Case Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(3) 1–8

DOI: 10.1177/0300060521996563
journals.sagepub.com/home/imr
SAGE

Non-Peutz–Jeghers syndrome-associated ovarian sex cord tumor with annular tubules treated by radiotherapy: a case report and literature review

Cheng Li[1], Reyida Aishajiang[1], Yongliang Teng[2], Tiankai Xu[1], Lijuan Ding[1] and Lihua Dong[1]

Abstract

There are no standard treatment options for metastatic and recurrent non-Peutz–Jeghers syndrome (PJS)-associated sex cord tumor with annular tubules (SCTAT). The effects of chemotherapy and/or radiotherapy are still not well-defined. Herein, we present a case of a metastatic and recurrent non-PJS-associated SCTAT showing high serum estradiol and progesterone concentrations after surgery and chemotherapy. Radiotherapy (50 Gy/25 fractions) triggered a sharp reduction in the sizes of the metastatic and recurrent masses, and estradiol and progesterone concentrations. Accordingly, we consider that radiotherapy might be effective and safe for metastatic and recurrent SCTAT. The roles of radiotherapy in non-PJS SCTAT should be further validated in large-scale prospective clinical trials.

Keywords

Ovarian tumors, sex cord tumor with annular tubules, Peutz–Jeghers syndrome, radiotherapy, surgery, metastasis

Date received: 26 August 2020; accepted: 22 January 2021

[1]Department of Radiation Oncology, The First Hospital of Jilin University, Changchun, China
[2]Department of Pathology, The First Hospital of Jilin University, Changchun, China

Corresponding authors:
Lijuan Ding, Department of Radiation Oncology, The First Hospital of Jilin University, 1 Xinmin Street, Changchun 130021, China.
Email: dinglijuan@jlu.edu.cn
Lihua Dong, Department of Radiation-Oncology, The First Hospital of Jilin University, 1 Xinmin Street, Changchun 130021, China.
Email: dlh@jlu.edu.cn

Introduction

Sex cord tumor with annular tubules (SCTAT) refers to a rare type of ovarian neoplasm accounting for approximately 5% of all ovarian neoplasms and 6% of sex cord stromal tumors.[1] The pathogenesis of SCTAT is still not well-defined. Peutz–Jeghers syndrome (PJS), a hereditary cancer syndrome characterized by mucocutaneous melanin pigmentation and gastrointestinal polyposis, has been well-acknowledged as an important cause in the pathogenesis of SCTAT.[2] For example, approximately 1/3 of SCTAT patients are reported to present with PJS.

Surgery is the major treatment option for SCTAT associated with or without PJS. However, little is known about the efficiency of chemotherapy and/or radiotherapy among patients with recurrence and metastasis. In addition, few studies have focused on the efficiency of radiotherapy for treating non-PJS associated SCTAT because of the disease rarity. In this study, we present a case of metastatic and recurrent SCTAT that was non-PJS-associated.

Case report

A 31-year woman presented to our department in December 2014 with irregular menstruation for 10 years. Abdominal ultrasonography showed a mass with a diameter of approximately 10 cm in the left ovary, and pathological diagnosis indicated SCTAT (Figure 1a and 1b). After tumor resection, her menstruation cycle became regular.

In November 2016, she was re-admitted to our department for irregular menstruation of 12 months' duration. No melanocytic macules were seen on her lips. Ultrasonography revealed a mass in the right ovary, and laparoscopic exfoliation was performed. α-inhibin and WT1 immunostaining results were positive (Figure 1c and 1d), and immune checkpoint evaluation showed increased levels of the *AKT2* gene copy. After surgery, her menstruation cycle became regular, but the estradiol and progesterone concentrations gradually increased.

In July 2017, positron emission tomography (PET)/computed tomography (CT) showed recurrence and multiple metastases to the mediastinum, right pericardium, bilateral hilum, left diaphragmatic angle, right lateral pulmonary pleura, left adrenal region, posterior pancreatic body, as well as the anterior uterine sides, and right anterior sacrum (Figure 2). The largest mass was located in the mediastinum and had a diameter of 10 cm. Between August 2017 and November 2017, she received four cycles of chemotherapy using paclitaxel combined with cisplatin, following by hysterectomy and salpingo-oophorectomy. Two cycles of chemotherapy were given between December 2017 and February 2018 using bleomycin, etoposide, and cisplatin (BEP). After treatment, the number and sizes of the masses decreased, among which the largest mass decreased to a size of approximately 4 cm. Nevertheless, serum estradiol and progesterone concentrations remained high.

In March 2018, the patient received radiotherapy with a dose of 50 Gy (25 fractions) for masses in the mediastinum and left adrenal region. Pre-radiotherapy CT revealed a mediastinal mass measuring 6.8 cm × 2.7 cm and a left adrenal region mass measuring 4.2 cm × 2.7 cm (Figure 3). Pre-radiotherapy estradiol and progesterone concentrations were 588 pmol/L and 5.51 nmol/L, respectively, and cancer antigen 125 (CA 125) and carcinoembryonic antigen (CEA) concentrations were normal. The patient also developed mild radiotherapy-associated esophagitis. Estradiol and progesterone concentrations decreased to <73 pmol/L and <1.31 nmol/L, respectively, approximately 4 months after radiotherapy. CT revealed a reduction in the size of the masses in the mediastinum (3.9 cm × 2.6 cm) and left

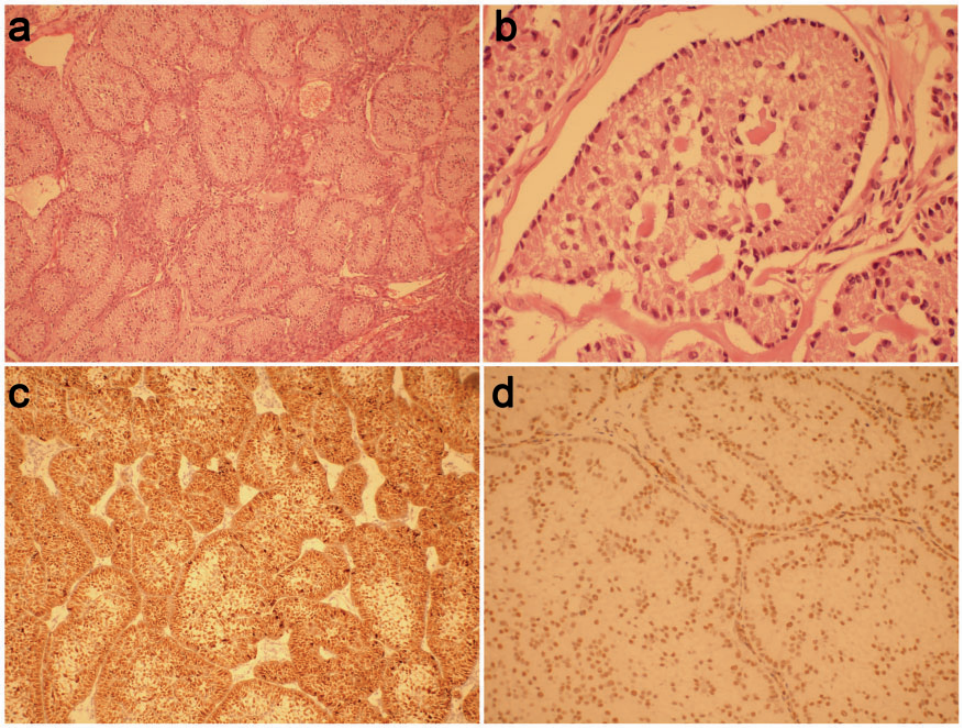

Figure 1. Pathological and immunohistochemical features of the case. (a) The cancer cells are arranged in a tubular pattern (magnification: ×100). (b) Acidophilic granules are visible in the ductules (magnification: ×400). The peripheral cell morphology is similar to that of the supporting cells, with light-staining cytoplasm and round or oval nuclei and small nucleoli. (c) Positive α-inhibin staining in the cytoplasm. (d). Positive nuclear WT1 staining.

adrenal region (3.3 cm × 2.8 cm) (Figure 4a and 4b); estradiol and progesterone concentrations were 108 pmol/L and 0.73 nmol/L, respectively, 4 months after radiotherapy. Twelve months later, CT revealed no increase in the sizes of the tumors (Figure 4c–4f), and the estradiol and progesterone concentrations were 80 pmol/L and 1.55 nmol/L, respectively. The patient showed no recurrence during the 14-month follow-up, and no adverse events (e.g., radiation-induced pneumonia) occurred.

Discussion

Generally, SCTAT patients combined with PJS have small and bilateral tumors. Tumors in non-PJS-associated SCTAT are large and unilateral, and have no calcification. Most lesions are clinically benign, with some patients (20%) showing low-grade malignancy.[3–6] Our patient was confirmed to have non-PJS SCTAT presenting with multiple lesions. The Ki-67 concentration was relatively low, but the degree of malignancy was high with multiple recurrences and metastases.

The diagnosis of SCTAT remains a clinical challenge, but this tumor has been documented as an estrogen-progesterone-secreting tumor. Therefore, the clinical manifestations of SCTAT are mainly associated with aberrant estrogen-progesterone secretion, such as irregular menstrual bleeding, postmenopausal bleeding, precocious

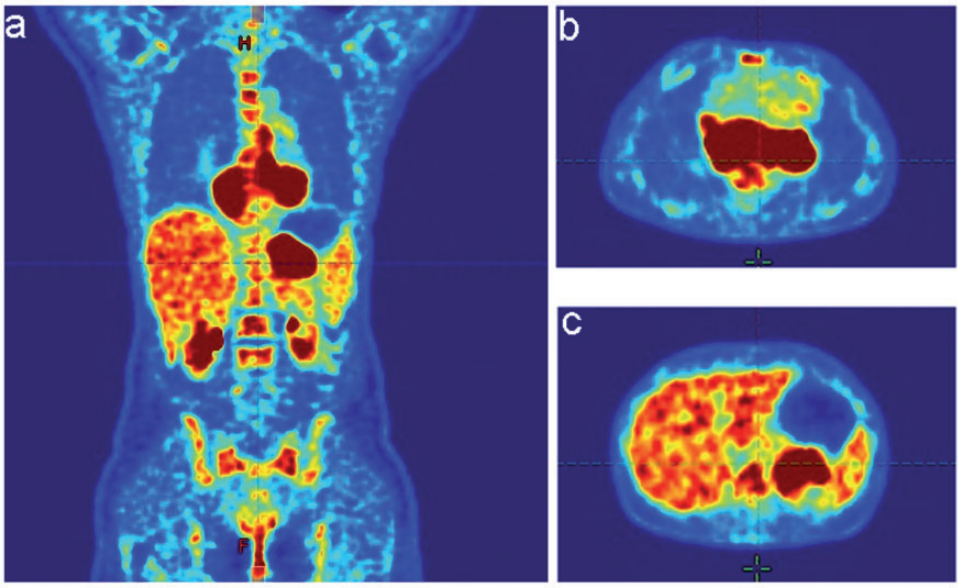

Figure 2. PET-CT findings. The images show intense fluorodeoxyglucose (FDG) uptake in the mediastinum, right pericardium, bilateral hilum, left diaphragmatic angle, right lateral pulmonary pleura, left adrenal region, posterior pancreatic body, anterior uterine sides, and right anterior sacrum (a). The mediastinal mass was the largest, with a diameter of 10 cm (b). The adrenal region mass (transverse view) (c).
PET-CT, positron emission tomography-computed tomography.

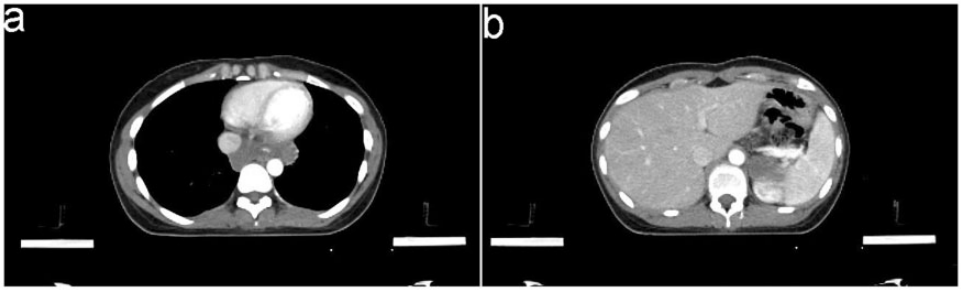

Figure 3. CT results before irradiation. The images show the mediastinal tumor measuring 6.8 × 2.7 cm (a) and the left adrenal region tumor measuring 4.2 × 2.7 cm (b).
CT, computed tomography.

puberty, premature ovarian failure, fibroadenoma, and endometriosis.[7,8] Serum estradiol and progesterone concentrations are usually elevated from disease onset, and decline dramatically after surgery. Concentrations may increase with tumor recurrence. There is no correlation between disease onset and serum estradiol and progesterone concentrations; however. Qian et al. demonstrated decreased estrogen and progesterone concentrations in five patients (45.5%) after treatment. Serum CA 125 and CEA were approximately normal in most patients, with few showing increased CA

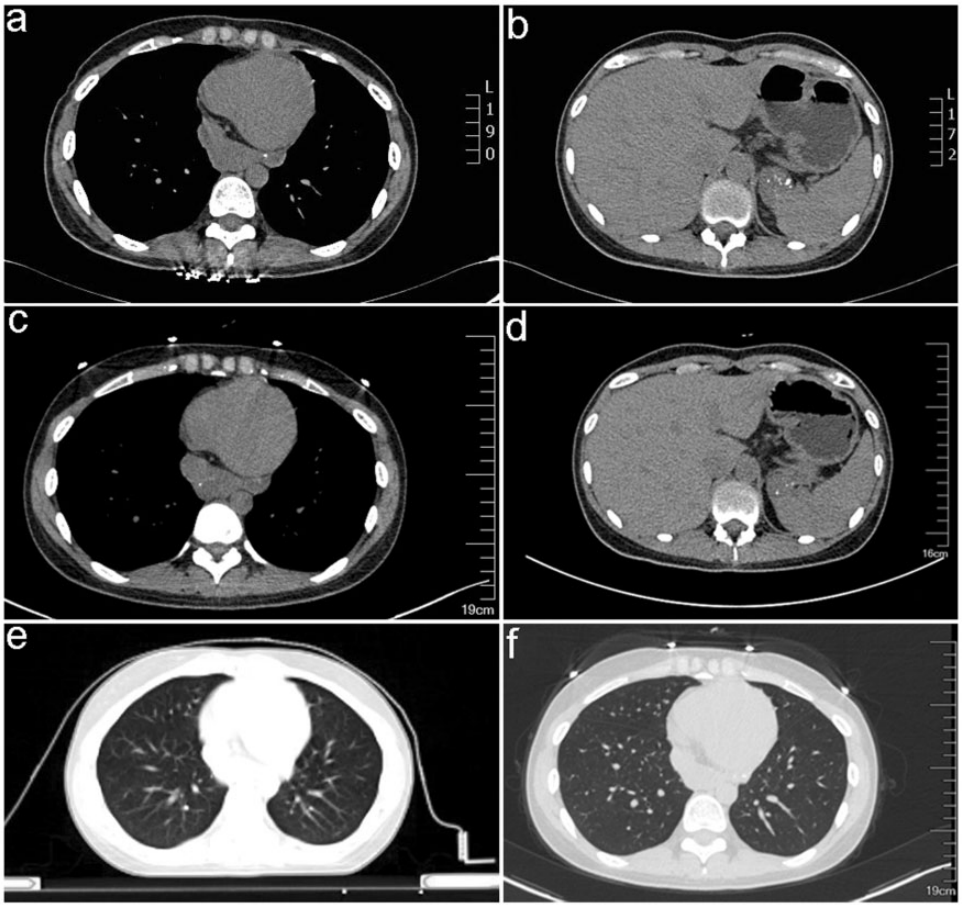

Figure 4. CT results 4 months after radiotherapy. The mediastinal and left adrenal masses decreased in size to 3.9 × 2.6 cm (a) and 3.3 × 2.8 cm (b), respectively. Twelve months after radiotherapy, the mediastinal mass (c) and left adrenal region mass (d) were similar and stable in size. No signs of radiation-induced pneumonia are seen (e, 1 month post-radiation; f, 12 months' post-radiation).

125 concentrations.[9–11] Our patient's estrogen and progesterone concentrations were high, and CA 125 and CEA concentrations were normal at recurrence. After treatment, her estrogen, and progesterone concentrations decreased significantly, which demonstrated a possible correlation between these concentrations and disease onset.

There are currently no standards for the treatment of SCTAT owing to its rarity; surgery is still the preferred treatment for affected patients. Recurrent tumors are generally ipsilateral to the primary tumor, and appear to spread mainly via the lymphatic route. The other reported sites of recurrence and metastasis were the pelvic, para-aortic, and supraclavicular lymph nodes, retroperitoneum, peritoneum, liver, and the kidney and lung.[12] Unlike patients with epithelial ovarian cancer, surgery is still the main treatment for patients with recurrent SCTAT. Little is known about the efficiency of chemotherapy and radiotherapy for

metastatic or recurrent SCTAT with or without PJS.[1,9] According to previous studies, patients showed complete response or partial response after BEP-based chemotherapy, and in one reported case, BEP combined with bevacizumab contributed to the patient's complete response. However, regarding radiotherapy for SCTAT, no randomized trials have been performed, and radiotherapy has been reported in only a few studies for metastasis or recurrence. Furthermore, the radiotherapy details, such as total dose, effectiveness, and adverse events remain unknown.[1–4,9,13]

Our patient developed recurrence twice, and with metastasis to multiple sites, namely as a large mediastinal mass, and masses in the right pericardium, bilateral hilum, and left adrenal region. After surgery and adjuvant chemotherapy, some of the metastatic tumors decreased in size, but the patient's serum estrogen and progesterone concentrations remained high. As bleomycin combined with radiotherapy may increase the risk of pulmonary damage,[14] we administered radiotherapy to the tumor bed at a total dose of 50 Gy/25 fractions over 5 weeks. Tumor shrinkage and decreased estrogen and progesterone concentrations indicated local control of the metastasis and recurrence.

We performed a complete literature search for non-PJS associated SCTAT and the treatment options of surgery and/or radiotherapy. Table 1 shows the identified studies involving 21 cases. Most of the cases showed partial or complete remission after treatment; however, some patients died.

There are limitations in this study, namely, we performed the immunohistochemistry in our lab, but the images were

Table 1. Summary of the treatment options and efficacy in non-PJS associated SCTAT

First author	Number of cases	Treatment	Outcome	Reference
Nosov et al.	1	Laparotomy, RSO, ipsilateral pelvic and paraaortic lymph node sampling, and partial omentectomy	No evidence of recurrence approximately 18 months after diagnosis	1
Shen et al.	6	LSO+TAH+RTR+RPL (n=2); RSO (n=2); RSO+TAH+RTR+RPL (n=1); LSO (n=1)	One death after LSO+TAH+RTR+RPL; 2 with recurrence after partial remission after surgery and radiotherapy; 3 with complete remission	2
Singh et al.	1	Left oophorectomy	No evidence of extra-ovarian extension/metastasis	7
Qian et al.	13	TAH+LSO+RTR (n=2); TAH+RSO+RTR+RPL (n=1); RSO (n=3); LSO (n=3); RTR+RPL (n=2); TAH+RSO+LSO (n=1); cystectomy (n=1)	One death; 3 with partial remission; 9 with complete remission	9

RSO, right salpingo-oophorectomy; LSO, left salpingo-oophorectomy; RTR, recurrent tumor resection; RPL, retroperitoneal lymphadenectomy; TAH, total abdominal hysterectomy.

not provided in this manuscript. This is a future area of focus in our research.

Conclusion

Radiotherapy might be beneficial for recurrent and metastatic non-PJS SCTAT that cannot be managed by complete resection, and a dose of 50 Gy might be safe and effective. The role of radiotherapy in non-PJS SCTAT must be confirmed in large-scale prospective clinical trials.

Ethics statement

The study protocols were approved by The Ethics Committee of The First Hospital of Jilin University. The patient provided written informed consent.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Lijuan Ding https://orcid.org/0000-0002-1692-5089

References

1. Nosov V, Park S, Rao J, et al. Non-Peutz-Jeghers syndrome associated ovarian sex cord tumor with annular tubules: a case report. *Fertil Steril* 2009; 92: 1497.e5–1497.e8. DOI: 10.1016/j.fertnstert.2009.07.1002.
2. Kwong LT, Kwok YF, Hui HF, et al. Ovarian sex cord stromal tumor with annular tubules in a 7-year-old child: a case report. *Gynecol Oncol Rep* 2019; 30: 100509. DOI: 10.1016/j.gore.2019.100509.
3. Thomakos N, Malakasis A, Machairiotis N, et al. Fertility sparing management in non-epithelial ovarian cancer. Which patients, what procedure and what outcome? *J Cancer* 2018; 9: 4659–4664. DOI: 10.7150/jca.26674.
4. Sho T, Yanazume S, Fukuda M, et al. Impact of taxane plus bevacizumab for ovarian sex cord tumor with annular tubules. *J Obstet Gynaecol Res* 2019; 45: 1423–1428. DOI: 10.1111/jog.13985.
5. Young RH. Ovarian sex cord-stromal tumors: reflections on a 40-year experience with a fascinating group of tumors, including comments on the seminal observations of Robert E. Scully, MD. *Arch Pathol Lab Med* 2018; 142: 1459–1484. DOI: 10.5858/arpa.2018-0291-RA.
6. Ishikawa H, Kiyokawa T, Takatani T, et al. Giant multilocular sex cord tumor with annular tubules associated with precocious puberty. *Am J Obstet Gynecol* 2012; 206: e14–e16. DOI: 10.1016/j.ajog.2011.09.025.
7. Singh M, Mandal S and Majumdar K. Sex cord tumor with annular tubules: an incidental finding in an endometriotic cyst–the first known cooccurrence. *Biomed Res Int* 2014; 2014: 970243. DOI: 10.1155/2014/970243.
8. Chatziioannidou K, Botsikas D, Tille JC, et al. Preservation of fertility in non-Peutz-Jegher syndrome-associated ovarian sex cord tumour with annular tubules. *BMJ Case Rep* 2015; 2015: bcr2014207841. DOI: 10.1136/bcr-2014-207841.
9. Qian Q, You Y, Yang J, et al. Management and prognosis of patients with ovarian sex cord tumor with annular tubules: a retrospective study. *BMC Cancer* 2015; 15: 270. DOI: 10.1186/s12885-015-1277-y.
10. Kulkarni N. Recurrence of non-syndromic sex cord stromal tumor with annular tubules of ovary: case report. *Iran J Pathol* 2015; 10: 61–64.
11. Puls LE, Hamous J, Morrow MS, et al. Recurrent ovarian sex cord tumor with annular tubules: tumor marker and chemotherapy experience. *Gynecol Oncol* 1994; 54: 396–401. DOI: 10.1006/gyno.1994.1232.
12. Momin YA, Kulkarni MP, Pandav AB, et al. Non Peutz-Jegher syndrome associated malignant sex cord stromal tumor with annular tubules. *Int J Appl Basic Med Res* 2013; 3: 126–128. DOI: 10.4103/2229-516x.117093.

13. Lele SM, Sawh RN, Zaharopoulos P, et al. Malignant ovarian sex cord tumor with annular tubules in a patient with Peutz-Jeghers syndrome: a case report. *Mod Pathol* 2000; 13: 466–470. DOI: 10.1038/modpathol.3880079.

14. Cella L, Liuzzi R, D'Avino V, et al. Pulmonary damage in Hodgkin's lymphoma patients treated with sequential chemo-radiotherapy: predictors of radiation-induced lung injury. *Acta Oncol* 2014; 53: 613–619. DOI: 10.3109/0284186x.2013.850739.