

Case report

Cytoreduction with hyperthermic intra peritoneal and intra thoracic chemotherapy for metastatic Sertoli-Leydig cell tumor of the ovary

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ABSTRACT

Sertoli Leydig cell tumor (SLCT) is a rare sex-cord stromal tumor of the ovary that generally has a benign course. Here, we report an unusual case of recurrent, metastatic SLCT and its unique management with a combination of cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, hyperthermic intrathoracic chemotherapy, and systemic chemotherapy.

1. Introduction

Sertoli Leydig cell tumor (SLCT) is a rare ovarian neoplasm that is a subtype of sex cord stromal tumors that compromise less than 0.1% of all ovarian neoplasms. Historically referred to as arrhenoblastoma and androblastoma, the vast majority of SLCTs tend to be unilateral with roughly only 2% of cases occurring as bilateral neoplasms (Young and Scully, 1985). SLCTs typically present between the second and third decades of life with the mean age of presentation at 25 years and fewer than 10% of cases occurring in women older than 50 years of age (Young and Scully, 1985). These tumors are infrequently seen in women of post-menopausal age and are typically clinically benign. Nearly 50% of cases present with signs of androgen excess manifested by amenorrhea. Other symptoms include acne, hirsutism, virilization, deepening of the voice, balding, and clitoral hypertrophy. The mainstay of treatment involves surgical intervention and adjuvant chemotherapy. The use of hyperthermic intraperitoneal chemotherapy (HIPEC) in disseminated epithelial ovarian cancer has been reported to improve recurrence free survival (Vermorken, 2006). The WHO has classified SLCTs into well, intermediate and poorly differentiated tumors and tumors with heterologous elements (Histological, 1999). Less than 20% of intermediate and poorly differentiated tumors become clinically malignant (Young and Scully, 1985; Roth et al., 1981). Metastases have been found in 12 – 22% of cases, commonly in the abdominopelvic cavity or the retroperitoneum (Roth et al., 1981; Lantzsch et al., 2001). Prognosis of SLCT needs to be correlated with the stage and degree of differentiation of the tumor (Roth et al., 1981; Zaloudek and Norris,

1984).

Here we present a case of a 58-year-old, post-menopausal woman with a poorly differentiated SLCT that metastasized into her abdomen and chest cavity. Our management strategy included surveillance and cytoreductive surgery with HIPEC and hyperthermic intrathoracic chemotherapy (HITOC) when necessary for multiple disease recurrences. This is the only reported case of thoracic metastasis of SLCT treated with HITOC.

2. Case report

A 58-year-old female presented with painless, progressive abdominal distension. An ovarian mass was subsequently found and a total abdominal hysterectomy, bilateral salpingo-ophorectomy, bilateral pelvic and periaortic lymphadenectomy, omentectomy, and staging for ovarian cancer was performed. The mass was confirmed with pathology to be an intermediately differentiated stage 1 SLCT. Random testosterone levels ranged from 4 to 10 ng/dl and patient had no signs of virilization. Following the tumor resection, patient did not receive chemotherapy and patient was monitored for tumor recurrence using cancer antigen 125 (CA-125). Initial CA-125 at disease presentation was 110 units/mL. Follow-up visits showed values (8–17 units/mL) that consistently remained within reference range and were not concerning for recurrence. A timeline of her clinical course is highlighted in Fig. 1.

Eighteen months following the initial procedure, she began to develop significant abdominal distension, discomfort, and heartburn; her CA-125 was elevated to 96 units/mL. An abdominal computerized

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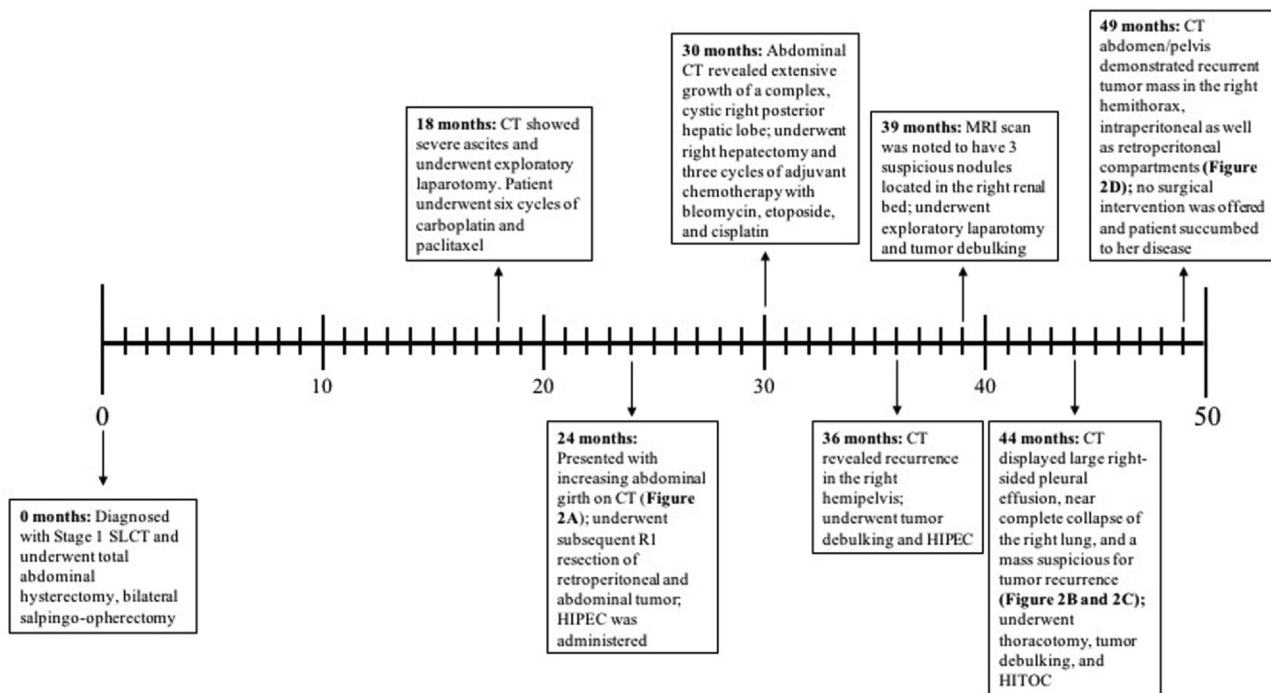


Fig. 1. A timeline of the clinical course in months. At 0 months, patient was diagnosed and treated for Stage 1 SLCT. Throughout her clinical course the patient underwent many surgical procedures and various iterations of chemotherapy. Ultimately, the patient entered hospice care after recurrent SLCT was found throughout her chest cavity and peritoneum. She passed away shortly after.

tomography (CT) showed significant ascites and a complex right upper quadrant mass, 21 cm in diameter, suspicious for recurrence of her SLCT. She subsequently underwent exploratory laparotomy with removal of the mass, cholecystectomy, and peritoneal and omental biopsies. Pathology confirmed that she had recurrent, intermediately differentiated SLCT with gallbladder and right pericolic gutter metastases. Following surgical debulking, she was administered six cycles of carboplatin and paclitaxel over the next six months.

Six months after the completion of chemotherapy, she presented to our cancer center with increasing abdominal girth, abdominal pain, and weight gain of twenty pounds over two months; her CA-125 was 450.9 units/mL. An abdominal CT showed massive ascites and a large amount of complex peritoneal fluid/gelatinous material (Fig. 2A). Over the next few weeks, her clinical condition deteriorated, and she was admitted to the hospital. She underwent a two-stage procedure, with initial emergent evacuation of nine liters of ascitic fluid and R1 resection of pelvic tumor. Two days later, she underwent subsequent R1 resection of retroperitoneal and abdominal tumor. Following tumor debulking, carboplatin, at a total dose of 1200 mg for 60 min in four liters lactated Ringer’s (LR) solution at 41.5 °C, was used for HIPEC. Histology of the retroperitoneal tumor showed diffuse sheets of immature, sarcomatoid Sertoli cells with marked nuclear atypia, confirming metastatic poorly differentiated SLCT (Fig. 2B-C).

Over the next fifteen months following her two-stage tumor

debulking operation, she underwent extended right hepatectomy, right adrenalectomy, and right diaphragm resection and repair and three cycles of adjuvant chemotherapy with bleomycin, etoposide, and cisplatin were administered. In addition, she underwent a fourth debulking procedure and a second round of HIPEC with 900 mg carboplatin in 3 L of LR solution for 45 min at 41.5–42 °C. Finally, she underwent an exploratory laparotomy with tumor debulking to remove the nodules and histology confirmed all three nodules were positive for metastatic SLCT. During this time her CA-125 was relatively low, ranging from 8.3 to 12.2 units/mL. Following each debulking procedure, histology confirmed each biopsy was consistent with metastatic poorly differentiated SLCT.

Five months following her exploratory laparotomy and tumor debulking, she presented with a large right-sided pleural effusion, near complete collapse of the right lung, and a mass suspicious for tumor recurrence, CA-125 was 109 units/mL (Fig. 3A). She underwent right thoracotomy with tumor debulking, complete decortication of the right hemithorax and HITOC which included 1200 mg carboplatin diluted in 4 L lactated Ringer’s solution with an inflow temperature of 41.5° for 45 min. Histology confirmed metastatic poorly differentiated SLCT, consistent with previous debulking procedures (Fig. 3B-C). Two months following, the CA-125 was 29.3 units/mL.

Five months later, CT of the abdomen/pelvis demonstrated recurrent tumor mass in the right hemithorax, intraperitoneal as well as

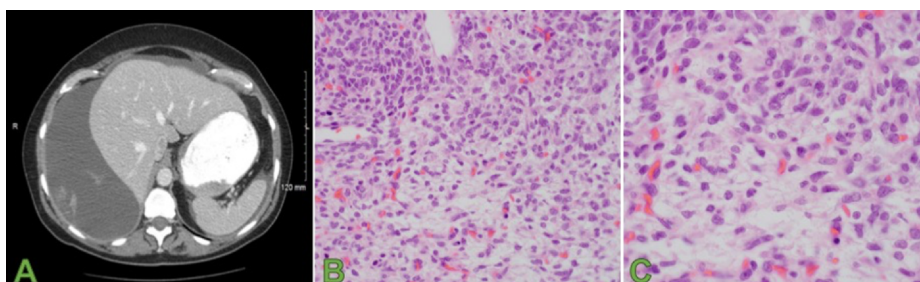


Fig. 2. A. At 24 months: CT abdomen and pelvis with contrast demonstrates interval development of pseudomyxomatous peritonei with a large amount of complex peritoneal fluid/gelatinous material containing thickened septations and swirling enhancement B. Retroperitoneal tumor showing diffuse sheets of immature, sarcomatoid Sertoli cells with marked nuclear atypia, confirming metastatic poorly differentiated SLCT (H&E 40×). C. Further magnification of retroperitoneal tumor at 100× (H &E).

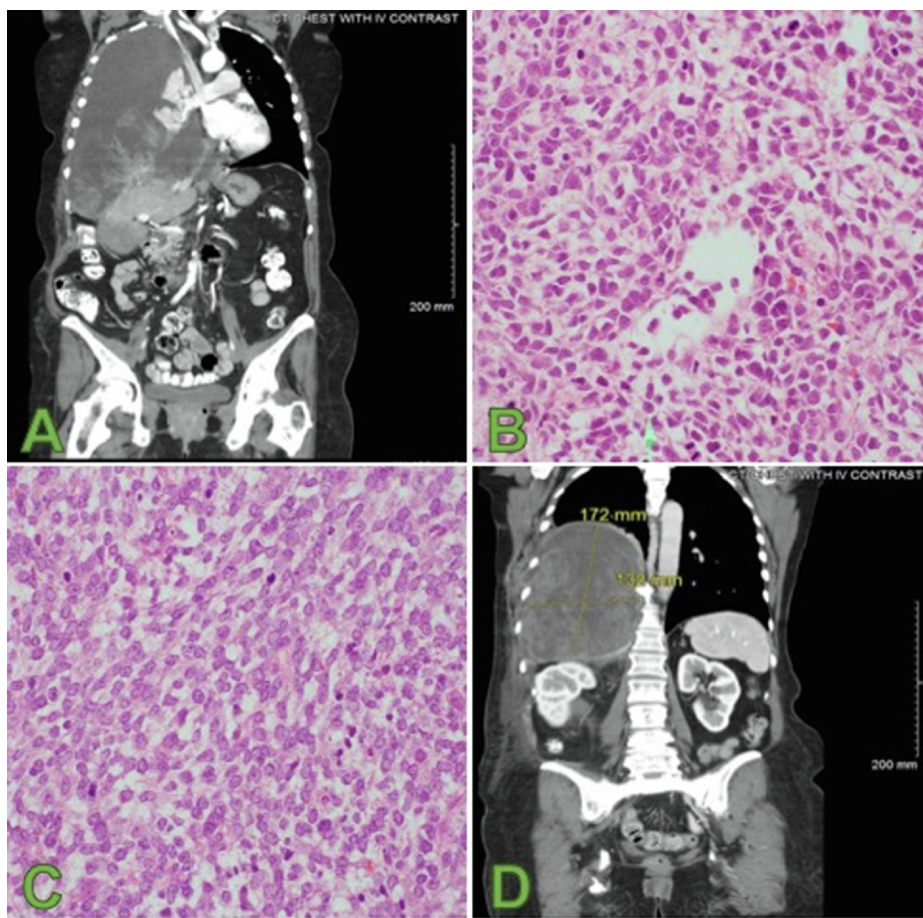


Fig. 3. **A.** At 44 months: CT chest with IV contrast displays a large right pleural effusion with near collapse of the right lung and mass suspicious for tumor recurrence. **B.** Right hemithorax tumor demonstrating metastatic poorly differentiated Sertoli-Leydig cell tumor (H&E 40 \times). **C.** Right lung tumor demonstrating metastatic poorly differentiated Sertoli-Leydig cell tumor (H&E 40 \times). **D.** At 49 months: CT chest with IV contrast shows new posterior right upper lobe pleural based pulmonary nodule, likely metastasis.

retroperitoneal compartments (Fig. 3D). To this point, our management strategy of surveillance and cytoreductive surgery with HIPEC and HITOC when necessary for multiple disease recurrence. However, she began experiencing severe headaches and diffuse chest pain that radiated to the right shoulder over the forthcoming weeks. At this time, there was no option for surgical intervention. Palliative care was consulted, and hospice care was soon planned with the patient expiring shortly after as a result of her disease.

3. Discussion

Management of SLCTs is challenging due to their rarity and uncertain malignant potential with surgery continuing to be the cornerstone. According to the latest NCCN guidelines for sex cord stromal tumors (SCSTs), total abdominal hysterectomy and bilateral salpingoophorectomy is recommended in patients with Stage 1 disease who have completed childbearing and unilateral salpingoophorectomy in those who have not and are desirous of maintaining fertility (Clinical Practice Guidelines In, 2020). Comprehensive surgical staging must be undertaken to exclude occult higher stage disease. The chemotherapy recommendation for Stage 1 low-risk patients is observation alone and for Stage 1 high/intermediate risk and Stage 2–4 patients is platinum-based chemotherapy and/or radiotherapy. Platinum-based chemotherapy includes a paclitaxel/carboplatin combination or BEP regimen (Bleomycin, Etoposide, and Cisplatin) for 3–4 cycles, which can be used in certain circumstances. In addition, etoposide are recommended, carboplatin and taxol based are preferred (Clinical Practice Guidelines In, 2020). For patients with recurrent SCST, recommendations include use of bevacizumab/leuprolide (for germ cell tumors), aromatase inhibitors, paclitaxel as a single agent or in combination with carboplatin/ifosfamide and radiation therapy (Clinical

Practice Guidelines In, 2020). Finan *et al* reported success in treatment of metastatic SLCTs with intra-arterial cisplatin, intravenous etoposide and pelvic radiation therapy, followed by intravenous (IV) doxorubicin and cyclophosphamide (Finan *et al.*, 1993).

Intra-peritoneal (IP) chemotherapy in the setting of advanced/recurrent epithelial ovarian tumors is recommended for Stage 3 patients with optimally debulked (< 1 cm) residual disease (Clinical Practice Guidelines In, 2020). IP therapy in Stage 2 patients is an option as well. Multiple phase 1 and 2 trials have been conducted to test the advantage of intra-peritoneal chemotherapy in the salvage setting using drugs such as methotrexate, melphalan, 5-fluorouracil, mitomycin-C, cisplatin, and carboplatin with response rates ranging from around 10–60% (Vermorken, 2006). The GOG172 trial showed a 16 month increase in survival in patients with Stage 3 cancer after IP therapy with cisplatin/paclitaxel compared to standard IV therapy (65.6 vs. 49.7 months, $p = 0.03$) (Armstrong *et al.*, 2006). Of note, there was an increase in manageable, short-term toxicities with IP compared to IV therapy. It was largely this trial that led to the 2006 announcement by NCI encouraging the use of IP chemotherapy in advanced ovarian cancer. In a recent retrospective study by Königsrainer *et al*, 31 patients with peritoneal recurrence of ovarian cancer were treated with cytoreductive surgery followed by HIPEC (Königsrainer *et al.*, 2011). They were able to achieve complete cytoreduction in 90% of patients and had no immediate (30-day/90-day) postoperative mortality although they did have incidences of postoperative complications.

The rarity of SLTC likely precluded the success of randomized controlled trials for evaluation of the benefit of cytoreduction and HIPEC for SLCT. Extending the principles of treatment of epithelial ovarian tumors to SLCT can be considered in these cases. Metastatic SLCT is vexing disease without clear standards after first line therapy, and while this patient's case does not provide comparative efficacy, it

seemed reasonably tolerable and may be an additional consideration.

As mentioned, our patient was postmenopausal at initial diagnosis without signs of virilization. She developed an aggressive metastatic tumor within 18 months of diagnosis and appropriate treatment of a Stage 1 SLCT. Our management strategy of surveillance and cytoreductive surgery with HIPEC and HITOC when necessary ensured a good quality of life despite numerous disease recurrences. This is the only reported case of thoracic metastasis of SLCT treated with HITOC. In conclusion, a combination of cytoreductive surgery and HIPEC/HITOC may be considered on an individualized basis in patients with metastatic SLCT.

4. Disclosure

There are no potential conflicts of interest or financial disclosures associated with the authors of this article.

Author contributions

Concept – NKL, MJR, BWL, MWB; Manuscript preparation – NKL, MJR, SK, BWL, MWB; Proof reading – NKL, MJR, SK, BWL, MWB

References

- Armstrong, D.K., Bundy, B., Wenzel, L., et al., 2006. Intraperitoneal cisplatin and paclitaxel in ovarian Cancer. *N. Engl. J. Med.* 354, 34–43.
- NCCN Clinical Practice Guidelines In Oncology: Ovarian Cancer. 2020;MS28–MS29.
- Finan, M.A., Roberts, W.S., Kavanagh, J.J., 1993. Ovarian Sertoli-Leydig cell tumor: success with salvage therapy. *Int. J. Gynecol. Can.* 3, 189–191.
- Scully RE. *Histological Typing of Ovarian Tumours* [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 1999 [cited 2019 Feb 1]. Available from: <http://link.springer.com/10.1007/978-3-642-58564-7>.
- Königsrainer, I., Beckert, S., Becker, S., et al., 2011. Cytoreductive surgery and HIPEC in peritoneal recurrent ovarian cancer: experience and lessons learned. *Langenbecks Arch. Surg.* 396, 1077–1081.
- Lantzsch, T., Stoerer, S., Lawrenz, K., et al., 2001. Sertoli-Leydig cell tumor. *Arch. Gynecol. Obstet.* 264, 206–208.
- Roth, L.M., Anderson, M.C., Govan, A.D., et al., 1981. Sertoli-Leydig cell tumors: a clinicopathologic study of 34 cases. *Cancer* 48, 187–197.
- Vermorken, J.B., 2006. Intraperitoneal chemotherapy in advanced ovarian cancer: recognition at last. *Ann. Oncol.* 17 (Suppl 10), x241–246.
- Young, R.H., Scully, R.E., 1985. Ovarian Sertoli-Leydig cell tumors. A clinicopathological analysis of 207 cases. *Am. J. Surg. Pathol.* 9, 543–569.
- Zaloudek, C., Norris, H.J., 1984. Sertoli-Leydig tumors of the ovary. A clinicopathologic study of 64 intermediate and poorly differentiated neoplasms. *Am. J. Surg. Pathol.* 8, 405–418.