Cystic trophoblastic tumor (CTT) is a rare testicular germ cell tumor (GCT) predominantly seen in post-chemotherapy patients. It is prognostically similar to teratoma and requires no additional chemotherapy in the absence of a non-teratomatous GCT component. We report a case of metastatic CTT in a patient with primary testicular teratoma without prior chemotherapy. Retroperitoneal lymph node metastases contained teratoma, embryonal carcinoma, and CTT. The CTT was β-hCG positive and SALL4 negative by immunohistochemistry (IHC). CTT can arise in metastatic testicular GCT in treatment naïve patients. An important differential diagnosis is choriocarcinoma due to treatment implications, and SALL4 IHC may help.

Introduction

Cystic trophoblastic tumor (CTT) is an uncommon testicular germ cell tumor (GCT), consisting of small cysts lined by mononucleated trophoblastic cells that demonstrate focal cytoplasmic positivity with β-human chorionic gonadotropin (β-hCG) immunohistochemistry (IHC). Ninety-eight cases have been reported since 1988. The vast majority occur as metastatic disease in post-chemotherapy retroperitoneal lymph node dissection (RPLND) specimens from patients with testicular GCTs. It is important to recognize this tumor, particularly its distinction from choriocarcinoma; CTT is prognostically similar to teratoma and no additional post-surgical chemotherapy is required in the absence of non-teratomatous GCT. Only 14 cases of CTT have been reported in patients without prior chemotherapy, all in the primary tumor. We report the first case of metastatic CTT arising in a patient with testicular GCT who did not receive prior chemotherapy, demonstrating a new setting for its occurrence. We also show potential utility of SALL4 IHC in distinguishing CTT from choriocarcinoma.

Figure 1. CT scan of abdomen and pelvis. Largest (2.0 cm) retroperitoneal lymph node (arrow) adjacent to left renal vein. A total of six enlarged retroperitoneal lymph nodes were seen, ranging from 0.5 to 2.0 cm, adjacent to the left renal, gonadal, and common iliac veins.
Case presentation

A 31-year-old male presented after 4 weeks of pain and increase in size of the left testicle. Ultrasound showed a 5.6 × 3.4 × 3.7 cm left testicle with a 3.8 × 3.5 × 3.4 cm cystic and solid mass. Pre-operative tumor markers are not available (SX).

Histopathology of the radical orchiectomy specimen demonstrated pure teratoma with background germ cell neoplasia in situ. Surgical margins were negative. No necrosis, angiolympathic invasion, rete testis involvement, or extension beyond the tunica albuginea were identified (pT1).

Tumor markers at 1-week post-orchiectomy showed: alpha fetoprotein = 9.4 ng/mL, β-hCG = 1 mIU/mL, and lactate dehydrogenase = 136 IU/L. Computed tomography (CT) scan of the abdomen and pelvis revealed multiple enlarged retroperitoneal lymph nodes, up to 2.0 cm (N1), indicative of nodal metastases (Fig. 1). CT scan of the chest was unremarkable.

RPLND was performed for his clinical stage IIA disease with the primary tumor showing teratoma only. Histopathology demonstrated metastatic GCT in twenty-eight of fifty-six lymph nodes

Table 1

| Site                | # Positive/# total | Metastatic component | # Of lymph nodes |
|---------------------|--------------------|----------------------|------------------|
| Inter-aortic caval  | 2/8                | Teratoma             | 1                |
| Para-caval          | 3/6                | Teratoma             | 1                |
| Para-aortic         | 18/31              | Teratoma             | 12               |
|                     |                    | EC                   | 4                |
|                     |                    | Teratoma/CTT         | 1                |
|                     |                    | Teratoma/EC/CTT      | 1                |
|                     |                    | Teratoma/EC/CTT      | 1                |
| Left common iliac   | 5/11               | Teratoma             | 2                |
|                     |                    | EC                   | 1                |
|                     |                    | Teratoma/EC          | 1                |
|                     |                    | Teratoma/CTT         | 1                |
| All sites           | 28/56              | Teratoma             | 16               |
|                     |                    | EC                   | 7                |
|                     |                    | Teratoma/EC          | 2                |
|                     |                    | Teratoma/CTT         | 2                |
|                     |                    | Teratoma/EC/CTT      | 1                |

* This was the largest lymph node at 30 mm; it contained the largest metastatic focus (30 mm) which demonstrated extranodal extension.

Figure 2. Lymph node with metastatic teratoma, CTT, and EC. CTT and EC marked by $ and #, respectively. Remainder of lymph node involved by teratoma (6× magnification) (A). Low power view of largest focus of CTT (28× magnification) (B). High power view of CTT showed single-layered (top) and multi-layered (bottom) epithelium with characteristic morphology (400× magnification) (C). IHC of CTT showed diffuse and variable cytoplasmic staining with β-hCG (top) and negative nuclear staining with SALL4 (middle) and OCT-4 (bottom) (400× magnification) (D). Focus of EC (256× magnification) with positive SALL4 staining (inset) (E). Continuity of CTT (left half; β-hCG-positive) with teratoma (right half; β-hCG-negative) (172× magnification) (F).
The largest metastatic focus was 3.0 cm and demonstrated extranodal extension (pN2) (upstaged to stage IIB). Metastatic elements comprised of teratoma in 21, embryonal carcinoma (EC) in 10, and CTT in 3 lymph nodes. Some lymph nodes contained more than one tumor type: 15 contained only teratoma, 7 with EC only, 2 with teratoma and EC, 2 with teratoma and CTT, and 1 with teratoma, EC, and CTT (Table 1).

CTT represented <10% of metastatic components, with small cystic foci (<0.4 cm) in 3 of 28 positive lymph nodes. The cysts were lined by single to several cell layer thick epithelium composed of mononuclear trophoblasts with smudged chromatin, abundant eosinophilic cytoplasm, and occasional cytoplasmic lacunae. The cysts contained variable amounts of eosinophilic, acellular, and fibrinoid material. No mitotic figures, hemorrhage, or necrosis were identified (Figs. 2 and 3). A small focus of CTT was also identified as part of and in continuity with the epithelium of a large teratomatous cyst, evident on both H&E and β-hCG IHC (Fig. 2F). IHC showed the CTT to be diffusely positive for β-hCG with variable staining intensity (Figs. 2 and 3) and negative for SALL4 (non-specific cytoplasmic staining seen) (Figs. 2 and 3) and OCT-4 expression (Fig. 2). EC was positive for SALL4 (Fig. 2) and OCT-4 and negative for β-hCG expression; teratoma was negative for β-hCG (Figs. 2 and 3), SALL4, and OCT-4 expression.

For the patient’s stage IIB (pT1 N2 M0 SX) good-risk non-seminomatous testicular cancer, three cycles of bleomycin, etoposide, and cisplatin were recommended. He opted to receive treatment elsewhere.

Discussion

To our knowledge, this is the first reported case of metastatic CTT in a patient with testicular GCT who did not receive prior chemotherapy. The CTT demonstrated histomorphology consistent with previous reports, but with diffuse β-hCG immunoreexpression instead of focal or absent.1–5 SALL4 expression in CTT, not previously reported, was negative.

Ninety-eight cases of CTT have been reported. Of note, CTT was previously named choriocarcinoma-like lesion (CCLL) with two subtypes: teratomatous CCLL and cystic atypical choriocarcinoma.1,2 However, the original authors now regard them as CTTs.3 The majority of CTTs are seen as metastatic disease (72%) and post-chemotherapy (83%). All previously reported metastatic CTT occurred post-chemotherapy, suggesting CTTs develop secondary to treatment. However, CTT has also been reported in 27 testicular primaries, of which 14 did not receive prior chemotherapy.1–5 Additionally, we now report the first case of metastatic CTT in a patient with testicular GCT without prior chemotherapy. Though the minority, these non-post-chemotherapy cases indicate that CTT represents one of the many distinct tumor types which occurs in the natural history of testicular GCTs, and its association with chemotherapy suggests it may be selected for by treatment. Given our understanding of post-pubertal teratoma as deriving

Figure 3. Separate focus of CTT with surrounding teratoma (100× magnification) (A). High power view of CTT demonstrating multilayered epithelium with characteristic morphologic features of degenerative appearing cells with abundant eosinophilic cytoplasm and smudged nuclear features; some cells also demonstrate intracytoplasmic vacuoles/lacunar spaces (400× magnification) (B). β-hCG IHC showed diffuse cytoplasmic staining in CTT but not teratoma (100× magnification) (C). SALL4 IHC showed non-specific staining of acellular debris associated with CTT, but not CTT cell nuclei (100× magnification) (D). Insets in C and D show high power views of β-hCG and SALL4 IHC, respectively (400× magnification).
from non-teratomatous GCTs, CTT may represent the intermediate stage in the transformation from choriocarcinoma to teratoma.3,5 This is supported morphologically by the mononuclear trophoblasts present in both choriocarcinoma and CTT, the similarity between CTT and some teratomatous epithelium, and the continuity of CTT with teratoma (observed only in the current and two previous cases).1 IHC lends further support, as both choriocarcinoma and CTT show β-hCG and inhibin positivity.1,3,5 However, only a minority of patients with CTT are found to have choriocarcinoma,1,3,5 which was not identified in our patient. This may be due to limited sampling or tumor transformation.3,5

While CTT may resemble teratoma and choriocarcinoma, it is most important to distinguish CTT from choriocarcinoma due to treatment implications. By themselves, teratoma and CTT are treated with surgery alone; choriocarcinoma would require additional chemotherapy.1,4 While choriocarcinoma and CTT are somewhat similar in their morphologic appearance and reactivity with β-hCG, CTT lacks the infiltrative, biphasic, and high mitotic activity of choriocarcinoma. Also, our case is the first CTT to be evaluated by SALL4 IHC and all foci of CTT showed negative expression. This suggests SALL4 may be useful in distinguishing this trophoblastic tumor from choriocarcinoma, which shows variable SALL4 expression in mononuclear cells.

**Conclusion**

CTT can arise in metastatic testicular GCT in treatment naïve patients. An important differential diagnosis is choriocarcinoma due to treatment implications, and SALL4 IHC may help.

**Conflicts of interest**

None.

**References**

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