Int J Clin Exp Pathol 2017;10(11):11230-11233
www.ijcep.com /ISSN:1936-2625/IJCEP0064365

Case Report

Struma ovarii with unique histological features: a case report

Mitsumasa Osakabe[1], Tomoyuki Fukagawa[1], Daisuke Fukagawa[1], Ryo Sugimoto[1], Noriyuki Uesugi[1], Kazuyuki Ishida[1], Hiroaki Itamochi[2], Toru Sugiyama[2], Tamotsu Sugai[1]

Departments of [1]Molecular Diagnostic Pathology, [2]Obstetrics and Gynecology, School of Medicine, Iwate Medical University, 19-1, Morioka 020-8505, Iwate, Japan

Received August 24, 2017; Accepted September 29, 2017; Epub November 1, 2017; Published November 15, 2017

Abstract: We present a case of struma ovarii with unique histological features. A 57-year-old woman presented with a 13-cm multilocular cystic ovarian tumor. Histological examination demonstrated both differentiated (follicular patterns) and de-differentiated (diffuse, trabecular and small-sized solid nests) patterns, suggesting a histological diagnosis of struma ovarii. To identify the pathogenesis of the tumor, immunohistochemical (TTF1, thyroglobulin, T3, E-cadherin, ZEB1, Slug, and Twist) and genetic (*KRAS* and *BRAF*) analyses were performed. TTF1, thyroglobulin, and T3 were detected in both tumor components. Additionally, although E-cadherin was detected in the differentiated component, loss of E-cadherin was obvious in the de-differentiated component. Finally, we examined ZEB1, Slug, and Twist expression to identify the role of epithelial-mesenchymal transition (EMT) in tumor pathogenesis. Slug, ZEB1, and Twist were not expressed in the differentiated component, but ZEB1 expression was observed in the de-differentiated component. Moreover, no *KRAS* or *BRAF* mutations were detected in either component. These findings suggested that the histological transition from the differentiated to de-differentiated tissue was closely associated with the loss of E-cadherin expression. This loss may have been related to increased ZEB1 expression and lack of neoplastic features due to the absence of *KRAS* and *BRAF* mutations.

Keywords: Ovary, struma ovarii, immunohistochemistry, epithelial to mesenchymal transition, ZEB1

Introduction

Struma ovarii is the most common type of ovarian monodermal teratoma. It is a mature teratoma composed of thyroid tissue [1]. Histological variations of struma ovarii include a diffuse pattern, a microfollicular pattern, a trabecular pattern, a pseudotubular pattern, and small clusters of tumor cells [2, 3]. The follicular pattern (including macro- and micro-follicular patterns) is regarded as a differentiated type of thyroid tumor due the similarity of its histological features to normal thyroid tissue, such as colloid formation and obvious follicular formation. On the other hand, the trabecular, small-clustered, and diffuse patterns are thought to be de-differentiated types, due to the lack of colloid and follicular formations. These findings may represent a histological progression from differentiated to de-differentiated tumors.

Epithelial to mesenchymal transitions (EMT) play an important role in carcinogenesis [4, 5]. EMT is defined as the loss of adherens junctions and cell polarity, which leads to an abnormal cellular arrangement (from a differentiated to a de-differentiated pattern). It is thought that these changes are caused by suppression of E-cadherin expression. E-cadherin expression is regulated by the transcription factors ZEB1, Slug, and Twist, which are all known inducers of EMT [6, 7]. No previous reports have explored the role of EMT during the histological change of struma ovarii from a differentiated to a de-differentiated tumor.

Here, we describe a struma ovarii with unique histological features that evoke the process of histological change of the thyroid tumor, and suggest a novel pathway towards the development of this tumor.

Case presentation

A 57-year-old woman presented with postmenopausal vaginal bleeding. She was diagnosed

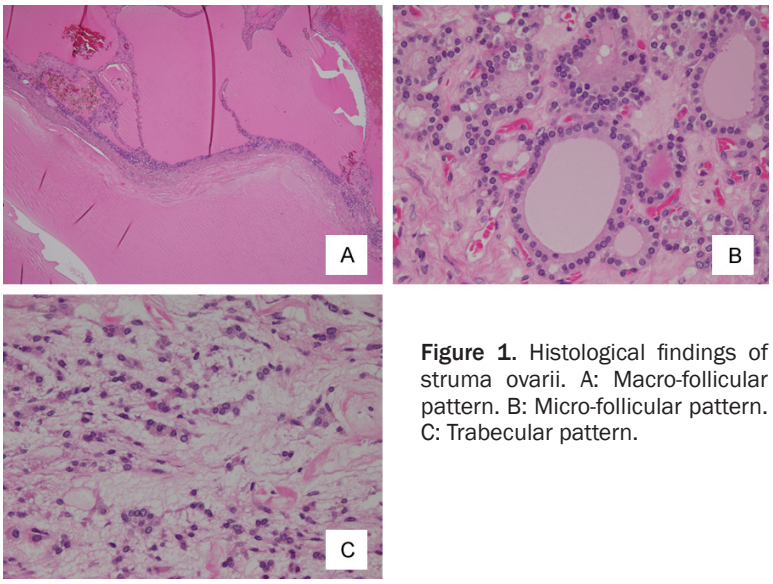

Figure 1. Histological findings of struma ovarii. A: Macro-follicular pattern. B: Micro-follicular pattern. C: Trabecular pattern.

with endometrial cancer and a right ovarian tumor. She underwent total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic lymphadenectomy. Her uterine tumor was diagnosed as endometrioid carcinoma, grade 1, FIGO stage IA.

Pathological findings of the struma ovarii

Macroscopically, the right ovary was enlarged with a maximum diameter of 13 cm. In addition, the ovary contained a multilocular cystic tumor with pale, yellow, solid components. Microscopically, the cysts were filled with colloid material and covered with flat and cuboidal epithelium (**Figure 1A**). Based on these histological findings, the tumor was diagnosed as struma ovarii. The solid component demonstrated two histological patterns. The first pattern was microfollicular (**Figures 1B**, **2A**) with colloid and follicular formations, resembling differentiated thyroid tissue. The second pattern consisted of trabecular growth of tumor cells and abundant stromal edema (**Figures 1C**, **3A**), resembling de-differentiated thyroid tumor tissue, based on undifferentiated histological findings and lack of colloid production.

To understand the association between the differentiated (micro-follicular) and de-differentiated (trabecular) pattern of the struma ovarii, immunohistochemical examination was performed using function markers of thyroid tissue (TTF-1, thyroglobulin, and T3) and EMT markers (ZEB1, Twist, and Slug). Immunohistochemical expression of TTF-1 (**Figures 2B**, **3B**), thyroglobulin (**Figures 2C**, **3C**), and T3 (**Figures 2D**, **3D**) was observed diffusely in both patterns. Whereas E-cadherin (**Figure 2E**) showed diffuse expression in the differentiated pattern, it was absent in the de-differentiated pattern (**Figure 3E**). Expression of Slug (**Figures 2F**, **3F**) and Twist (**Figures 2G**, **3G**) was not seen in either pattern, and ZEB1 was expressed in the de-differentiated pattern only (**Figure 3H**).

Finally, we evaluated *KRAS* and *BRAF* mutations in the struma ovarii in order to identify the neoplastic nature of the tumor. No *KRAS* or *BRAF* mutations were detected in either pattern.

Discussion

Struma ovarii is the most common type of ovarian monodermal teratoma. These tumors generally have simple histological features; however, diverse histological features have been reported [1, 2]. In the present report, we described a case of struma ovarii with unique histological features composed of both differentiated and de-differentiated patterns, the latter of which showed diffuse, trabecular, or small-nested solid features lacking colloid and follicular formations.

To examine the function of each histological pattern, we examined the expression of the thyroid markers TTF1, thyroglobulin, and T3. Each of these molecules were expressed in both histological patterns. This finding suggests that the de-differentiated tissue may have acquired mature thyroid function. This suggestion is supported by the finding that the serum T3 level was elevated in this patient.

Slug, ZEB1, and Twist are transcription repressors that suppress E-cadherin expression [8]. These proteins are known to be closely associated with reduced expression of E-cadherin, and suggest the presence of an EMT phenomenon. Although expression of Slug and Twist was not found in either the differentiated or

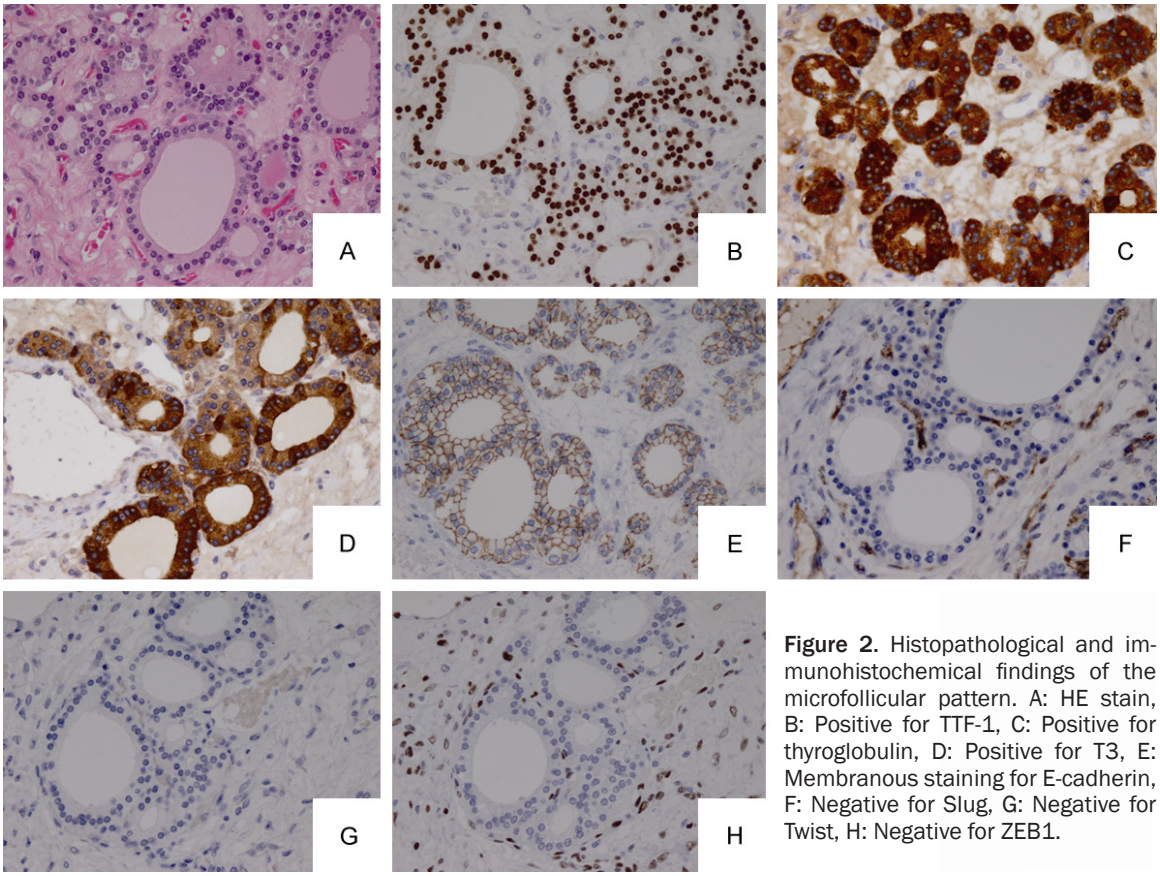

Figure 2. Histopathological and immunohistochemical findings of the microfollicular pattern. A: HE stain, B: Positive for TTF-1, C: Positive for thyroglobulin, D: Positive for T3, E: Membranous staining for E-cadherin, F: Negative for Slug, G: Negative for Twist, H: Negative for ZEB1.

undifferentiated pattern, ZEB1 was expressed in the de-differentiated pattern. This finding suggests that the transition from differentiated to de-differentiated tissue is induced by the expression of ZEB1, which in turn inhibits expression of E-cadherin. We suggest that the expression of EMT-related proteins may play an important role in the pathogenesis of struma ovarii.

A recent study found that *KRAS* and *BRAF* mutations are frequently found not only in thyroid carcinomas and adenomas, but also in adenomatous nodules, suggesting that these mutations may indicate the neoplastic nature of tumors [9]. Furthermore, it has previously been shown that *KRAS* and *BRAF* mutations occur in papillary thyroid carcinoma presenting as struma ovarii [10]. In this study, we examined *KRAS* and *BRAF* mutations in order to characterize the neoplastic nature of the struma ovarii. Interestingly, we did not identify any *KRAS* and *BRAF* mutations in the tumor tissue examined. This finding suggests that the tumor did not acquire neoplastic features. Accordingly, we suggest that proliferating thyroid tissue in struma ovarii may be hyperplastic rather than neoplastic.

In summary, we described a case of struma ovarii with unique histological features. Two different histological patterns, including differentiated (micro and macro-follicular features) and de-differentiated (diffuse, trabecular and small-nested features), were found in the struma ovarii. Although expression of E-cadherin was observed in differentiated pattern, E-cadherin was not expressed in un-differentiated pattern. In addition, ZEB1 was found in un-differentiated-pattern (not expressed in differentiated pattern). We suggest that EMT may play a role in the development of strumaovarii.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Tamotsu Sugai, Department of Molecular Diagnostic Pathology, Iwate Medical University, Morioka 020-8505, Iwate, Japan. Tel: +81-19-651-5111; Fax: +81-19-629-1436; E-mail: tsugai@iwate-med.ac.jp

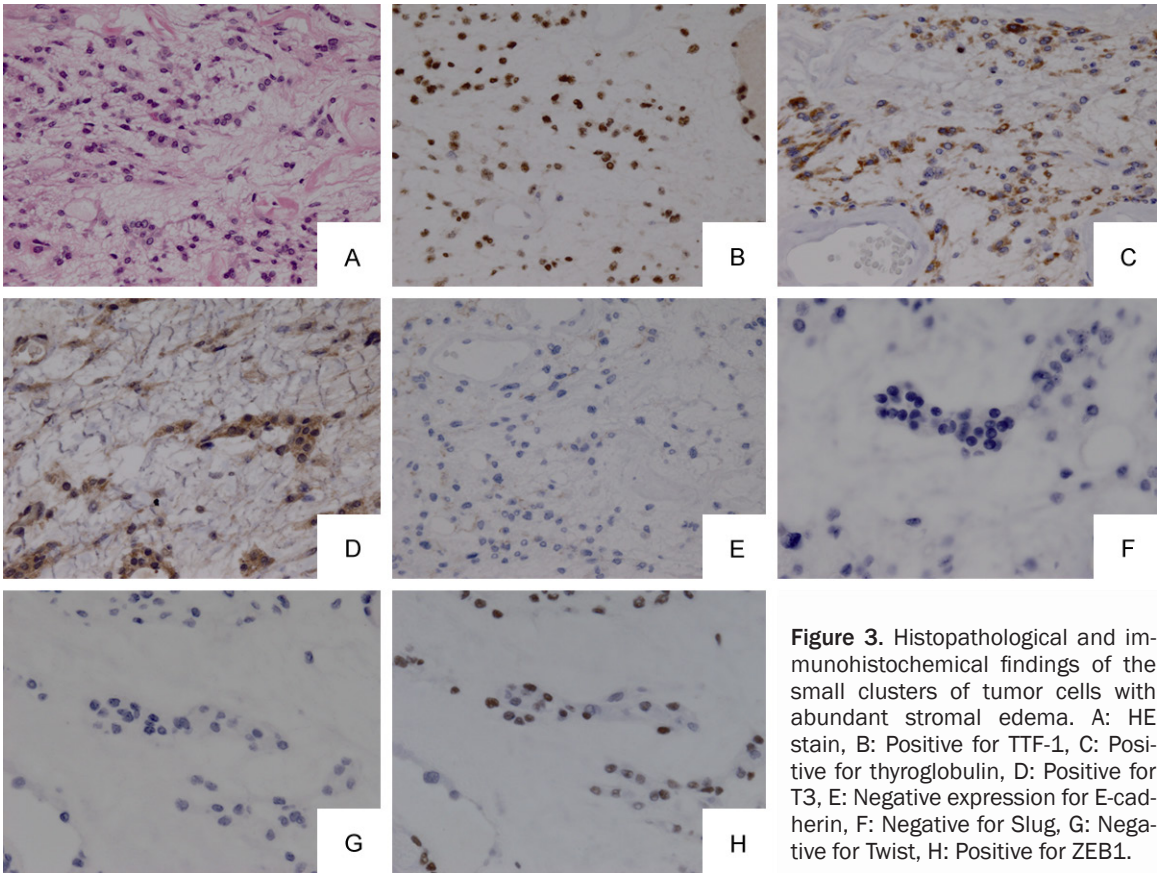

Figure 3. Histopathological and immunohistochemical findings of the small clusters of tumor cells with abundant stromal edema. A: HE stain, B: Positive for TTF-1, C: Positive for thyroglobulin, D: Positive for T3, E: Negative expression for E-cadherin, F: Negative for Slug, G: Negative for Twist, H: Positive for ZEB1.

References

[1] Prat J, Nogales FF, Cao D, Vang R, Carinelli SG and Zaloudek CJ. Monodermal teratomas and somatic-type tumours arising from a dermoid cyst. World Health Organization Classification of Tumours of Femal Reproductive Organs. In: Kurman RJ, Carcangiu ML, Herrington CS and Young RH, editors. Lyon: IARC Press; 2014. pp. 63-66.

[2] Szyfelbein WM, Young RH and Scully RE. Struma ovarii simulating ovarian tumors of other types. A report of 30 cases. Am J Surg Pathol 1995; 19: 21-29.

[3] McCluggage WG and Young RH. Immunohistochemistry as a diagnostic aid in the evaluation of ovarian tumors. Semin Diagn Pathol 2005; 22: 3-32.

[4] Thiery JP, Acloque H, Huang RY and Nieto MA. Epithelial-mesenchymal transitions in development and disease. Cell 2009; 139: 871-890.

[5] Polyak K and Weinberg RA. Transitions between epithelial and mesenchymal states: acquisition of malignant and stem cell traits. Nat Rev Cancer 2009; 9: 265-273.

[6] Peinado H, Olmeda D and Cano A. Snail, Zeb and bHLH factors in tumour progression: an alliance against the epithelial phenotype? Nat Rev Cancer 2007; 7: 415-428.

[7] Wang J, Lee S, Teh CE, Bunting K, Ma L and Shannon MF. The transcription repressor, ZEB1, cooperates with CtBP2 and HDAC1 to suppress IL-2 gene activation in T cells. IntImmunol 2009; 21: 227-235.

[8] Eger A, Aigner K, Sonderegger S, Dampier B, Oehler S, Schreiber M, Berx G, Cano A, Beug H and Foisner R. DeltaEF1 is a transcriptional repressor of E-cadherin and regulates epithelial plasticity in breast cancer cells. Oncogene 2005; 24: 2375-2385.

[9] Schulten HJ, Salama S, Al-Ahmadi A, Al-Mansouri Z, Mirza Z, Al-Ghamdi K, Al-Hamour OA, Huwait E, Gari M, Al-Qahtani MH and Al-Maghrabi J. Comprehensive survey of HRAS, KRAS, and NRAS mutations in proliferative thyroid lesions from an ethnically diverse population. Anticancer Res 2013; 33: 4779-4784.

[10] Tan A, Stewart CJ, Garrett KL, Rye M and Cohen PA. Novel BRAF and KRAS mutations in papillary thyroid carcinoma arising in strumaovarii. Endocr Pathol 2015; 26: 296-301.