—Case Reports—

Krukenberg Tumor: Metastasis of Meckel's Diverticular Adenocarcinoma to Ovaries

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Abstract

A 56-year-old female presented with abdominal pain, weight loss and fatigue. Computed tomography revealed an abdominopelvic mass and ascites. At surgery she had carcinomatosis and bilateral ovarian metastases arising from a cancer in a Meckel's diverticulum. Histology identified the primary to be a signet-ring cell adenocarcinoma within the Meckel's with ovarian metastases. This is the first report of a Krukenberg tumor from a Meckel's diverticulum. A discussion of malignancies within a Meckel's diverticulum is provided.
(J Nippon Med Sch 2009; 76: 96–102)

Key words: Meckel's diverticulum, Krukenberg tumor, signet-ring cell gastric adenocarcinoma, ovaries

Introduction

Meckel's diverticulum is the commonest congenital anomaly of the small intestine. Located on the antimesenteric border of the ileum, it results from incomplete obliteration of the omphalomesenteric duct during embryogenesis. The majority of Meckel's diverticula are benign and discovered incidentally, though rarely they may present with gastrointestinal bleeding, obstruction, diverticulitis, or as a neoplastic process. We report a case of signet-ring cell gastric adenocarcinoma arising from ectopic gastric tissue in a Meckel's diverticulum of a 56-year-old female. The tumor presented as bilateral ovarian masses from a metastatic signet-ring cell adenocarcinoma, thus defining itself as an unusual Krukenberg. A Krukenberg tumor, rare in itself, is found mostly in young pre-menopausal women and is bilateral in more than 80% of cases. The most common site of the primary tumor is the stomach (70%). The tumor may also originate in the colon, appendix or breast. The prognosis of a Krukenberg tumor is very poor with no established treatment. Early diagnosis and surgical resection of localized disease are the only hope for a favorable outcome.

Case Report

A 56-year-old Dominican female was admitted to our institution for an elective total abdominal

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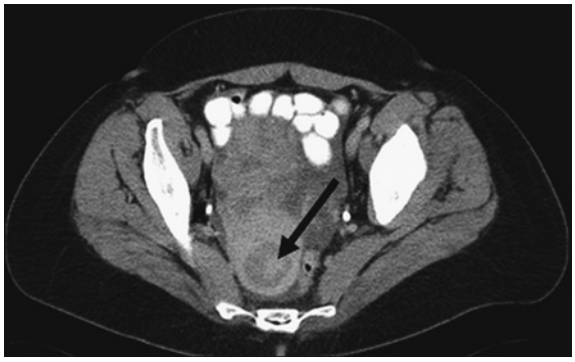

Fig. 1 CT scan of the pelvis demonstrates a large, solid, right adnexal mass (**arrow**). The mass measured 6.7 cm in largest diameter and was surrounded by ascitic fluid.

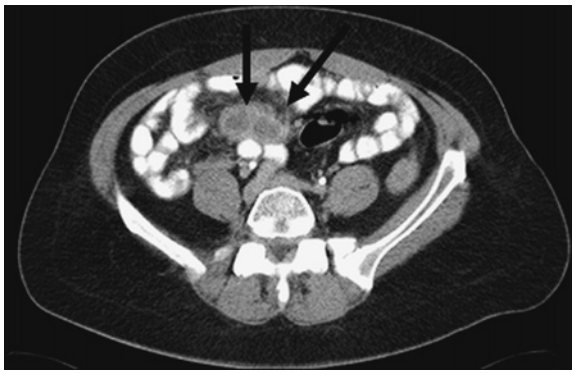

Fig. 2 CT scan of the abdomen exhibits low density mesenteric masses (**arrows**) with surrounding soft tissue stranding suggesting a inflammatory or neoplastic process.

hysterectomy and bilateral salpingo-oophorectomy. The patient had presented a month prior to the date of surgery with symptoms of abdominal pain, fatigue, weight loss (14 kg), and decreased appetite of several months duration. A computed tomography (CT) of the abdomen and pelvis performed as part of the work-up revealed a large, solid right adnexal mass (6.7 cm in largest diameter), trace ascites (**Fig. 1**), and several low density mesenteric masses (**Fig. 2**).

Her past medical history included gastroesophageal reflux disease treated with proton-pump inhibitors. Surgical history included a breast biopsy (benign), breast reduction, and a pilonidal cyst excision. She was G_4P_{3013}, and three years post-menopausal. Her family history was significant for prostate cancer (father), ovarian carcinoma (sister), and stomach cancer (maternal aunt). Recent

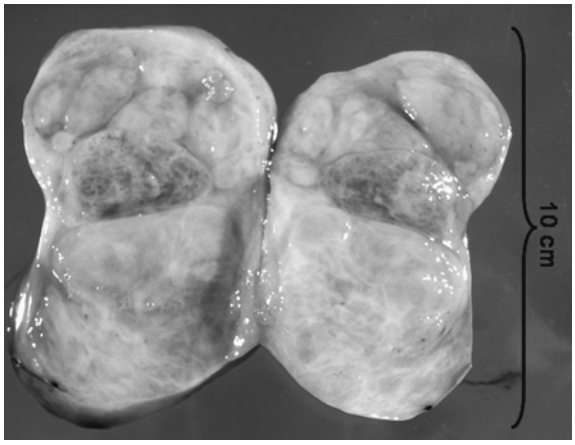

Fig. 3 Longitudinal cross-section of the enlarged (10 cm) right ovary with Krukenberg tumor. The smooth and solid texture, and firm, nodular and bosselated contour is typical of metastatic involvement of the ovary.

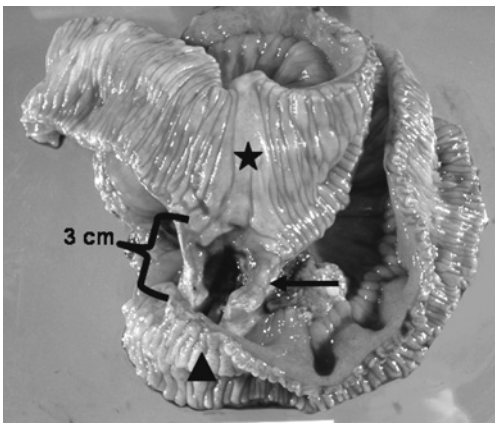

Fig. 4 A dissected view of the ulcerated Meckel's diverticulum (**arrow**) and ileum (**star**). The diverticulum is seen adherent to the adjacent loop of small bowel (**triangle**).

screening exams included a Papanicolaou (Pap) smear, a colonoscopy, an upper gastrointestinal endoscopy, and a mammogram. All tests were normal except for the Pap smear that revealed a low-grade squamous intraepithelial lesion (LGSIL).

The patient was taken to the operating room for a total abdominal hysterectomy, bilateral salpingo-oophorectomy. At surgery, a 10 cm, smooth, firm and nodular right ovary was noted and excised (**Fig. 3**). Frozen section of the right ovary (weighing 221 g and measuring 11.5 × 9.5 × 5.5 cm) along with the fallopian tube (measuring 6.5 cm long) revealed a serous carcinoma. A total abdominal hysterectomy and left salpingo-oophorectomy was completed.

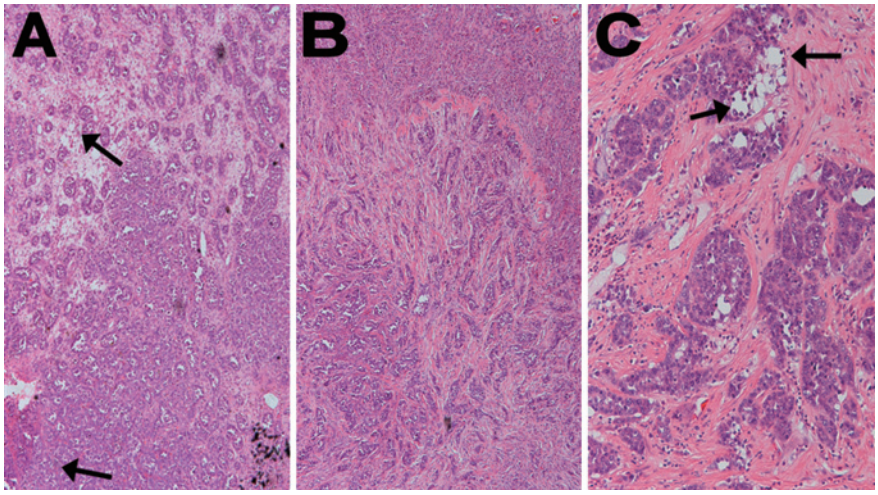

Fig. 5 Photomicrograph of the hematoxylin-eosin stained specimens of the right (5A) and left (5B) ovaries, and Meckel's diverticulum (5C) demonstrating invasive poorly differentiated adenocarcinoma. The tumor consisted of two components: stromal and epithelial, the latter is composed of mucin-laden signet-ring cells with eccentric hyperchromatic nuclei, characteristic of a Krukenberg tumor. The cellular cytoplasm can be eosinophilic and granular, pale and vacuolated (**arrows**, 5C), or bull's eye/targetoid (**arrows**, 5A) in appearance with a central eosinophilic body composed of a mucin droplet.

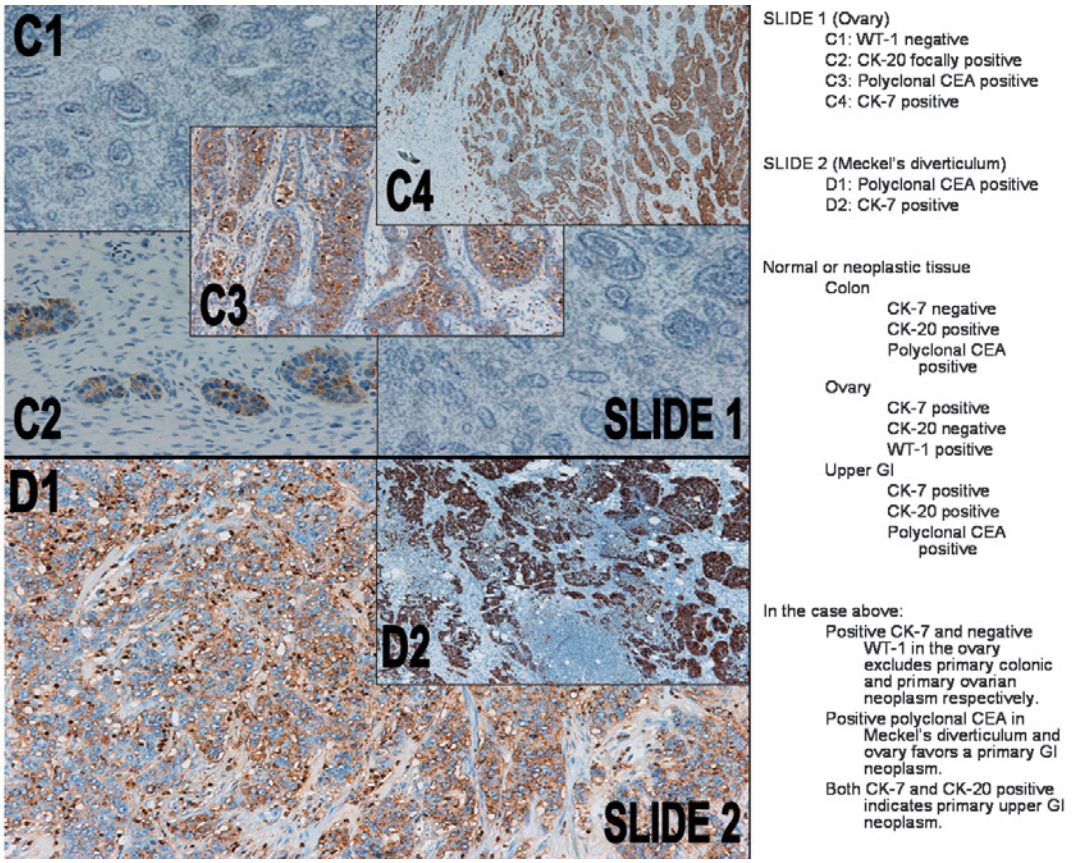

Fig. 6 Slide 1 (Ovary) and Slide 2 (Meckel's diverticulum) exhibit immunoreactivity to epithelial markers such as cytokeratins. Tissue specimens from both the ovaries and Meckel's diverticulum were histologically alike and demonstrated similar immunohistochemical reactions—staining positive for CK 7, CK 20 and polyclonal CEA markers—depicting metastatic adenocarcinoma of ectopic gastric tissue in a Meckel's diverticulum, excluding primary colonic or ovarian origin.

Further examination of the abdomen revealed an ulcerated mass at the tip of Meckel's diverticulum with involvement of adjacent small bowel loops **(Fig. 4)** adherent to the superior mesenteric artery (SMA). The right hemi-abdomen was notable for miliary spread of the tumor over Gerota's fascia and up to and involving the right hemidiaphragm. A right hemicolectomy with resection of 32 cm of small bowel including a 3 cm Meckel's diverticulum and omentectomy was performed. The SMA was skeletonized to debulk the tumor. There was obvious lymph node involvement at the base of the small bowel mesentery in addition to the peritoneal deposits noted above. The appendix appeared normal.

Histopathological evaluation revealed a right fallopian tube and ovary containing poorly differentiated adenocarcinoma with focal signet-ring intracellular mucin **(Fig. 5A)**; a left ovary with poorly differentiated adenocarcinoma **(Fig. 5B)**; and an ulcerated 3.5 cm invasive poorly differentiated adenocarcinoma arising in a Meckel's diverticulum **(Fig. 5C)**. The tumor was transmural and invaded into an adjacent small bowel wall up to the muscularis propria. Extensive perineural and lymphovascular invasion was noted with metastatic disease in two of eight mesenteric lymph nodes. Tumor found in the ovary and the Meckel's diverticulum was histopathologically similar. Tissues of the left fallopian tube, uterine endometrium, omentum, ileum, colon, cecum and appendix revealed no evidence of malignancy or metastasis. The cervix revealed LGSIL and squamous metaplasia as seen on the Pap smear.

Post-operatively, the patient's hospital course was complicated by a urinary tract infection, a prolonged post-operative ileus, and an intra-abdominal abscess requiring CT-guided placement of a drainage catheter and bowel rest. She was subsequently discharged home in stable condition.

Discussion

Meckel's diverticulum is the persistent remnant of the proximal end of the embryonic yolk stalk, or the omphalomesenteric/vitelline duct, which typically disappears by the seventh week of gestation. The incidence of Meckel's diverticulum is reported to be 0.5–2% in autopsy series[1]. In the developing embryo, the vitelline duct is lined with pluripotent cells, having the ability to differentiate into many different tissue types. The most common type of heterotopic tissue found within a Meckel's diverticulum is gastric mucosa (50%), with pancreatic and colonic mucosa occurring less frequently. A Meckel's diverticulum is the most common congenital anomaly of the small bowel and is typically asymptomatic in all age groups. However, as age increases the incidence of symptomatic Meckel's diverticular disease decreases from 5% at infancy to 1.5% by age 40.

Generally speaking, Meckel's diverticulum follows the rule of 2's: it affects 2% of the population, 2% of patients are symptomatic, it is usually found 2 feet from the ileocecal valve on the antimesenteric side, symptoms normally manifest before the age of 2 years, ectopic tissue can be found in 1 out of 2 patients, most are about 2 inches long, and the ratio of male-to-female incidence is 2 : 1. Meckel's diverticula are a true diverticulum which means they possess all layers of the small bowel from the mucosa to the serosal layer. Typically they receive their blood supply from a remnant of the vitelline artery which emanates from the SMA[2].

Ectopic gastric mucosa within a Meckel's diverticulum may secrete hydrochloric acid which can lead to peptic ulceration and bleeding. Hence, it may present with painless lower GI bleeding, called diverticulosis. This is the most common presentation in children. Symptomatic ulceration may also mimic symptoms of appendicitis, with right lower quadrant pain, diarrhea, nausea or vomiting, and fever. Moore et al. published a series of 50 symptomatic patients who were found to have Meckel's diverticula[3]. A preoperative diagnosis of acute appendicitis was made 40% of the time. Yamaguchi et al.[4] reported on 600 patients, 287 of which were symptomatic, and only 34 of which had a pre-operative diagnosis of Meckel's diverticulum. In this report, Meckel's diverticula were associated with a variety of complications: obstruction, 36.5%; intussusception, 13.7%; diverticulitis, 12.7%; perforation, 7.3%;

Table 1 Comparative symptoms, initial diagnoses, metastases, treatment and outcome of Meckel's diverticular adenocarcinomas reported in the literature

Reference	Symptoms/ Initial diagnosis	Histology of tumor in Meckel's	Metastatic site (s)	Treatment	Outcome
Martin et al.[25]	Rectal hemorrhage Intestinal lymphoma	Adenocarcinoma, well-differentiated	Mesenteric lymph nodes	Surgical excision	Not reported
Rieber et al.[9]	Progressive dysphagia with weight loss Gastro-esophageal mass	Adenocarcinoma, early moderately-differentiated within an area of metaplasia	Synchronous gastric adenocarcinoma (not metastatic)	Surgical excision	No recurrence at 1 year
Lippe et al.[8]	Obstructive symptoms with leukocytosis Acute abdomen	Signet-ring cell adenocarcinoma, poorly-differentiated	Peritoneum, liver	Surgical excision and chemotherapy	Death 14 weeks after diagnosis
Parente et al.[1]	Chronic intermittent obstruction with weight loss Small bowel tumor	Adenocarcinoma, moderately-differentiated	Liver, mesenteric lymph nodes	Surgical excision (unresectable metastases) and chemotherapy	Alive with no disease progression at 4 months post-op
Kusumoto et al.[5]	Post-prandial abdominal pain Small bowel tumor	Adenocarcinoma, moderately-differentiated	Urinary bladder, mesenteric lymph nodes	Surgical excision and chemotherapy	Alive with no disease progression at 6 months post-op
Lin et al.[26]	Acute obstructive symptoms Obstructive sigmoid malignancy	Adenocarcinoma, well-differentiated	None	Surgical excision (Hartmann's procedure)	No recurrence during colostomy reversal at 6 months
Current Case	Abdominal pain, fatigue and weight loss Ovarian malignancy	Signet-ring cell adenocarcinoma, poorly-differentiated	Lymph nodes, right fallopian tube, ovaries	Surgical excision and chemotherapy	Alive with disease progression at 4 months post-op

hemorrhage, 11.8%; neoplasm, 3.2%; and fistula, 1.7%. Approximately 50% of the patients were adults and in this population intestinal obstruction occurred far more often than hemorrhage at a ratio of 5 : 1. The etiology of intestinal obstruction in adults was attributed to intussusception, volvulus, internal hernia, or a neoplasm.

A primary malignant tumor arising within a Meckel's diverticulum is extremely rare, with an incidence of 1.5–3.2%[1], and has a male predominance[5]. Several neoplasms have been reported arising in the Meckel's diverticulum such as benign lipomas[2], carcinoid tumors[2,6], GIST tumors[7], and signet-ring cell adenocarcinomas[8]. Stromal or carcinoids are the most commonly found tumors at this site. Occurrence of adenocarcinoma in a Meckel's diverticulum is very rare with only 16 cases reported before 1963, and another 9 cases between 1963 and 1990[5]. Clinical features and physical findings associated with a neoplasm in a Meckel's diverticulum may range from acute abdomen with severe gastrointestinal hemorrhage or perforation, to chronic symptoms of obstruction and anemia. Factors contributing towards malignant

degeneration of ectopic gastric mucosa remain unclear. Some speculate that ectopic gastric mucosa may have an increased malignant potential in comparison to normal bowel mucosa[5]. *Helicobacter pylori* is a well known carcinogen that is implicated in the pathogenesis of gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma[1]. However, its role in pathogenesis of primary malignancy within the Meckel's diverticulum remains doubtful. Reiber et al.[9] reported a case of synchronous gastric adenocarcinoma with a second primary in the Meckel's diverticulum. They detected numerous *Helicobacter pylori* in the moderately differentiated adenocarcinoma from the gastroesophageal junction, but none in the neoplastic tissue of the Meckel's diverticulum.

The diagnosis of a Meckel's diverticulum is difficult to make preoperatively let alone identifying a neoplasm within it. Most Meckel's diverticula are diagnosed incidentally on a barium study or at laparotomy, laparoscopy or autopsy. A Meckel's scan, in which 99-m-technetium-pertechnetate is infused and preferentially taken up by gastric mucosa (of at least 1.8 cm^2) can be useful but the accuracy in adults (46%) is much less than in children[10,11]. Adjunctive agents such as pentagastrin (increases Tc uptake) and cimetidine (decreases Tc release by gastric mucosa) may enhance detection rates[12,13]. Interestingly, angiography of the SMA may also be useful if a vitelline artery is identified feeding the Meckel's diverticulum, but this is present only 10% of the time.

Treatment of a neoplasm within a Meckel's diverticulum typically involves diverticulectomy and an appendectomy with primary small bowel anastomosis. More extensive procedures, as in the presented case, are individualized if additional disease or metastases are present. The role and benefit of adjuvant chemotherapy (5-fluorouracil, cisplatin, oxaliplatinin or mitomycin-C) has not been defined but is usually provided[1,5]. Lippe et al.[8] reported on a young female with a signet-ring cell adenocarcinoma in a Meckel's diverticulum who received post-operative chemotherapy but lived only 14 weeks post-diagnosis. In general, the prognosis of a Meckel's diverticular malignancy appears poor, and dependent upon multiple factors including age of the patient, metastasis, histological type and biologic aggressiveness of the neoplastic process.

Tumors from distant primary sites can metastasize to the ovary, accounting for 5–6% of all ovarian malignancies. Commonly, the tumors originate from the female genital tract, breast and gastrointestinal tract. A unique type of metastatic ovarian tumor is a Krukenberg tumor, which is a metastatic signet-ring cell adenocarcinoma. It accounts for 1–2% of all ovarian tumors with higher frequency (17.8%) in Japan where gastric carcinoma is more prevalent[14,15]. The most common primary site is the stomach (70%) followed by the colon, appendix and breast. Rare cases originating from carcinomas of the gallbladder[16], the ampulla of Vater[17] and the urinary tract[18] have also been reported.

Krukenberg tumors are found most often in young women usually in their fifth decade of life. Common presenting symptoms are abdominal pain and distension. It may be associated with virilization secondary to ovarian stromal hormone secretion, and ascites. Krukenberg tumors with right hydrothorax and ascites referred to as Pseudo-Meigs' syndrome have also been reported[19,20]. The lymphatic system is the most probable route of metastasis in a Krukenberg tumor, but cases without lymphatic involvement have also been reported suggesting peritoneal seeding[21]. Krukenberg tumors are bilateral in more than 80% of cases. The ovaries are usually solid with smooth capsular surfaces and asymmetrically enlarged **(Fig. 3)**. Microscopically, the tumor characteristically reveals mucin-laden signet-ring cells within the ovarian stroma **(Fig. 5)**. Immunohistochemical evaluation may aid in distinguishing primary ovarian carcinomas from metastatic carcinomas. Ovarian neoplasms are cytokeratin (CK) 7^+ and CK 20^-, and colonic primaries are CK 7^- and CK 20^+. CK 7^+ and CK 20^+ suggest a metastatic upper gastrointestinal carcinoma, mainly gastric **(Fig. 6C2 and 6C4)**. The mortality of Krukenberg tumor is significantly high, with most patients surviving less than 2 years[22,23]. The prognosis is worse and surgical resection futile if the primary tumor remains covert or residual

disease is present after intervention. To date, adjuvant chemotherapy used (irinotecan, cisplatin or mitomycin-C) appears to have no significant effect on prognosis[21,24].

Adenocarcinoma arising out of ectopic gastric mucosa in a Meckel's diverticulum has been only rarely reported (6 cases) (see **Table 1**)[1,5,8,9,25,26]. To the best of our knowledge this report is the only case of metastases to the ovaries, by definition a Krukenberg tumor, from ectopic gastric mucosa in a Meckel's diverticulum. In our case, the diagnosis of gastric adenocarcinoma was established only after precise immunohistochemical analysis of the tissue obtained from surgically excised ovaries and the Meckel's diverticulum (**Fig. 6**). Despite lack of demonstrable benefit, given the young age and excellent performance status of our patient, adjuvant chemotherapy with oxaliplatin and 5-fluorouracil was started.

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(Received, October 28, 2008)
(Accepted, December 17, 2008)