CASE REPORT

Recurrence of immature ovarian teratoma as malignant follicular carcinoma with liver and peritoneal metastasis 22 years after completion of initial treatment

Nicholas Brian Shannon,¹ Norman Hok Ling Chan,² Melissa Ching Ching Teo³

¹Department of General Surgery, Singapore General Hospital, Singapore

²Department of Pathology, Singapore General Hospital, Singapore

³Division of Surgical Oncology, National Cancer Centre Singapore, Singapore

Correspondence to

Dr Melissa Ching Ching Teo, melissa.teo.c.c@singhealth.com.sg

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SUMMARY

Growing tumour syndrome (GTS) is a rare event in which germ cell tumours treated with chemotherapy undergo maturation, acquire resistance to chemotherapy and regrow. The optimum treatment strategy is complete surgical excision. We report on a case of GTS with malignant metastases to the liver presenting 22 years after completion of treatment for immature teratoma, successfully managed with surgical resection alone.

BACKGROUND

Growing tumour syndrome (GTS) is a rare event in which non-seminatous germ cell tumours (NSGCTs) exhibit tumour growth during or after systemic chemotherapy with the histological presence of only mature teratoma at the time of tumour resection. This can occur after a significant disease-free period or after initial reduction in size following chemotherapy with subsequent regrowth. As GTS is resistant to chemotherapy and radiotherapy, such cases should be managed with complete surgical resection. We report on a case in which late recurrence of disease exhibited malignant transformation, and control in this setting was achieved with definitive surgical resection, demonstrating the feasibility of upfront metastasectomy, followed by observation.

CASE PRESENTATION

The patient presented here is a 57-year-old woman with no history of alcohol or tobacco consumption. She is not married, is without children and previously worked in a bank. Her history at the time of presentation included an immature ovarian teratoma treated with a total hysterectomy, bilateral salpingo-oophorectomy in 1992 followed by adjuvant chemotherapy (five cycles of MTX/VP16). She was also noted to have a liver nodule resection in 1994 and was told that the histology indicated benign disease. Aside from well-controlled hypertension, there was no other medical or surgical history of note. She presented to us after a rise in carcinoembryonic antigen (CEA) from 5.8 (2011) to 47.3 (2013) was noted during follow-up for her ovarian teratoma.

Relevant investigations carried out before her presentation to us were as follows:

CT (18 January 2013) reported right pelvic cyst 2.9 cm, subsequent MRI (26 February 2013) reported right adrenal cyst 3 × 2.8 cm. A PET scan (6 January 2014) reported a low-grade level 2 cervical lymphadenopathy; a 2.5 cm subcarinal lymph node with mild (standard uptake value 3.7) uptake. Ultrasound of the liver (8 February 2014) noted a 2 cm liver lesion suspicious for metastasis from unknown primary. Biopsy of liver lesion (5 March 14) was reported as follicular cancer on histological examination, consistent with thyroid metastasis. A subsequent review of the histopathology was confirmatory of follicular neoplasm, positive for thyroglobulin, TTF1 and CK7 immunohistochemistry.

INVESTIGATIONS

A repeat preoperative PET scan (29 April 2014) was performed to determine the nature of the pelvic lesion and exclude other sites of metastases apart from the definite liver metastasis. The scan was suspicious for metastasis with a heterogeneously avid right pelvic soft-tissue density abutting the bladder and sigmoid colon with grossly stable focal uptake at the lateral margin, with no abnormal uptake in the previously noted subcarinal lymph node. Preoperative tumour markers included an elevated CEA (147 µg/L), with normal CA125 (cancer antigen 125, 11.7 U/mL) and AFP (alpha-fetoprotein, 2.1 µg/L).

A preoperative thyroid radiotracer scan and ultrasound (2 May 2014) were negative for a thyroid primary cancer and thyroid function tests were within normal limits (T4 13.9 pmol/L, thyroid-stimulating hormone 1.91 mU/L), although thyroglobulin was elevated (159 µg/L). Thyroglobulin antibodies remained within normal limits (<10 U/mL).

There was no significant dysregulation noted in liver function tests (total bilirubin 6 µmol/L, alkaline phosphatase 114 U/L, alanine aminotransferase 19 U/L, aspartate aminotransferase 21 U/L, gamma-glutamyl transferase 26 U/L).

DIFFERENTIAL DIAGNOSIS

The initial suspicion after biopsy of the liver lesion was that of thyroid follicular carcinoma with metastasis to liver. After discussion at a multidisciplinary

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team meeting (MDTM), additional investigations were carried out to identify the primary lesion and determine the extent of metastatic disease. Unfortunately, histology from the original resection of the ovary is not available for review (as it was resected elsewhere 22 years ago and not available for review). We surmise that the original diagnosis was a teratoma, based on the different components identified in the peritoneal implants and on the morphology of the liver metastasis. F, investigations of the neck fail to show a primary thyroid neoplasm (or evidence of metastasis of papillary or follicular carcinoma above the diaphragm). The only possible source for the metastatic follicular carcinoma discovered in the liver is from the ovary.

TREATMENT

After discussion at multidisciplinary tumour board, the decision was made for cytoreductive surgery for the pelvic mass and liver metastasis and for hyperthermic intraperitoneal chemotherapy (HIPEC), if frozen section analysis confirmed the diagnosis of metastatic ovarian cancer. Cytoreductive surgery would provide definitive diagnosis of disease and potentially avoid ablation of normal thyroid tissue as part of medical ablation, which would subsequently require lifelong thyroid replacement. Indications for HIPEC would be if there was a single liver lesion amenable to wedge resection and the lesions were supportive of ovarian cancer. HIPEC would be contraindicated if the lesions were not supportive of ovarian cancer, if there were more than a single liver lesion or if the liver lesions were bulky and/or difficult to resect.

Surgical resection (6 May 2014) was planned for the pelvic cystic mass along with a liver resection of the segment VI liver metastasis.

The procedures were carried back to back on the same day rather than as a staged procedure. First, the liver resection was performed after confirmation of the absence of other metastatic liver lesions. A frozen section analysis confirmed the presence of metastatic follicular carcinoma in the liver lesion, with adequate clear resection margins attained.

Second, resection of two pelvic masses (2 cm and 8×7 cm in size) was performed, along with peritonectomy of diseased peritoneum in the pelvis and right paracolic gutter. The final Peritoneal Cancer Index score was 9. Multiple small bowel/mesentery nodules were noted, but were deemed negative for malignancy on frozen section analysis.

The decision was made not to proceed with HIPEC due to the possibility of the lesion being an ovarian stromal tumour.

The final histological reports were of a 5×5×4 cm mature cystic teratoma adjacent to the rectum, with mature thyroid tissue present in a pararectal and peritoneal nodule, and mucinous implants located at the right paracolic peritoneum, pelvis and appendix without involvement of the vermiform appendix (table 1). Well-differentiated to moderately well-differentiated follicular carcinoma was reported in a 1.7×1.5×2.5 cm liver lesion. Resection margins were all widely clear. Postoperative day 6 CEA remained raised at 42.2 µg/L, but downtrending (preoperative at 147 µg/L, postoperative day 3 at 62 µg/L).

The overall impression was that of a combined mucinous/teratomatous ovarian tumour or somatic malignancies arising from an ovarian teratoma with subsequent implantation, consistent with the growing tumour syndrome.

After further MDTM discussion, the decision was made to observe. It was felt that there was little role for upfront 'adjuvant fashion' radioiodine ablation (RAI) given R0 resection with widely clear margins, with the avoidance of thyroid ablation with RAI. The options remained for treatment later with

Table 1 Histology reported from surgical specimens

Surgical specimen	Histopathological report
Liver segment 6	Follicular carcinoma consisting of thyroid follicles with malignant features, well differentiated to moderately well differentiated (figure 1A)
Mucoid material from right paracolic gutter	Free mucin present, no neoplastic epithelium seen
Right lower peritoneal nodule	Mature cystic teratoma containing non-neoplastic mature thyroid tissue (figure 1B)
Mesenteric nodule, small bowel	Benign fibrous nodule
Right pelvic lesion	Mucinous implants with fibrotic reaction around
Tumour over the ascending colon	Benign fibrous nodule with mature fat
Nodule over rectum	Mature cystic teratoma (figure 1C)
Ileocolic lymph node	Mucinous implants with fibrotic reaction around mucin pools
Small bowel mesentery nodule	Benign regional lymph node
Vermiform appendix	Extra appendiceal mucinous implant with fibrous reaction, no connection to the appendiceal lumen
Right paracolic peritoneum	Mucinous implants with fibrotic reaction and surface mucin

radioactive ablation should the thyroid malignancy recurred and for repeat cytoreductive surgery should the mucinous ovarian tumour recur. The patient was discharged well with a follow-up plan of 6 monthly CEA levels and CT.

OUTCOME AND FOLLOW-UP

A follow-up CT scan performed on 30 October 2014, 6 months after surgery, was reported as showing calcified peritoneal nodules near the anterior abdominal wall close to the laparotomy scar, in the rectovesical pouch, pelvic mesentery and in the left paracolic gutter and cystic lesions next to the rectosigmoid junction near the external iliac artery. The lesions were

Figure 1 (A) Metastatic nodule to liver. *Well-circumscribed nodule with follicular architecture consistent with metastasis from thyroid tissue. Nodule made of dense compact and microfollicular pattern characteristic in keeping with malignant thyroid tissue. †Rim of benign hepatocytes adjacent to nodule. (B) Peritoneal deposits of teratoma. Different components are illustrated as follows. *Mature thyroid tissue, non-neoplastic; please note different size in thyroid follicles. †Mature cartilaginous airway. (C) Mature teratoma demonstrating mature cartilaginous airway with respiratory type epithelium.

thought to represent residual benign fibrous nodules. Subsequent follow-up CT scans (16 April 2015, 19 October 2015 and 12 April 2016) have continued to report these as stable and have not revealed any new peritoneal deposits, lymphadenopathy or distant metastases.

Our last follow-up with the patient was on 13 April 2016. She remains well. All tumour markers (last CA125 38.8, CA15-5 11.7, CA19-9 8.6, CEA 3.4, AFP 2.8) and thyroid function tests (last thyroid-stimulating hormone 4.17, T4 14.2) have remained within normal limits.

DISCUSSION

GTS was first described in 1982 by Logothetis *et al*¹ but remains a rare clinical entity. Diagnosis relies on three criteria: (1) normalisation of elevated serum tumour markers, (2) tumour growth during or after systemic chemotherapy and (3) histological presence of only mature teratoma at tissue resection. It may occur in 2%–7% of NSGCTs.^{2–4}

GTS present as regrowth of NSGCT following an initial period of disease control with chemotherapy, most commonly in the retroperitoneum. Despite usually being seen during chemotherapy, or shortly after, GTS has been reported up to 9 years following completion of treatment for NSGCT.⁵ On imaging, GTS tumours demonstrate cystic components with necrosis, although tumour growth is the only consistent feature of GTS. A median growth rate of 0.5 cm/month in GTS has been reported.⁶ Although the liver is an atypical site for GTS, the appearance of mature cystic teratoma in the liver has previously been reported in two patients with immature ovarian tumours undergoing chemotherapy.⁷

There are two predominant theories as to the mechanism behind GTS: (1) chemotherapy stimulates differentiation of immature teratomatous tissue into mature tissue, and (2) chemotherapy results in selective abrogation of abnormal dedifferentiated tissue, leaving mature teratoma (MT) behind. Evidence for clonal selection of less abnormal phenotype in postchemotherapy MT suggests the latter theory may be correct,⁸ and this view is strengthened by the observation that the presence of MT in NSGCT conveys increased risk of GTS following treatment.

GTS are unresponsive to chemotherapy and radiation therapy and so are best treated with surgical resection.^{5,6} With adequate treatment, GTS have a good prognosis with 5-year survival of 89% achieved.⁵ Completeness of surgical resection is important due to a high recurrence rate when resection is incomplete (72%–83%) compared with 0%–4% in those who undergo complete resection.⁹ Delay in treatment has been associated with increased morbidity and death, usually due to complications secondary to compression of adjacent structures,^{2,4,10} and as such surveillance is not recommended. Andre *et al*¹⁰ identify several factors identifying NSGCT at high risk of GTS: (1) presence of MT in NSGCT, (2) no reduction in the size of metastases during chemotherapy and (3) presence of MT in postchemotherapy residual masses. Patients identified as high risk based on these factors should undergo closer monitoring to detect early GTS when it is more amenable to surgical resection. While mature tumours have been reported to undergo malignant transformation at a rate of 3% including malignant NSGCT, sarcoma, squamous cell carcinoma, adenocarcinoma, carcinoid and pancreatic

neuroendocrine tumor,¹⁰ whether this is representative of rate of transformation GTS is unclear, although transformation of GTS to sarcoma has been previously reported.¹¹

The case presented here represents the longest reported interval period prior to the development of GTS, with the patient presenting 22 years since completion of therapy for immature teratoma. Furthermore, the recurrence of disease in the liver and transformation to malignant follicular carcinoma are atypical features of GTS. In this setting, we have demonstrated the feasibility of upfront metastasectomy to achieve disease control and observation in patients in whom R0 resection can be achieved.

Learning points

- Growing tumour syndrome (GTS) is a rare condition in which tumour growth is seen following initial control of immature teratoma with chemotherapy.
- As GTS are resistant to chemotherapy and radiation therapy, complete surgical resection is the mainstay of management.
- Morbidity and mortality in GTS are typically due to complications resulting from compression of adjacent structures.
- With adequate treatment, GTS have a good prognosis with a 5-year survival of 89%.

Contributors All of the authors have participated in the research design, analysing of data and writing of the paper. The authors have reviewed the manuscript and approved it for submission. NBS participated in writing the article and received informed consent from the patient. NHLC is responsible for histological review and diagnosis and critically revised the article. MT is responsible for surgical care of the patient and critically revised the article.

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REFERENCES

- 1 Logothetis CJ, Samuels ML, Trindade A, *et al*. The growing teratoma syndrome. *Cancer* 1982;50:1629–35.
- 2 Jeffery GM, Theaker JM, Lee AH, *et al*. The growing teratoma syndrome. *Br J Urol* 1991;67:195–202.
- 3 Tonkin KS, Rustin GJ, Wignall B, *et al*. Successful treatment of patients in whom germ cell tumour masses enlarged on chemotherapy while their serum tumour markers decreased. *Eur J Cancer Clin Oncol* 1989;25:1739–43.
- 4 Tongaonkar HB, Deshmone VH, Dalal AV, *et al*. Growing teratoma syndrome. *J Surg Oncol* 1994;55:56–60.
- 5 Li S, Liu Z, Dong C, *et al*. Growing teratoma syndrome secondary to ovarian giant immature teratoma in an adolescent girl. *Medicine* 2016;95:e2647–8.
- 6 Lee DJ, Djaladat H, Tadros NN, *et al*. Growing teratoma syndrome: clinical and radiographic characteristics. *Int J Urol* 2014;21:905–8.
- 7 Lorusso D, Malaguti P, Trivellizzi IN, *et al*. Unusual liver locations of growing teratoma syndrome in ovarian malignant germ cell tumors. *Gynecol Oncol Case Rep* 2011;1:24–5.
- 8 Castedo SM, de Jong B, Oosterhuis JW, *et al*. Chromosomal changes in mature residual teratomas following polychemotherapy. *Cancer Res* 1989;49:672–276.
- 9 Spiess PE, Kassouf W, Brown GA, *et al*. Surgical management of growing teratoma syndrome: the M. D. Anderson cancer center experience. *J Urol* 2007;177:1330–4.
- 10 André F, Fizazi K, Culine S, *et al*. The growing teratoma syndrome: results of therapy and long-term follow-up of 33 patients. *Eur J Cancer* 2000;36:1389–94.
- 11 DeLeo MJ, Greco FA, Hainsworth JD, *et al*. Late recurrences in long-term survivors of germ cell neoplasms. *Cancer* 1988;62:985–8.

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