

CASE REPORT

Primary tiny pure signet-ring cell carcinoma of vermiform appendix presenting as bilateral huge Krukenberg tumors

Tadashi Terada*

Department of Pathology, Shizuoka City Shimizu Hospital, Shizuoka, Japan

Received: December 30, 2015

Accepted: March 9, 2016

Online Published: March 24, 2016

DOI: 10.5430/crcp.v3n3p1

URL: <http://dx.doi.org/10.5430/crcp.v3n3p1>

ABSTRACT

Primary signet-ring cell carcinoma (SRCC) of vermiform appendix is extremely rare; only three cases have been reported in the English literature. A 52-year-old woman presented with abdominal mass. Physical examination revealed bilateral huge tumors in her ovarian sites. Blood tests demonstrated anemia and elevated tumor markers (CEA, 40 ng/ml; CA125, 580 ng/ml; CA72.4, 1771 U/ml; STN-AG, 19,000 U/ml; sialyl LE, 75 U/ml). Serum AFP, CA19-9, and CA15-3 were within normal limits. Upper and lower gastrointestinal endoscopy revealed no remarkable pathology. CT and MRI showed huge bilateral ovarian solid tumors without clinically apparent other tumors. The clinical diagnosis was primary bilateral ovarian tumors and bilateral oophorectomy was performed. During operation, several quick frozen sections were performed and both ovarian tumors (left: 18 cm, right: 13 cm) were found to be Krukenberg tumors. Accordingly, gynecologists did comprehensive abdominal examination to find out the primary site. They found a small tumor (3 cm × 1 cm) in the distal part of vermiform appendix, frozen sections of which revealed an SRCC. Cytologic evaluation of associated ascites at the operation was positive for carcinoma cells. Then the diagnosis of primary SRCC of appendix with both ovarian metastases (Krukenberg tumors) with peritoneal dissemination was given. Subsequent formalin fixation pathological examination gave the diagnosis. Immunohistochemically, the signet ring cells were positive for cytokeratin (CK) AE1/3, CK CAM5.2, CK8, CK18, CK19, CK20, EMA, CEA, CA19-9, p53, Ki-67 in 50% of tumor cells, CDX2, and MUC2. They were negative for CK34βE1, CK5/6, CK7, CK14, p63, vimentin, TTF-1, MUC1, MUC5AC, MUC6, NSE, synaptophysin, chromogranin, and CD56. She was now treated with chemotherapy 3 months after the operation.

Key Words: Vermiform appendix, Signet ring cell carcinoma, Krukenberg tumor, Histopathology, Immunohistochemistry

1. INTRODUCTION

Appendiceal cancer is very rare; it account for only 0.5% of all gastrointestinal neoplasms.^[1] According to a nationwide cancer database (SEER), the age-adjusted incidence of appendiceal malignancies was 0.12 cases per 1,000,000 people per year.^[1] Primary appendiceal cancer is diagnosed in only

0.9%-1.4% of appendectomy specimens.^[2] Furthermore, signet-ring cell carcinoma (SRCC) of vermiform appendix is extremely rare, accounting for 0.43% of all appendiceal malignancies.^[1] To the best of the author's knowledge, there have been only three case reports of appendiceal SRCC.^[3-5]

Krukenberg tumor is defined as metastatic mucinous/SRCC

*Correspondence: Tadashi Terada; Email: piyo0111jp@yahoo.co.jp; Address: Department of Pathology, Shizuoka City Shimizu Hospital, Miyakami 1231 Shimizu-Ku, Shizuoka 424-8636, Japan.

of ovaries and typically originates from primary tumors of the gastrointestinal tract, most often stomach and colon in addition to the breast and endometrium, despite the recorded rare cases of primary Krukenberg tumors of ovaries.^[6,7] Recently, Krukenberg tumors with original sites of appendix, pancreas and biliary tracts have been reported.^[7-9]

Herein, reported is a very rare case of primary appendiceal pure SRCC presented as bilateral huge ovarian tumors (Krukenberg tumors). Most SRCC shows diverse patterns of adenocarcinoma other than SRCC features. In this article, "pure" SRCC implies SRCC composed exclusively of signet-ring cells.

2. CASE REPORT

A 52-year-old Japanese woman presented with abdominal mass, fullness and pain. The patient was admitted to the gynecologic clinic of our hospital. Physical examination revealed bilateral huge tumors in her ovarian sites. Blood tests demonstrated anemia and elevated tumor markers (CEA, 40 ng/ml; CA125, 580 ng/ml; CA72.4, 1771 U/ml; STN-AG, 19,000 U/ml; sialyl LE, 75 U/ml). Serum AFP, CA19-9, and CA15-3 were within normal limits. Upper and lower gastrointestinal endoscopy revealed no remarkable pathologic features. CT and MRI showed huge bilateral ovarian solid tumors without clinically apparent other tumors. The clinical diagnosis was primary bilateral ovarian tumors and bilateral oophorectomy was performed. During operation, several quick frozen sections were performed and both ovarian tumors (left: 18 cm, right: 13 cm) were found to be Krukenberg tumors. Accordingly, gynecologists did comprehensive abdominal examination to find out the primary site. They found a small tumor (3 cm × 1 cm) in the distal part of vermiform appendix, frozen sections of which revealed a pure SRCC. Cytologic evaluation of associated ascites at the operation were positive for carcinoma cells. Then the diagnosis of primary pure SRCC of appendix with both ovarian metastases (Krukenberg tumors) with peritoneal dissemination was given.

Subsequent gross examination of the both ovaries and the appendix, which was performed in formalin-fixed organs, revealed a left ovarian huge solid tumor, measured 16 cm × 17 cm × 17 cm (see Figure 1A) and right ovarian tumor measuring 13cm × 12 cm × 14 cm (see Figure 1B). The cut surfaces of both tumors were smooth and mucinous. The appendix contained a small (3 cm × 1 cm) white tumor at its tip (see Figure 1C). Histologically, the tumors of both ovaries (see Figure 2A) and appendiceal tip (see Figures 2B-2C) showed the same morphology, composed exclusively of SRCC. The primary appendiceal SRCC was originated

from the mucosa and invaded the submucosa, muscle layer, subserosa and serosa and extended to the abdominal cavity. Many lymphovascular permeations by the SRCC cells were recognized.

Immunohistochemical panels were applied using Dako Envision method (Dako, Glostrup, Denmark), as previously reported.^[10-13] The signet ring cells of the ovarian tumors and appendix were positive for cytokeratin AE1/3, cytokeratin CAM5.2, cytokeratin 8 (see Figure 3A), cytokeratin 18, cytokeratin 19, cytokeratin 20 (see Figure 3B), epithelial membrane antigen, carcinoembryonic antigen (see Figure 3C), cancer antigen-19-9, p53, Ki-67 (50%), caudal-related homeobox-2 (CDX2), and mucin core protein-2 (see Figure 3D) while negative for cytokeratin 34βE1, cytokeratin 5/6, cytokeratin 7, cytokeratin 14, p63, vimentin, thyroid transcription factor-1 (TTF-1), mucin core protein-1, mucin core protein-5AC, mucin core protein-6, neuron-specific enolase, synaptophysin, chromogranin, and CD56. Subsequently, chemotherapy was given for 3 months after operation.

3. DISCUSSION

Krukenberg tumor is defined as an ovarian carcinoma composed exclusively of signet-ring adenocarcinoma cells. It is classified into primary and secondary (metastatic).^[7] Primary one is very rare, while secondary Krukenberg tumor is relatively common. Most of the latter are ovarian metastases from gastric signet-ring cell carcinoma, and a few from signet-ring cell carcinoma in other gastrointestinal tracts. In general, when signet-ring cell carcinoma was found in the gastrointestinal tract in case of Krukenberg tumor, the case is generally regarded as secondary Krukenberg tumor. It should be noted that there are small foci of SRCC in gastrointestinal tract that are not detected in cases of primary Krukenberg tumor; such case is in fact secondary Krukenberg tumor.^[7] In the present case, tumors were seen in bilateral ovaries and vermiform appendix. Although the author thinks that the ovarian tumor can be primary Krukenberg tumor in the current case,^[19] he thinks that secondary Krukenberg tumor is far more likely. The ovarian tumors (13 cm and 17 cm) were larger than appendiceal tumor (3 cm). In the appendiceal tumor, the tumor cells were seen to arise from mucosa and lymphovascular permeations were noted, strongly suggesting the diagnosis of appendiceal primary. In addition, the metastatic pattern of lymphatic flow and blood flow is much more favor of secondary Krukenberg tumor: primary Krukenberg tumor metastasized to only vermiform appendix is quite unlikely. Signet-ring carcinoma far more commonly occur in gastrointestinal mucosal epithelium with abundant mucins and it is never epithelial phenotypes in epithelial (mesothelial) tumors of ovary.

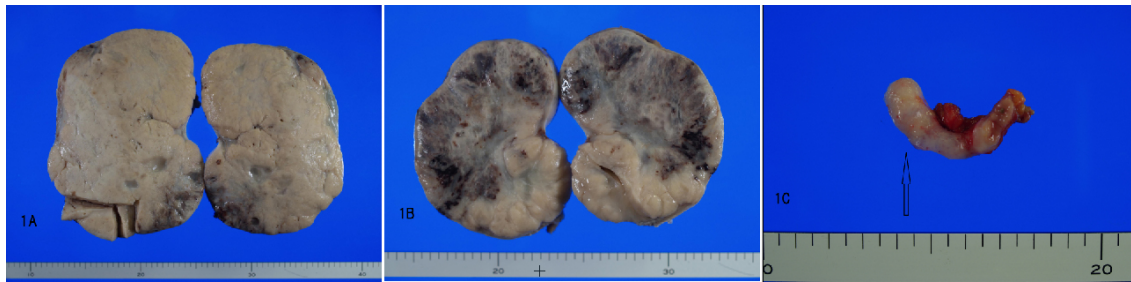


Figure 1. Gross findings of the both ovaries and appendix

A: The left ovary showed a huge solid tumor measuring 16 cm × 17 cm × 17 cm. The cut surface is slimy and solid. B: The right ovary showed a huge solid tumor measuring 13 cm × 12 cm × 14 cm. The cut surface is slimy and solid. Focal areas show hemorrhage. C: The vermiform appendix shows a tumor measuring 1 cm × 3 cm (arrows) in the distal (left) appendix.

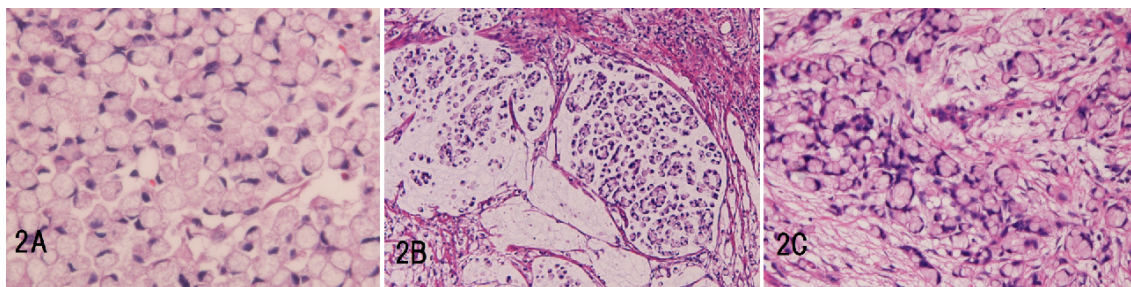


Figure 2. Histological findings of ovarian and appendiceal tumor

A: The ovarian tumor is composed exclusively apparent signet ring cell carcinoma cells. HE, ×200. B: Low power view of the appendiceal tumor. Pure signet ring cell carcinoma is apparent. There is a little mucin in this section. HE, ×50. C: Higher power view of the appendiceal tumor. Apparent signet ring cell carcinoma cells are seen. HE, ×200.

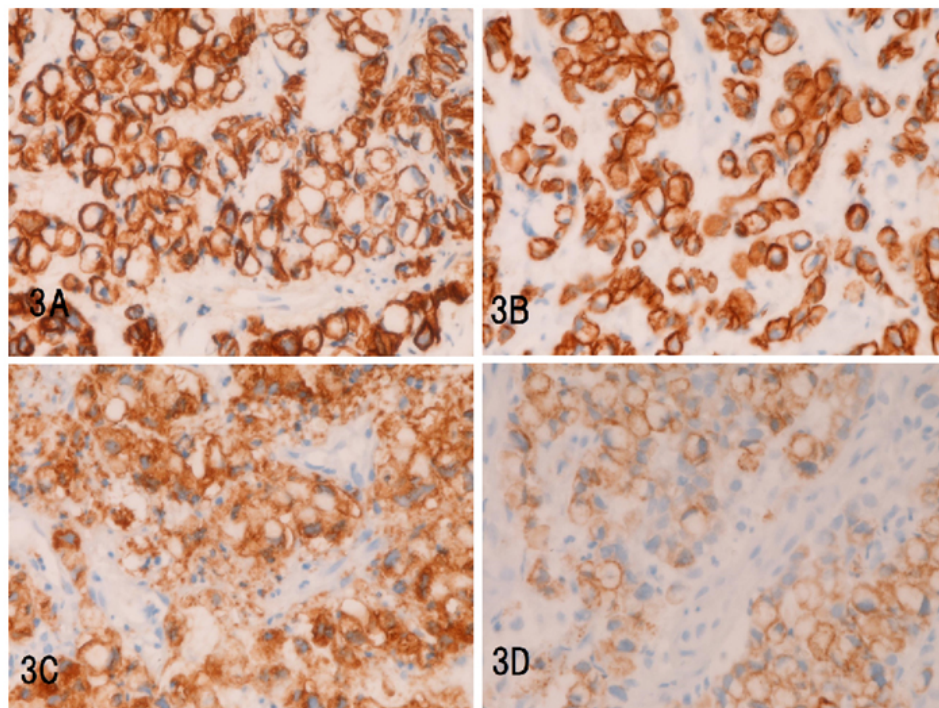


Figure 3. Immunohistochemistry

The signet ring cell carcinoma cells of both ovarian tumors and the appendiceal tumor are positive for cytokeratin 18 (A), cytokeratin 20 (B), CEA (C), and MUC2 (D). Immunostaining, ×200.

The current case is the fourth reported case of primary SRCC of the appendix^[3-5] and the first report of primary pure SRCC clinically manifesting as ovarian Krukenberg tumor. According to WHO blue book, only appendiceal adenocarcinoma containing more than 50% of SRCC elements is called appendiceal SRCC.^[14] The present case was composed exclusively of SRCC, thus the current case fulfilled the criteria of primary pure appendiceal SRCC. Both ovarian tumors of the present case were huge with no preoperative endoscopic and imaging (CT and MRI) diagnosis of primary tumor. For this reason, the gynecologists considered that the ovarian tumors as primary ovarian tumors. Then the doctors successfully found the small appendiceal tumor by the scrutiny of the abdominal cavity. Vermiform appendix is a small organ, and lesions of the appendix are difficult to be detected by endoscopy and imaging techniques including CT and MRI. After exclusion of primary gastrointestinal tumor and following meticulous examination of Vermiform appendix, the gynecologists and pathologist considered the appendiceal SRCC with bilateral ovarian tumors as Krukenberg ovarian tumor. In this case, pathologic examination of quick frozen sections played a critical role for correct diagnosis of this primary very rare primary pure appendiceal SRCC.

Extensive immunohistochemical testing was performed in the current study. This is the second case of this kind of study after Suzuki *et al.*^[3] The cytokeratin profile indicated that the SRCC cells have a wide range of cytokeratin expression.

Cytokeratin-7-/cytokeratin-20+ pattern is compatible with appendiceal (as colonic) origin. Epithelial membrane antigen was positive while vimentin was negative, suggesting that the present tumor is epithelial origin. Protein expression of p53 was strongly expressed, suggesting p53 gene mutations. Ki-67 labeling was high (50%), suggesting a high cellular proliferative activity. The present SRCC expressed carcinoembryonic antigen and carcinoma antigen-19-9, indicating that the present tumor is a variant of adenocarcinoma. On the other hand, the tumor cells were negative for TTF-1, indicating no association with pulmonary phenotypes. The profile of mucin core proteins suggest that product of MUC2 genes are up-regulated, while products of MUC1, MUC5AC and MUC6 genes not. The negative reaction for neuron-specific enolase, chromogranin, synaptophysin and CD56 indicates that the present tumor is not goblet cell carcinoid. Although there were slight differences of the antigenic expression, the immunoprofile of the current case appear similar to that of SRCC of other organs.^[3,15-18]

In summary, the author reported the fourth case of primary pure appendiceal SRCC, and the first case of this tumor manifesting as bilateral ovarian tumors (Krukenberg tumors) clinically. An extensive immunohistochemical study was also performed.

CONFLICTS OF INTEREST DISCLOSURE

The author declares no conflict of interest.

REFERENCES

- [1] McCusker ME, Cote TR, Clegg LX, *et al.* Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. *Cancer*. 2002; 94: 3307-12. PMID: 12115365. <http://dx.doi.org/10.1002/cncr.10589>
- [2] O'Donnell ME, Badger SA, Beattie GC, *et al.* Malignant neoplasms of the appendix. *Int J Colorectal Dis*. 2007; 22: 1239-48. PMID: 17447078. <http://dx.doi.org/10.1007/s00384-007-0304-0>
- [3] Suzuki J, Kazama S, Kitayama J, *et al.* Signet ring cell carcinoma of the appendix manifesting as colonic obstruction and ovarian tumors: report of a case. *Surg Today*. 2009; 39: 235-40. PMID: 19280284. <http://dx.doi.org/10.1007/s00595-008-3839-y>
- [4] Ho KY, Jung CK, Oh SN, *et al.* Primary signet ring cell carcinoma of the appendix: a rare case report and our 18-year experience. *World J Gastroenterol*. 2008; 14: 5763-8. <http://dx.doi.org/10.3748/wjg.14.5763>
- [5] Mastoraki A, Papanikolaou IS, Kanakis D, *et al.* A case of signet ring cell carcinoma of the appendix: dilemma in differential diagnosis and management. *J Gastrointest Cancer*. 2010; 41: 141-4. PMID: 20058100. <http://dx.doi.org/10.1007/s12029-009-9123-6>
- [6] Prat J, Morice P. Secondary tumours of the ovary. In: Tavassoli FA, Devilee P eds. *World Health Organization Classification of Tumours. Pathology and genetics of the breast and female genital organs*. Lyon: IARC Press; 2003. p193-6.
- [7] Kiyokawa T, Young RH, Scully RE. Krukenberg tumors of the ovary: a clinicopathologic analysis of 120 cases with emphasis on their variable pathologic manifestations. *Am J Surg Pathol*. 2006; 30: 277-99. PMID: 16538048.
- [8] Hristov AC, Young RH, Vang R, *et al.* Ovarian metastases of appendiceal tumors with goblet cell carcinoidlike and signet ring cell patterns: a report of 30 cases. *Am J Surg Pathol*. 2007; 31: 1502-11. PMID: 17895750. <http://dx.doi.org/10.1097/PAS.0b013e31804f7aa1>
- [9] Uhacek P, Mlynec M, Durcansky D. Appendiceal adenocarcinoma presenting with bilateral Krukenberg tumors. *J Obstet Gynecol Res*. 2007; 33: 211-4. PMID: 17441899. <http://dx.doi.org/10.1111/j.1447-0756.2007.00496.x>
- [10] Terada T, Kawaguchi M, Furukawa K, *et al.* Minute mixed ductal-endocrine carcinoma of the pancreas with predominant intraductal growth. *Pathol Int*. 2002; 52: 740-6. PMID: 12685552. <http://dx.doi.org/10.1046/j.1440-1827.2002.01416.x>
- [11] Terada T, Taniguchi M. Intraductal oncocytic papillary neoplasm of the liver. *Pathol Int*. 2004; 54: 116-23. PMID: 14720143. <http://dx.doi.org/10.1111/j.1440-1827.2004.01594.x>

- [12] Terada T, Takeuchi T, Taniguchi M. Hepatobiliary cystadenocarcinoma with cystadenoma elements of the gall bladder in an old man. *Pathol Int.* 2003; 53: 790-5. PMID: 14629305. <http://dx.doi.org/10.1046/j.1440-1827.2003.01559.x>
- [13] Terada T. Ductal adenoma of the breast: Immunohistochemistry of two cases. *Pathol Int.* 2008; 58: 801-5. PMID: 19067857. <http://dx.doi.org/10.1111/j.1440-1827.2008.02315.x>
- [14] Carr NJ, Sobin LH. Adenocarcinoma of appendix. In: Bosman FT, Carneiro F, Hruban RH, Theise ND eds. *WHO Classification of tumours of the digestive system.* IARC: Lyon; 2010. p122-5.
- [15] Terada T. Primary signet-ring cell carcinoma of the lung: a case report with an immunohistochemical study. *Int J Clin Exp Pathol.* 2012; 5: 171-4. PMID: 22400080.
- [16] Terada T. Primary signet-ring cell carcinoma of the pancreas diagnosed by endoscopic retrograde pancreatic duct biopsy: a case report. *Endoscopy.* 2012; 44 Suppl 2: E141-2. PMID: 22619039. <http://dx.doi.org/10.1055/s-0030-1257045>
- [17] Terada T. Primary signet-ring cell carcinoma of the ampulla of Vater: a case report with an immunohistochemical study. *Appl Immunohistochem Mol Morphol.* 2012; 20: 427-8. PMID: 22710820. <http://dx.doi.org/10.1097/PAI.0b013e31823b7052>
- [18] Terada T. Primary pure signet ring cell adenocarcinoma of the non-Barrett's esophagus: a case report with immunohistochemical study. *Endoscopy.* 2011; 43 Suppl 2 UCTN: E397-8.
- [19] Primary signet ring cell mucinous ovarian carcinoma: a case report and literature review. *Case Rep Oncol.* 2010; 3: 451-7. PMID: 21611142. <http://dx.doi.org/10.1159/000323003>