cells were positive for (B) pan-cytokeratin and (C) CD99 and partially positive for (D) SALL4 (200× original magnification).

to 525 IU/mL. The patient received an additional 2 cycles of ifosfamide–paclitaxel, 2 cycles of high-dose carboplatin–etoposide, and autologous stem-cell transplantation. Given the intractable growth of the tumour, pelvic exenteration was performed.

The pelvic exenteration specimen showed a prostate grossly obliterated by a heterogeneous, ill-defined, tan-white to red-brown soft mass, with extensive hemorrhage

FIGURE 3 (A) The tumour showed mixed solid and glandular growth patterns (100× original magnification). (B) Schiller–Duval bodies were occasionally seen (400× original magnification).

FIGURE 4 The tumour cells were positive for (A) Cytokeratin AE1/3 and (B) SALL4, but negative for (C) OCT-3/4. Focal positivity for (D) alpha-fetoprotein, (E) Glypican, and (F) CDX2 was observed (100× original magnification).

FIGURE 5 Serum alpha-fetoprotein was closely followed and showed a limited chemotherapy response by the prostatic yolk sac tumour, followed by rapid progression, with a poor outcome.

and necrosis, measuring 5.2×3.4×1.5 cm. The histology of the tumour was identical to that seen in the prostate biopsy, and the tumour cells were focally positive for AFP and Glypican [Figure 4(E)]. The tumour cells had replaced the prostate and seminal vesicles, extending to the muscular walls of rectum and bladder, as well as to the pelvic wall. Lymphovascular invasion was also present.

After the surgery, the residual tumour continued to grow within the pelvis, with extension to the perineum and direct invasion of the left symphysis pubis and pre-sacral space. A liver metastasis of 2.2 cm persisted. The patient developed sepsis and succumbed 18 months after the initial diagnosis of prostatic yst.

DISCUSSION

Extragenadal yst is a rare neoplasm that arises from the midline along the rostrocaudal axis, including brain¹¹, head and neck¹², mediastinum¹³, retroperitoneum, and pelvic regions¹⁴. The tumour cells likely originate from transdifferentiated cancer stem cells within somatic tissues or from primordial germ cells or primordial germ cell precursor cells arrested during their migration in early embryonic development^{15,16}. As recognized by Teilum in 1959¹⁷, yst is a pluripotent germ cell neoplasm that has the potential to differentiate into a tumour with a wide variety of morphologies, reminiscent of extraembryonic (yolk sac, allantois) and embryonic endoderm derivatives (thyroid, lung, intestine, liver)¹⁶. For that reason, extragenadal yst remains a great challenge in both diagnosis and clinical management.

Here, we report a case of primary yst of the prostate. The patient presented clinically with nonspecific urinary symptoms and was initially treated for prostatitis. Aggravation of the symptoms led to radiologic identification of a prostatic mass and probable liver metastasis. An initial liver biopsy revealed a small round blue cell tumour that could not be definitively classified at the time. Because of the unusual site in the prostate and nonspecific morphology patterns, the profile of strongly positive cytokeratin and CD99 staining raised concern for prostatic sarcoma despite partly positive staining for SALL4. The transmembrane CD99 protein is most commonly expressed in Ewing sarcoma, lymphoma, leukemia, and sex cord stromal tumours¹⁸. However, positivity for CD99 is nonspecific, and its expression has been reported in yst¹⁹. Conversely, SALL4 is a sensitive marker for nonteratomatous germ cell tumour and is rarely expressed in mesenchymal tumours²⁰.

It is essential to identify yst by both specific and nonspecific features because it carries a poor prognosis requiring aggressive clinical management²¹. All cases of primary yst of the prostate (Table 1), except for one with unknown histology, demonstrated at least 1 of 3 main characteristic features²: a reticular or microcystic pattern (4 of 8 cases), Schiller–Duval bodies (6 of 8 cases), and intracytoplasmic or extracellular hyaline globules (4 of 8 cases). However, initial diagnoses other than yst were considered in 5 of 9 cases (56%), likely because of undersampling and nonspecific patterns (solid or glandular), a wide range of ages (1–51 years), and a low index of suspicion. Schiller–Duval bodies are more common in prostatic yst than in yst arising

from gonadal²² or other extragonadal sites¹⁴. However, that specific pattern might not be the predominant morphology and can present as “Schiller–Duval-like”⁵ or atypical or focal Schiller–Duval bodies^{5,7}.

In addition to morphology features, immunohistochemical studies facilitate the identification of a yst component, which can also arise in the background of mature and immature teratoma⁸, carcinoma of somatic origin¹⁴, or a mixed tumour, with a component of seminoma⁷. A panel of cytokeratins, SALL4, AFP, and OCT-4 is most useful for distinguishing yst from other germ cell tumours. Embryonic-derived tumours such as embryonal carcinoma or seminoma express high levels of OCT-4^{23,24}; yst is negative for OCT-4. Yolk sac tumour, choriocarcinoma, and teratoma can be positive for cytokeratins, AFP, and Glypican, but the latter two entities are mostly negative for SALL4 and placental alkaline phosphatase. In addition, endodermal lineage markers TTF1 (lung), CDX2 (intestine), and Hep Par 1 (liver) are variably expressed in yst and to some degree correlate with various yst morphologies²⁵. The expression of those markers (diffuse versus focal, strong versus weak) should be appropriately interpreted to distinguish between extragenadal yst and metastasis from lung, gastrointestinal, or hepatocellular carcinomas.

Since the introduction of cisplatin into the management of germ cell tumours in the 1970s²⁶ and the advent of preoperative neoadjuvant chemotherapy²⁷, the prognosis of patients with germ cell tumours has improved. However, the clinical outcome of prostatic yst, like extragenadal yst from other sites, is worse than for gonadal yst (Table 1). In 6 of 9 cases of prostatic yst (67%, including the present case), the patients died within 18 months of the initial diagnosis. Of those patients, 5 received a combination of radical prostatectomy and cisplatin-based chemotherapy, with the tumour showing no or a limited response in 4 cases. The 3 remaining patients receiving cisplatin-based chemotherapy showed long-term disease-free survival (1–4 years). The determinant of the rate of response to chemotherapy is not known. Interestingly, of 3 patients who had an excellent chemotherapy response, 2 had Klinefelter syndrome, and 1, with a prior testicular seminoma, had completed post-orchietomy chemotherapy. In addition to a limited response to preoperative neoadjuvant chemotherapy, other poor prognostic factors include a large tumour load; incomplete resection, with residual tumour; and late-stage disease, with lymph node and distant metastasis^{3–7}.

SUMMARY

Primary yst of the prostate is a very rare tumour that is diagnostically challenging because of its unusual anatomic location and diverse histologic patterns, especially when it presents with predominantly nonspecific solid or glandular morphologies, with sheets of small round blue cells. A high index of suspicion, clinicopathologic correlation, and appropriate immunohistochemical studies facilitate an accurate diagnosis. Appropriate clinical management includes preoperative neoadjuvant chemotherapy, radical surgery, and postoperative treatment, with subsequent close monitoring of serum AFP.

TABLE I Clinicopathologic features of prostatic yolk sac tumour

Reference	Age (years)	Initial diagnosis	Tumour size (cm)	Morphology	Treatment	Clinical outcome
Benson <i>et al.</i> , 1978 ⁴	51	Bladder carcinosarcoma	NA	Solid, papillary and glandular, cysts, Schiller–Duval bodies and PAS-positive globules	Radical prostatectomy, chemoradiation	Died of disease, after 10 months
Dalla Palma <i>et al.</i> , 1988 ⁵	29	Prostatic adenocarcinoma	NA	Solid nests and channels in reticular pattern, pseudopapillary and polyvesicular patterns, “Schiller–Duval-like” diastase-resistant PAS-positive and AFP-positive hyaline bodies	Radical prostatectomy, chemotherapy	Died of disease, after 10 months
Schriber <i>et al.</i> , 1990 ⁹	40	Prostate tumour	6	Microcystic, papillary and solid pattern, Schiller–Duval bodies, focal AFP positivity	Chemotherapy, radical cystoprostatectomy, removal of rectum	Died of complications, after 4 months
Tay <i>et al.</i> , 1995 ¹⁰	43	Yolk sac tumour	10	Pleomorphic, atypical Schiller–Duval bodies, PAS-positive hyaline globules, cytokeratin-positive, focal AFP positivity	Cisplatin-based chemotherapy, radical cystoprostatectomy	No evidence of disease, after 20 months
Namiki <i>et al.</i> , 1999 ⁸	33	Yolk sac tumour, teratoma	6.5	Solid and microcystic	Cisplatin-based chemotherapy, radiation	No evidence of disease, after 4 years
Han <i>et al.</i> , 2003 ⁷	24	Primary prostatic tumour and seminoma	6	Papillary and glandular in fibrous or myxoid stroma, most AFP-positive, focal Schiller–Duval bodies, many PAS-positive hyaline bodies, focal seminoma	Total cystoprostatectomy, cisplatin-based chemotherapy	Died of disease, after 8 months
Furr <i>et al.</i> , 2015 ⁶	36	History of testicular seminoma	NA	Histology not provided, tumour involving prostatic urethra	Cisplatin-based chemotherapy, prostatectomy	No evidence of disease, after 12 months
Abdelhalim <i>et al.</i> , 2016 ³	1.1	Primary yolk sac tumour	5.8	Solid sheets, microcystic and glandular structures with myxoid stroma,	Radical prostatectomy, cisplatin-based chemotherapy	Died of disease, after 17 months
Present study	26	Small round blue cell tumour	12.2	Glandular, cord-like, solid and papillary architectures, occasional Schiller–Duval bodies	Chemotherapy, radical cystoprostatectomy, removal of rectum	Died of disease, after 18 months

NA = not available; PAS = periodic acid–Schiff; AFP = alpha-fetoprotein.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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