CASE REPORT

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Rare primary peritoneal mucinous adenocarcinoma in a 69-year-old man

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Abstract

Primary peritoneal mucinous adenocarcinoma is rare in men. The low-grade tumor consisted of mucin-producing columnar cells with minimal nuclear atypia. Relationship to pseudomyxoma peritonei and disseminated peritoneal adenomucinosis is discussed.

KEYWORDS

autopsy, CA125, CA19-9, CEA, MUC1, primary peritoneal mucinous adenocarcinoma

1 **INTRODUCTION**

A 69-year-old man suffered from lethal peritoneal carcinomatosis. At autopsy, no primary lesion was identified in the gastrointestinal, pancreatobiliary, respiratory, urinary, and male reproductive organs. The tumor consisted of mucin-containing and gland-forming columnar cells with minimal nuclear atypia. The final diagnosis was primary peritoneal mucinous adenocarcinoma in a man.

Primary peritoneal adenocarcinoma, first described by Swerdlow in 1959,¹ theoretically originates from the peritoneum-lining cells, and predominantly occurs in women. Serous adenocarcinoma accounts for the majority of primary peritoneal carcinoma, with histopathological features identical to those of ovarian origin, while mucinous adenocarcinoma, endometrioid adenocarcinoma, and clear cell carcinoma are rare.^{2,3} Recently, a new theory has been proposed for the origin of peritoneal carcinoma in women; namely, the primary site is supposed to be located at the distal fimbrial end of the fallopian tube.^{4,5}

So far, only a small number of male cases of primary serous adenocarcinoma of the peritoneum have been reported,⁶⁻¹¹ In 2018, Wang, et al. described a male case of primary peritoneal mucinous adenocarcinoma, as the rarest of the rare.¹² This should be the second case of primary peritoneal mucinous adenocarcinoma in a man.

Mucinous tumors occupying the abdominal cavity have been called classically as pseudomyxoma peritonei (PMP)^{13,14} and more recently as disseminated peritoneal adenomucinosis (DPAM), representing a benign form of PMP.^{15,16} Low-grade PMP or DPAM is characterized by peritoneal dissemination of mucinous epithelial cells accompanying little or mild cytological atypia or infrequent mitotic activity, with or without associated appendiceal mucinous adenoma or adenocarcinoma. Reportedly, more than half of low-grade PMP or DPAM are of vermiform appendix origin.^{13–19} In the present male autopsy case, the primary lesion was identified neither in the gastrointestinal tract, including the stomach, vermiform appendix and colon, and pancreas, nor in the epididymis and tunica

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vaginalis testis. At autopsy, the entire peritoneum was uniformly infiltrated by mucin-secreting columnar tumor cells of low-grade malignancy. The histopathological features of this extremely rare tumor are described, and the origin of low-grade peritoneal mucinous adenocarcinomas in male patients is discussed.

2 CASE PRESENTATION

A 69-year-old Japanese man without particular past medical history visited a local hospital with a complaint of abdominal distension. The ascitic fluid was aspirated to be diagnosed as peritoneal carcinomatosis cytologically. The laboratory data were as follows: blood urea nitrogen 38.7 mg/dl, creatinine 1.67 mg/dl, Na 132 mEq/L, K 5.5 mEq/L, and Cl 94 mEq/L. The increased levels of creatinine and potassium ion as well as the decreased levels of sodium and chloride ions indicated mild renal dysfunction. Serum tumor markers were elevated: carbohydrate antigen 19-9 (CA19-9) 36,510 U/ml (standardized value <37) and carcinoembryonic antigen (CEA) 85 ng/ml (standardized value <5.0). He underwent positron emission tomography-computed tomography scans and the upper gastroduodenal endoscopy, but no primary tumor was pointed out. Because of an advanced stage of the disease, he stayed at home, receiving a conservative therapy with central venous hyperalimentation. No anti-cancer medication was given. After vomiting with mild hematemesis, he died in an emergency suite of the hospital. The total clinical course was 3 months. The medico-legal autopsy was performed 36 h after death, according to the strong request of his family.

3 | AUTOPSY FINDINGS

The patient was 175-cm tall and weighed 76 kg. Rigor mortis was strongly developed in all joints throughout his body. Livor mortis was mildly purple-red on back of the trunk and posterior surfaces of his extremities. The abdomen was markedly distended, and the lower limbs were highly edematous. A hyperalimentation port was placed under the right clavicle.

The omentum and abdominal and pelvic cavities were massively occupied by slightly elastic soft tumors actively forming white-yellow-colored mucin, and 700 ml of viscous ascitic fluid was associated. Grossly, the mucinous tumors did not invade the abdominal organs, but the adipose tissue of the omentum and around the abdominal organs were diffusely replaced by the tumors, and the liver surface was viscous in appearance (Figure 1). No primary lesion was identified in the gastrointestinal tract, including the stomach and colon. No abnormal thickening of the gastric wall was noted. The vermiform appendix was devoid of mucinous neoplasm. The pancreas, gallbladder, bile ducts, liver, spleen, adrenal glands, kidneys, ureters, testis, epididymis, prostate, and lungs were free of primary tumor. No lymph nodal metastasis was observed.

4 | MICROSCOPIC FINDINGS

Microscopically, the disseminated tumor cells were mucous columnar in appearance and often formed glandular structures of varying sizes. Cilia were not observed. A large amount of mucin was secreted into the glandular spaces. The nuclei were minimally atypical (Figure 2A,B). Mitoses were scarcely noted. There was microscopic infiltration into the capsule of the liver and spleen (Figure 2C). At the invasion front in the abdominal adipose tissue, increased nuclear atypia with mild nuclear pleomorphism was recognized (Figure 2D). No distant metastasis was observed.

Reflux esophagitis was regarded as the cause of hematemesis seen in the agonal stage of illness. The liver shows moderate fatty changes of large droplet type. Bronchopneumonia with infection of Gram-positive cocci was multifocally observed. The renal parenchyma was microscopically unremarkable.

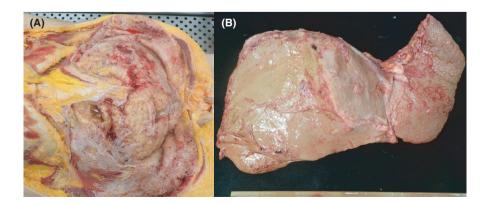
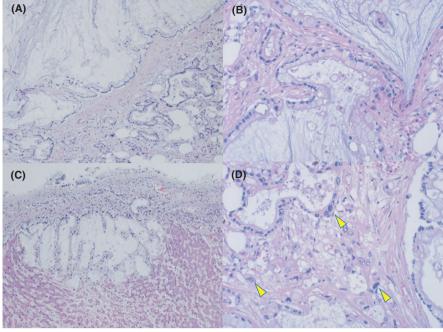


FIGURE 1 Gross appearance of the abdominal cavity (A) and liver (B). Massive dissemination of mucinous tumor is seen on the abdominal organs, including the liver surface

FIGURE 2 Microscopic appearance of the disseminated tumor (hematoxylin and eosin stain). A&B: The disseminated mucin-producing tumor cells show minimal nuclear atypia. Glandular structures of various sizes are observed. B displays a high-powered view. C: The tumor cells focally extend to the liver capsule and partially infiltrate the liver parenchyma. D: At the site of invasion, increased nuclear atypia and pleomorphism are discerned (arrowheads) Clinical Case Reports

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IMMUNOHISTOCHEMICAL 5 FINDINGS

Immunohistochemical analysis of the peritoneal tumor cells was performed with an amino acid-polymer method (Simple Stain-Max, Nichirei, Tokyo, Japan), using formalin-fixed, paraffin-embedded sections. For the amplification of antigenicity, heat-induced epitope retrieval was performed before immunostaining. The diaminobenzidine coloring reaction gave a browncolored-positive signals. The nuclei were lightly stained with hematoxylin.

Regarding the expression of mucin (MUC) core proteins, MUC1 (CA15-3: detected with a monoclonal antibody DF3) was diffusely expressed, and MUC2 (intestinal goblet cell type mucin) and MUC5AC (gastric foveolar cell mucin) were focally positive. MUC6 (pyloric gland/mucous neck cell mucin) was negative. The tumor cells were also diffusely immunoreactive for CA19-9, CEA, and CA125 (MUC16). Cytokeratin 7 (CK7) and CK20 were partly positive in the same area, whereas CK5/6 was negative. Caudal-type homeobox protein-2 (CDX2) was not expressed in the nuclei of the tumor cells. Negative markers included synaptophysin, chromogranin A, calretinin, D2-40, WT-1, p16, p53, estrogen receptor (ER), progesterone receptor (PgR), androgen receptor (AR), and forkhead box protein A1 (FOX-A1). Ki-67 (MIB-1) labeling was as low as 5%. Representative immunostained features are illustrated in Figure 3.

The invasive foci with increased nuclear atypia were negative for MUC2 and MUC5AC. p53 was focally expressed in the nuclei, and Ki-67 labeling index was 10-20%.

DISCUSSION 6

We report herein an extremely rare male case of primary peritoneal mucinous neoplasm. The mucin-producing tumor cells of low-grade malignancy massively proliferated on the abdominal and pelvic cavities. The primary lesion of the mucinous malignancy was not identified in the gastrointestinal, pancreaticobiliary, respiratory, urinary, and male reproductive organs. The vermiform appendix remained intact.

Primary peritoneal mucinous neoplasm can also be named as PMP or DPAM of unknown origin.¹³⁻¹⁶ Lowgrade PMP or DPAM is characterized by peritoneal dissemination of mucinous epithelial cells accompanying little cytological atypia or mitotic activity, as was so in the present case. It has been reported that more than half of low-grade PMP or DPAM are of appendiceal origin, and in female cases, the ovary should be another important site of origin.¹³⁻¹⁹ In fact, primary peritoneal carcinoma occurs predominantly in women.^{2,3} In some male cases of PMP or DPAM, the primary lesion was undetectable,¹⁷⁻¹⁹ and theoretically, they may correspond to the lesion of the primary peritoneal mucinous neoplasm in men.

In general, cancers of unknown primary site are defined as tumors that have metastatic malignancies but whose primary tumor cannot be identified despite thorough examinations.²⁰ It has been described that about 2% of malignant tumors in adults are included in this category. The median survival period is 4-12 months, and the 5-year survival rate is low with a poor prognosis when compared with other cancers.^{21,22}

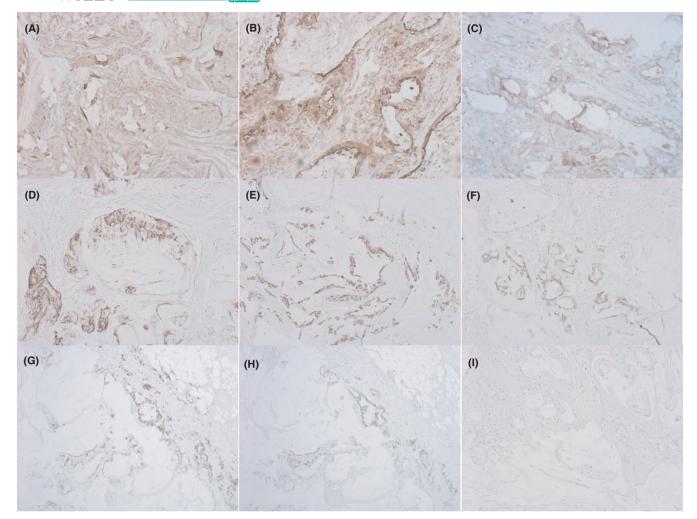


FIGURE 3 Immunohistochemical features of the mucinous neoplasm. The tumor cells are immunoreactive for CA19-9 (A), CEA (B), CA125 (C), MUC1 (D), MUC2 (E), MUC5AC (F), CK7 (G), and CK20 (H), but negative for CDX2 (I). The tumor cells diffusely express CA19-9 and CEA. The expression of CA125, MUC1, and CK7 and negativity of CDX2 are consistent with primordial celomic-lining cells, while gastrointestinal differentiation is partly seen according to the focal expression of MUC2, MUC5AC, and CK20. G&H illustrate the same microscopic area

It has long been supposed that primary peritoneal carcinoma develops from a primordial body cavity epithelium, which lines the peritoneum including the ovarian surface.^{1,2} It encompasses the same pathological spectrum as ovarian superficial epithelial/interstitial malignancies: Serous adenocarcinoma is seen in most cases, whereas clear cell, mucinous, and endometrioid adenocarcinomas also occur infrequently. The phenomenon has been called as müllerian epithelial metaplasia or the secondary müllerian system.^{23,24} However, a novel important finding has recently been described: Primary peritoneal adenocarcinomas of women originate from carcinoma *in situ* of the fallopian tube at the distal end (fimbriae) of the tube of müllerian origin.^{4,5}

Primary peritoneal adenocarcinomas in men are extremely rare, and a small number of cases of peritoneal serous adenocarcinoma have been reported in men.⁶⁻¹¹ Serous papillary carcinoma and clear cell carcinoma arising from the epididymis and tunica vaginalis testis of müllerian duct origin have been reported.^{25–27} In the present male case, the histological type was not serous adenocarcinoma but low-grade mucinous adenocarcinoma. Mucinous adenocarcinomas are commonly encountered in the pancreas, stomach, colon, vermiform appendix, lung, ovary, and breast.²⁸ No primary lesions were identified in these organs in the present case. We microscopically evaluated the epididymis, a male counterpart of the fallopian tube, the tunica vaginalis testis, and a remnant of the müllerian duct, but no *in situ* malignancy was identified, as far as we examined.

The most important immunohistochemical finding was the negativity of CDX2, hence excluding the possibility of enteric origin of the present tumor. CDX2, an intestine-specific intranuclear transcription factor, is expressed in the normal mucosal epithelial cells from the duodenum to rectum, as well as in adenocarcinomas of intestinal origin.^{29,30} Mucinous tumors of appendiceal origin consistently express CDX2³¹ and CK20.³² Regarding the expression of mucin core proteins, MUC1 (visualized with a monoclonal antibody DF3 against CA15-3)³³ was diffusely expressed, and the tumor cells were focally positive for MUC2 and MUC5AC. MUC6 was negative. MUC1 is commonly expressed in cancers of the breast, prostate, pancreas, uterus, and ovary, whereas gastrointestinal adenocarcinomas are infrequently immunoreactive for MUC1.34 Expression of MUC1 is closely correlated with the aggressiveness of the gastric cancer cells.³⁵ MUC2 is a mucin core protein of intestinal goblet cell origin.³⁴⁻³⁶ MUC5AC is a mucin core protein of gastric foveolar epithelial cells, and MUC6 belongs to a mucin core protein of gastric pyloric/cardiac glands, gastric mucous neck cells, and duodenal Brunner's glands.^{35,37} These findings suggest a partial differentiation toward the gastric- and intestinal-type cells. It has been clarified that the mucinous tumors of pancreatic origin often express gastric mucins, and occasionally intestinal mucin.³⁸ The MUC1 expression in pancreatic mucinous tumors indicates aggressive nature of the lesion.³⁹ In the present case, no pancreatic tumor was observed. The focal and comparable expression of CK7 and CK20 in the tumor cells was also compatible with focal gastrointestinal differentiation.40

CA19-9 and CEA were diffusely immunoreactive in the mucinous tumor cells, and the serum levels of both indicators were abnormally high. Both tumor markers are frequently expressed in gastrointestinal adenocarcinomas, but they may be immunoreactive in non-gastrointestinal adenocarcinomas, including the ovary, breast, and lung.⁴¹ It has been reported that cancers of unknown primary origin with high CA19-9 and CEA levels had a poor prognosis.¹¹

CA125 (MUC16) was also diffusely expressed in the present tumor cells. It has been described that CA125 is expressed in normal and neoplastic mesothelial cells and epithelial cells of müllerian origin, including fallopian tube epithelial cells and most ovarian carcinomas.⁴² The tumor cells were devoid of the expression of hormone receptors (ER, PgR, and AR) and FOX-A1, a hormone receptor-related intranuclear transcription factor.43 The negative findings exclude the possibility of differentiation toward müllerian epithelial cells. The lack of expression of CK5/6, calretinin, D2-40, and WT-1, commonly expressed in normal and neoplastic mesothelial cells,⁴⁴ indicates that the tumor is distinguished from malignant mesothelioma. The tumor cells were negative for p53 and p16. It is known that p16 is expressed in high-grade serous adenocarcinoma of the ovary, whereas p53 is negative,⁴⁵

and p16 may be focally positive in mucinous ovarian adenocarcinoma. $^{\rm 46}$

All these gross, microscopic and immunohistochemical features are consistent with peritoneal surface cell origin of the low-grade mucinous neoplasm seen in the present male patient.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of the present study.

AUTHOR CONTRIBUTIONS

Both authors have sufficiently participated in the work to take public responsibility for appropriate portions of the content. FS performed the autopsy, made histopathological diagnosis, analyzed the data, and contributed to writing the manuscript. YT analyzed immunohistochemical features and brushed the manuscript up. Both authors agreed with the content of the manuscript submitted for publication.

ETHICAL APPROVAL

All the procedures were in accordance with the ethics standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1964 and later versions.

CONSENT

The patient's wife gave us an informed consent to publication as a case report.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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