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Case report

Malignant struma ovarii presenting with follicular carcinoma: A case report with molecular analysis

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ABSTRACT

Malignant struma ovarii presenting with follicular carcinoma is extremely rare, and its mechanism of tumorigenesis remains unknown. Here, we present a case of malignant struma ovarii with peritoneal dissemination of follicular carcinoma, for which a molecular analysis for major oncogenic gene alterations in follicular thyroid carcinoma was performed. A 39-year-old nulliparous woman was referred with a diagnosis of highly differentiated follicular carcinoma of ovarian origin. Primary thyroid cancer was not diagnosed, and she had a normal thyroid function. ^{123}I scintigraphy revealed multiple peritoneal dissemination that was surgically resected. Histologically, the tumor consisted of numerous follicles without nuclear features of papillary thyroid carcinoma. Tumor samples were investigated for 50 cancer-related genes, including *RAS, BRAF*, and *p53*, and *PPARg-PAX8* gene fusion by targeted DNA sequencing and fluorescence in situ hybridization, respectively. No major oncogenic gene alterations were detected. These negative findings suggest a different mechanism of tumorigenesis from that of adult-type follicular thyroid carcinoma.

1. Introduction

Struma ovarii is a specialized or monodermal teratoma predominantly composed of mature thyroid tissue, and its malignant counterpart has thyroid cancer components. Malignant struma ovarii (MSO) presenting with follicular-type carcinoma is extremely rare. Most MSO lesions histologically appear as papillary carcinoma; approximately 50 cases of MSO with follicular-type carcinoma have been reported in the English literature (Table 1). Recently, driver gene alterations of thyroid cancer have been elucidated, and a few reports showed that MSO presenting with papillary carcinomas harbored *BRAF* or *RAS* gene mutations (Gobitti et al., 2017; Tan et al., 2015) that are frequently observed in papillary thyroid carcinoma (Cancer Genome Atlas Research, 2014). However, MSO with follicular carcinoma (MSOFC) has not been assessed for known major molecular alterations in follicular thyroid carcinoma such as *RAS* gene mutations and *PPARg-PAX8* fusion (Raman and Koenig, 2014; Vasko et al., 2003).

The histological diagnosis of MSOFC is often challenging, because it is frequently impossible to evaluate capsular invasion in the ovary. In these cases, a diagnosis of MSOFC is based on the evidence of malignant behaviors such as the presence of vascular invasion, dissemination, or metastasis. Therefore, the identification of a specific molecular alteration in MSOFC can be a useful biomarker for the prediction of malignant behavior of MSOFC even when confined to the ovary.

Herein, we report a case of MSOFC presenting with peritoneal dissemination for which we performed molecular analysis including DNA sequencing, immunohistochemistry, and fluorescent in situ hybridization (FISH) for major pathogenic molecular alterations in thyroid follicular carcinoma. To the best of our knowledge, this is the first report of MSOFC with detailed molecular analysis.

2. Case presentation

A 39-year-old nulliparous woman was referred with a diagnosis of highly differentiated follicular carcinoma of ovarian origin (HDFCO). She underwent left salpingo-oophorectomy for mature cystic teratoma with thyroid tissue in the left ovary 16 years ago and cystectomy for right struma ovarii 8 years ago. Two years ago, an approximately 4 cm wide ovarian mass was detected that had increased in diameter up to 7 cm. Furthermore, other new lesions were found in the pelvic cavity.

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Table 1
Previously reported cases of malignant struma ovarii with follicular carcinoma.

#	First author	Year	Age	Extraovarian spread	Treatment of extraovarian disease	Prognosis and follow-up
1	De Graaff	1983	72	Peritoneal dissemination	Omentectomy	NED, 3 yrs
2	Willemse	1987	36	Peritoneal dissemination	RAI	Rec, 4 mo
3	O'Connell	1990	35	No	None	NED
4	Zakhem C1	1990	52	No	None	NED, 1.7 yrs
5	Zakhem C2	1990	30	No	None	NED, 2.7 yrs
6	Kragel	1991	37	Peritoneal dissemination	None	NED, 5 yrs
7	Thomas C1	1992	17	Peritoneal dissemination	RAI	NED, 2 yrs
8	Thomas C2	1992	35	Peritoneal dissemination	Omentectomy	NA
9	Ito	1992	36	Bone metastasis	Chemotherapy	NED, 1 mo
10	Balasch	1993	36	Peritoneal dissemination	RAI to be considered	NA
11	Ayhan	1993	66	Peritoneal dissemination	Omentectomy	AWD, 8 yrs
12	Tokuda	1993	25	Cranial metastasis	Resection	NED
13	Karseladze	1994	49	Peritoneal dissemination	Chemotherapy	NED, 16.3 yrs
14	Piana	1994	26	No	None	NED 1 yr
15	Brenner	1996	49	Urinary bladder metastsis	RAI	NED, 3.2 yrs
16	Tennvall C1	1997	50	Peritoneal dissemination	Omentectomy, RAI	NED, 6 yrs
17	Tennvall C2	1997	43	Peritoneal dissemination	None	Died(GBC), 4 mo
18	Mango	1997	47	Pelvic bone metastasis	RAI	AWD, 4 mo
19	Barrande	1997	31	No	RAI	NED, 6 mo
20	Bhansali	1999	47	No	Radiation	NED, 4 yrs
21	Takeuchi C1	2000	43	Peritoneal dissemination	Omentectomy	NED, 7 yrs
22	Takeuchi C2	2000	70	Peritoneal dissemination	Omentectomy, PLND	NED, 2 yrs
23	Rotman-Pikielny	2000	46	Liver metastasis	RAI	AWD, 6 mo
24	Konez	2000	45	Liver metastasis	RAI	NA
25	Chan	2001	27	Bone metastasis	RAI	AWD, 8 mo
26	Checrallah	2001	38	Lung and bone metastasis	RAI	AWD, 6 yrs
27	DeSimone	2003	32	No	RAI	NED, 1.2 yrs
28	Kdous	2003	45	No	None	NED, 1 yr
29	Brogsitter	2004	50	Peritoneal dissemination	RAI	NED, 6 mo
30	Ihalagama	2004	27	Pritoneal cyology positive	RAI	NED 1.5 yrs
31	Garcia	2005	22	Invasion to adjucent tissue	Resection	NED, 6 yrs
32	McDougall	2006	17	Liver and bone metastasis	RAI	AWD, 4 yrs
33	Zekri	2006	26	Lung and bone metastasis	RAI	AWD, 15 yrs
34	Roth, C1	2008	32	Peritoneal dissemination	RAI	Rec, 26 yrs
35	Roth, C2	2008	49	Peritoneal dissemination	Chemotherapy	NED, 16.3 yrs
36	Roth, C3	2008	50	Peritoneal dissemination	Resection & RAI	NED, 6 yrs
37	Roth, C4	2008	70	Peritoneal dissemination	RAI	DOD, 3 yrs
38	Prasad	2008	40	Pelvic mass	Resection & RAI	NED, 4 yrs
39	Kim	2009	49	Peritoneal dissemination	Omentectomy	NA
40	Michels	2010	41	Peritoneal dissemination	RAI	AWD, 3 mo
41	Selvaggi	2012	50	Peritoneal dissemination	Omentectomy	NED, 1 yr
42	Shirimali, C1	2012	52	Vaginal vault mass	RAI	NA
43	Shirimali, C2	2012	59	Peritoneal dissemination	RAI	NA
44	Shirimali, C3	2012	53	Peritoneal dissemination	RAI	NA
45	Carey	2014	70	Peritoneal dissemination	RAI	NA
46	Ukita	2014	45	Lung and bone metastasis	Chemotherapy	AWD, 20 yrs
47	Cong	2015	38	Lung metastasis	RAI	AWD, 3 yrs
48	Kobayashi	2015	49	Spinal metastasis	Radiation	AWD, 9 mo
49	Ranade	2015	55	Peritoneal dissemination	RAI	AWD, 3 mo
50	Park	2015	35	Peritoneal dissemination	RAI	NED, 25 mo
51	Anagnostou	2016	64	Peritoneal dissemination	Omentectomy	NED, 4 yrs
52	Riggs	2018	32	Peritoneal dissemination	Laparoscopic resection	NED, 1 yr
53	*Present case*	2019	39	Peritoneal dissemination	Resection & RAI	AWD, 2 yrs

Abbreviations; RAI, radioactive iodine therapy; NED, no evidence of disease; Rec, recurrence; NA, not available; AWD, alive with disease; GBC, gallbladder cancer; DOD, death of disease; C# denotes case# in the same report; PLND, pelvic lymph node dissection.
The complete list of all the reference above is provided as Supplementary material.

These lesions were surgically resected and histologically diagnosed as peritoneal dissemination of HDFCO. She had no primary thyroid cancer, and thyroid function test results (serum T3, T4, and TSH) were normal. At our hospital, ^{123}I scintigraphy revealed multiple lesions in the abdominopelvic cavity and she underwent an abdominal hysterectomy, right salpingo-oophorectomy, and partial omentectomy for residual tumors. All macroscopic tumors were removed. She was discharged without any complications. Although no macroscopic residual disease was found intraoperatively, intraperitoneal microscopic residual disease was detected via ^{123}I scintigraphy performed 6 weeks after the surgery. Additional radioactive iodine therapy (RAI) was planned for the residual disease, and total thyroidectomy was performed in preparation for RAI. Pathological examination revealed an adenomatous goiter without any malignant features. Two months after thyroidectomy, RAI was initiated. After completing 4 cycles of RAI, the patient has been alive with residual disease for 2 years after the gynecologic surgery.

2.1. Pathological findings

Macroscopically, there were multiple tan-colored solid tumors on the omentum (Fig. 1A and B), and the largest mass was 4 × 3 × 2.5 cm in size. Microscopically, there were many follicles of various sizes composed of tumor cells without nuclear features of papillary thyroid carcinoma such as overlapping nuclei, irregular contours, nuclear grooves, pseudo inclusions, and chromatin clearing. Microscopic lesions were also found in the right ovary and on the uterine serosa. No carcinoid component was observed. Tumor cells showed mild nuclear

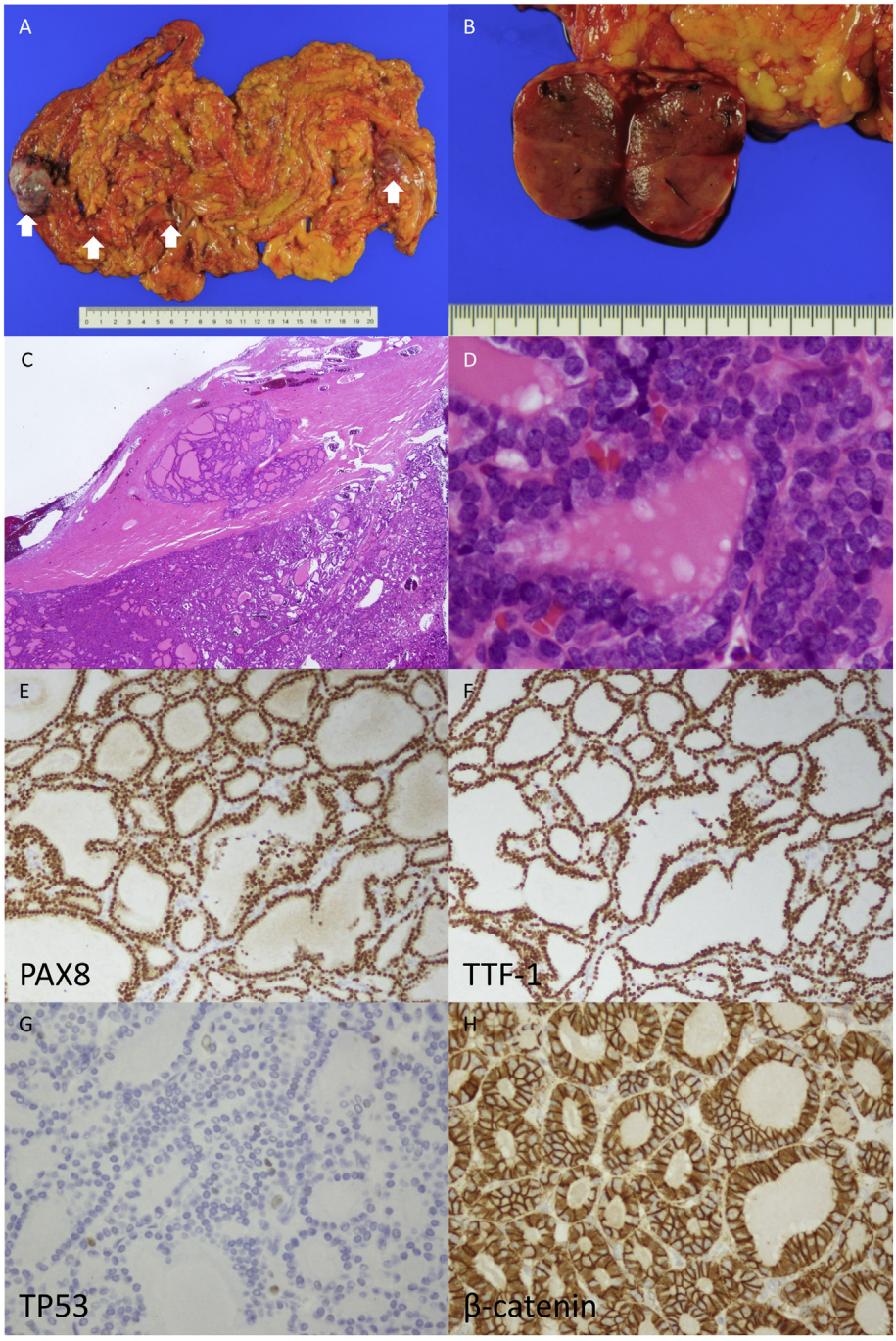

Fig. 1. Malignant struma ovarii presenting with follicular carcinoma. (A) There are multiple tumor nodules on the omentum. (B) The cut surface of the tumor is tan-colored and solid. (C) At low magnification, there are follicles of various sizes containing pink-colored colloid resembling thyroid follicular tumor. (D) At higher magnification, no nuclear features suggesting papillary carcinoma, nuclear groove, ground-glass appearance, and intranuclear cytoplasmic inclusion are observed. Immunohistochemically, tumor cells show diffuse positivity for PAX8 (E) and TTF-1 (F). Scattered p53 positive tumor cells showing a wild-type staining pattern (G). Nuclear accumulation of β-catenin is not observed. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

atypia and formed numerous micro- to normal-sized follicles, resembling a thyroid follicular tumor rather than non-neoplastic thyroid tissue. Immunohistochemically, tumor cells showed diffuse positivity for TTF-1 and PAX8 (Fig. 1E and F). The final pathological diagnosis was peritoneal dissemination of MSOFC.

2.2. Molecular analysis

All molecular analyses were approved by the institutional review board of our hospital. A representative section of an omental lesion was selected for all subsequent analyses. Immunohistochemical analyses for p53, β-catenin, $BRAF^{V600E}$, and PTEN and split FISH assay for *PPARgamma* rearrangement were performed on formalin-fixed paraffin-embedded specimens. Targeted sequencing of 50 cancer-related genes (the Ion Ampliseq™ Cancer Hotspot Panel version 2) was performed using DNA extracted from the resected tumor tissue. All the targeted genes are listed in the supplementary materials and methods. These 50 genes included well-known proto-oncogenes and tumor suppressor genes such as *BRAF*, *EGFR*, *ERBB2*, *HRAS*, *KIT*, *KRAS*, *NRAS*, *PIK3CA*, *PTEN*, *APC*, *CTNNB1*, *RET*, and *TP53*. Details of the methods of molecular analysis mentioned above are provided in the supplementary materials and methods.

The results of these analyses are described below. Immunohistochemically, tumor cells showed scattered positivity for p53, the so-called wild-type pattern (Fig. 1G). Nuclear accumulation of β-catenin was not observed (Fig. 1H). The tumor cells tested negative for $BRAF^{V600E}$. Split probe FISH assay for PPARgamma showed no split signals in the nuclei of tumor cells (Fig. 2). Target sequencing revealed no pathogenic/oncogenic mutations in the 50 cancer-related genes, including *BRAF*, *EGFR*, *HRAS*, *KRAS*, *NRAS*, *KIT*, *CTNNB1*, and *TP53*.

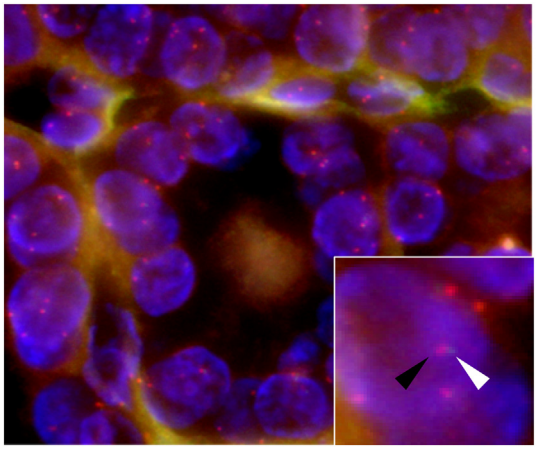

Fig. 2. Split probe fluorescence in situ hybridization assay for *PPAR-gamma* gene rearrangement. Red signal (distal gene region) and green signal (proximal gene region) were not split in the nuclei of tumor cells. The black and white arrowheads indicate red and green signals, respectively (inset). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Discussion

We, herein, reported a rare case of MSOFC presenting with peritoneal dissemination for which we performed a molecular analysis. The major known driver gene alterations in follicular thyroid carcinoma were not detected, which implied the possibility of a different mechanism of tumorigenesis for MSOFC.

MSOFC is extremely rare, and about 50 cases have been reported, including HDFCO (the so-called peritoneal strumosis) and MSO with typical follicular carcinoma (Table 1). To date, there has been only one case of death due to this tumor with a poorly differentiated follicular carcinoma component (Roth et al., 2008). Most cases did not show dismal prognoses; however, the long-span of recurrent disease deteriorates the quality of patients' lives.

Making a diagnosis of MSOFC is challenging, especially for cases confined to the ovaries, and histomorphological features play a limited role in predicting subsequent malignant behavior. The present case was diagnosed as mature teratoma with thyroid tissue 16 years ago and the same tumor cells formed multiple lesions in the right ovary 8 years ago, on the peritoneum, and omentum 2 years ago. Unless peritoneal dissemination, evidence of malignant behavior, was detected, a diagnosis of MSOFC could not be rendered. This is because the tumor confined to the ovary showed no histological evidence of malignancy such as vascular invasion. Therefore, any specific molecular abnormalities in MSOFC would become useful biomarkers for predicting peritoneal dissemination or metastasis.

Driver gene mutations of thyroid cancer have been well investigated, and a correlation with histological subtypes has also been reported (Cancer Genome Atlas Research, 2014; Raman and Koenig, 2014; Vasko et al., 2003). The majority of papillary thyroid cancers are reported to have $BRAF^{V600E}$, *RAS*, and *RET* genetic alterations, which are most often mutually exclusive (Cancer Genome Atlas Research, 2014). Moreover, follicular thyroid cancers harboring either *RAS* mutations or *PAX8/PPARG* gene fusion comprise approximately 80% of cases (Gianoukakis et al., 2011). Furthermore, less differentiated carcinomas, such as anaplastic carcinomas, have been reported to harbor *p53* mutations or abnormalities in β-catenin signaling. The phosphatidylinositide 3-kinase (PI3K)/AKT pathway is also affected and can occur by activating mutations in *PIK3CA* or *AKT1*, or loss of *PTEN*. A few reports showed that *BRAF* mutations frequently occur in MSO with papillary carcinoma but not benign tumors (Schmidt et al., 2007), and *RAS* mutations were reported in MSO with follicular variants of papillary carcinoma (Tan et al., 2015). These authors postulated that MSO with papillary carcinoma might share a mechanism of carcinogenesis with papillary thyroid carcinoma. Recently, Park et al. first reported a case of MSOFC without mutation of $BRAF^{V600E}$, *RAS* (*HRAS* codon 61, *NRAS* codon 61, and *KRAS* codon 12/13), and *PAX8/PPARG* gene fusion (Park et al., 2015). Unfortunately, detailed materials and methods of the analysis are not given in the article. In line with this previous report, we did not detect any major molecular alterations in this case, regardless of more extensive analyses, including mutation analyses of 50 cancer-related genes. These negative findings may suggest different mechanisms of tumorigenesis in MSOFC. Interestingly, infrequent *RAS* mutations and *PPARgamma* rearrangement is reported as a unique feature of pediatric follicular thyroid carcinoma. Vuong et al. reported that only 12.2% (5/41) of *NRAS* mutations and no *PPARgamma* rearrangements occurred in 41 pediatric cases of follicular thyroid carcinoma (Vuong et al., 2017). We, therefore, speculate that MSOFC is a type of malignant transformation of monodermal teratoma and may be similar to pediatric follicular thyroid carcinoma rather than the adult-type.

Since we investigated only one case and analyzed a limited number of gene alterations, a strong conclusion could not be drawn. We expect that our findings will be validated in another cohort of MSOFC cases and evoke additional analyses. The identification of new driver gene alterations may require more extensive investigations such as whole-exome sequencing.

Summarily, we described a case of MSOFC without the major pathogenic molecular alterations of adult-type follicular thyroid cancer. These results imply the possibility of a different tumorigenesis pathway of MSOFC from that of thyroid follicular carcinoma. Further studies are needed to identify biomarkers for predicting malignant behavior.

Consent

Written informed consent was obtained from the patient for the publication of this case report.

Author contributions

Dr. Tsukada and Dr. Yoshida drafted and revised the manuscript and prepared the figures. Dr. Tsukada and Dr. Ishilawa collected the clinical data. Dr. Shiraishi and Dr. Asami performed all the mutation analysis. Dr. Ishikawa and Dr. Kato revised the manuscript. All the authors have read and approved the final manuscript.

Declaration of Competing Interest

We have no conflict of interest to declare. This work was supported by grants-in-aid from the Mitsui Life Social Welfare Foundation and the Public Foundation of the Vaccination Research Center.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2019.100498.

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