Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Primary appendiceal adenocarcinoma presenting as advanced ovarian cancer: a case report

Kung-Chuan Cheng
Chang Gung Memorial Hospital Kaohsiung Branch
Ko-Chao Lee
Chang Gung Memorial Hospital Kaohsiung Branch
Hong-Hwa Chen
Chang Gung Memorial Hospital Kaohsiung Branch
YC Ou (tedycou@gmail.com)
Chang Gung Memorial Hospital Kaohsiung Branch

Case report

Keywords: Krukenberg's tumor, ovarian metastasis, primary appendiceal cancer, advanced stage ovarian cancer

Posted Date: September 8th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-42721/v2

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Background

Although Primary appendiceal malignancies are rare accounting for less than 1% of all gastrointestinal tumors, the incidence of ovarian metastasis in appendiceal adenocarcinoma is encountered in 16.7 to 37% of all ovarian malignancy. The diagnosis is usually made after an exploratory laparotomy. Most of these tumors present with nonspecific symptoms, such as abdominal pain, abdominal fullness and huge pelvic mass, mimicking advanced stage ovarian cancer.

Case Presentation

We described two menopausal women who were referred to our institution under the diagnostic impression of advanced stage of primary ovarian cancer. However, both patients were eventually found to have primary appendiceal adenocarcinoma with ovarian metastasis at laparotomy. Initial symptoms, intraoperative finding, pathology finding, and postoperative clinical courses were documented.

Conclusions

Comparing with primary ovarian tumor, ovarian metastasis is relatively rare. The clinical presentation can be misleading and the differential diagnoses of primary appendiceal cancer should be considered when preoperative workup is planned.

Introduction

In 1896, Friedrich Ernst Krukenberg described a new type of ovarian tumor in 5 cases. Six years later, this new kind of ovarian tumor have been recognized as a metastasis from other primary malignancy. Since then, "Krukenberg tumor" has become a eponym for metastatic ovarian tumor[1].

The most common primary site of Kurkenberg tumor is stomach, followed by colorectum, appendix, and breast. Other rare primary site described in literature are gallbladder, biliary tract, pancreas, small intestine, ampulla of Vater, cervix, and urinary bladder. In a case series, gastric and colorectal cancer accounts for about 90% of the primary site of KT[2, 3].

Kurkenberg tumor is rare and only represent for 1-2% of all ovarian tumors in most Western series. However, in Eastern population in which the incidence of gastric cancer is higer, KTs may represent up to 21.5% of all ovarian metastases[4].

Although primary adenocarcinoma of the appendix only accounts for approximately 1% of all neoplasms of gastrointestinal origin, the incidence of ovarian metastasis in appendiceal adenocarcinoma is encountered in 16.7 to 37% of cases[5, 6].

According to World Health Organization, the diagnostic criteria of KT is based on the presence of following characteristics: Stromal involvement, ovarian stromal sarcomatoid proliferation, and mucin-producting neoplastic signet ring cells (at least more than 10%)[7]. In general, three theory have been purposed to explain the possible spreading route of KT: 1) lymphatic spread 2) peritoneal spread 3) hematogenous diffusion[4].

Usually, these tumors are diagnosed postoperatively because of unspecific presentation or detected as an incidental finding during exploration for other surgical pathology. Even though abdominal ultrasound and computed tomography might be used, it is difficult to differentiate KT from other abdominal malignancies, including ovarian carcinoma. Here two patients with KT from an occult primary appendiceal adenocarcinoma are described that could only be identified at exploratory laparotomy. Clinical and pathological features of appendiceal tumors with ovarian metastasis are reviewed as well.

Case Presentation

Case 1

In 2013, a 56-year-old female patient (gravida 7, para 4, abortion 3) presented with abdominal fullness. A pelvic ultrasound showed a complex mass of 18x20cm on the left side of the uterus with no free fluid in the abdominal cavity. The results of preoperative examinations, including chest X-ray, colonoscopy, and gastroscopy were all within normal range as were her hematology profile, serum chemistries, urinalysis and CA-125 values. Her serum carcinoembryonic antigen (CEA) level was 17.1ng/mL, and CA-125 was 9.6 U/ml. Abdominal computed tomography (CT) scan showed a 21.4x14.4cm heterogeneous mass in the right lower abdomen and pelvis with a small amount of ascites in the pelvis. Ovarian cancer was then suspected (Figure 1). At explorative laparotomy, a right ovarian tumor measuring 21 x 15 cm and a left ovarian tumor measuring 3 x2 cm were found. Further exploration of the abdomen revealed a mucinous content tumor of about 2 x 2cm in the tip of the appendix with mild lumen narrowing. Appendectomy was performed for frozen section pathology, and the result was adenocarcinoma of the appendix; therefore, bilateral salpingo-oophorectomy, infracolic omentectomy and radical right hemicolectomy with ileotransverstomy and lymph node dissection were performed. The definitive pathological findings were as follows: left ovarian tumor was solid 18.5 x 15.5 x 14.0cm and right ovarian tumor was 5.8 x 3.3 x 3.2cm in size, histologically composed of multiple cystic tumors lined by neoplastic mucin-producing columnar epithelial cells bearing low-grade nuclei. The appendix was 8cm with a diameter of 1.5cm. The tumor had grown through the submucosa and muscular layers (Figure 2). Immunohistochemical (IHC) staining including cytokeratin (CK) 7, CK20, Villin, CDX2, and PAX-8 were performed for both the appendiceal and ovarian specimens, and both series were positive for CK20, Villin, and CDX2, and negative for PAX-8. CK7 was negative in appendix but positive in ovaries. The results were consistent with an adenocarcinoma of the appendix. Postoperatively, the patient received chemotherapy with oxaliplatin 85 mg/m^2 as a 2-hour infusion on day 1, leucovorin 400 mg/m^2 as a 2-hour infusion on day 1, followed by a loading dose of fluorouracil (5-FU, 400 mg/m^2) IV bolus on day 1, then 5-FU (2,400 mg/m^2) administered via ambulatory pump for a period of 46 hours every 2 weeks for 6 months. Forty-two

months after first diagnosis, the patient underwent thoracoscopic wedge resection for a newly developed solitary lung metastasis. Since then, the patient was under regular follow-up and showed no evidence of recurrence for another 46 months.

Case 2

A 54-year-old female (gravida 6, para 4, abortion 2) complained of epigastric fullness for one month at gynecological check-up. A pelvic ultrasound indicated complex masses of 15x15cm bilaterally to the uterus and profuse ascites in the abdominal cavity. Barium enema was normal. The serum CA-125 level had increased to 94 U/mL and CEA level had increased to 17.6 ng/mL. Her hematology profile, serum chemistries, urinalysis and chest X-ray were normal. At explorative laparotomy, bilateral ovarian masses and multiple metastases to the omentum, subdiaphragm and subhepatic areas were found, and further exploration of the abdomen revealed a ruptured appendix with tumor seeding. Debulking surgery with total abdominal hysterectomy, bilateral salpingo-oophorectomy, appendectomy, left hemicolectomy with anastomosis, supracolic omentectomy, and pelvic lymphadenectomy were therefore performed. The definitive pathological findings were as follows: both ovaries were solid tumors measuring 3.5x2.0x1.2cm and 4.0x2.5x1.4cm in size encased with mucinous materials. The histological tests revealed a composition of profuse mucinous pools with clusters of neoplastic mucinous epithelial cells bearing low-grade nuclei. The appendix was enlarged with cystic swelling measuring 3.8cm with a diameter of 1.7cm and the external surface was coated with mucinous substance. The tumor had grown through the submucosa, muscular and serosa layers. IHC staining with CK7 and CK20 were performed for the appendiceal and ovarian specimens, and both series were positive for CK20 (Figures 3 and 4) and negative for CK7. The results were consistent with an adenocarcinoma of the appendix. Postoperatively, the patient received chemotherapy with oxaliplatin 85 mg/m^2 as a 2-hour infusion on day 1, leucovorin 400 mg/m^2 as a 2-hour infusion on day 1, followed by a loading dose of 5-FU (400 mg/m^2) IV bolus on day 1, then 5-FU (2,400 mg/m^2) administered via ambulatory pump for a period of 46 hours every 2 weeks. The treatment course was 6 months. She developed a recurrent abdominal carcinomatosis causing intestinal obstruction 14 months after laparotomy, and expired 4 months later.

Discussion And Conclusions

Primary appendiceal cancer with ovarian metastasis often presents with vague and nonspecific abdominal symptoms, and usually mimics advanced-stage ovarian primary malignancy. Because of the rarity of this disease and limited information provided by preoperative imaging, it is difficult to confirm the diagnosis before the operation; therefore the case is often mistaken as primary gynecological tumor rather than metastatic ovarian tumor, or KT[8].

Reported factors that account for misdiagnosis include lack of history of gastrointestinal symptoms, abdominal distention, elevated serum tumor marker such as CA 125 levels, and outside pathology reports in support of ovarian primary[9]. Oncological surgeons should keep in mind that primary appendiceal cancer is a possible origin source when the diagnosis of ovarian tumor cancer is confirmed.

The results of permanent IHC staining for CK are different for primary appendiceal cancer and primary ovarian cancer. In primary adenocarcinomas of the large intestine and appendix, it is uniformly stained positively for CK 20 and presents typically in a diffuse pattern. Although CK20 is also positive for 75% of primary ovarian mucinous carcinomas, the staining is commonly patchy. In contrast, primary ovarian epithelial tumors of all cell types are stained for more than 96% of cases and the cytoplasm are typically strongly marked[10, 11]. However, permanent result of IHC staining is usually confirmed after surgery. If the diagnosis of primary appendiceal cancer can be established intraoperatively, it would not only lead to a correct diagnosis and optimal surgery but also avoid any subsequent operation; otherwise, occult appendiceal metastases might occur in patients with primary epithelial ovarian cancer (5-10% in early stage) and are diagnosed only after microscopic examination of the appendix[12, 13]. Appendectomy should be part of staging surgery in patients with presumed ovarian cancer, especially in muscinous ovarian cancer. In these two cases, the appendix was generally normal excepted a 1cm nodule near the tip in case 1, and ruptured in case 2. However, we should keep in mind that sometimes appendiceal cancer may appear even the appendix is macroscopically normal.

Adnexal tumors are common among women of all ages and malignant ovarian tumors need to be recognized in order to expedite appropriate treatment. Survival from primary appendiceal cancer depends on extent of tumor, tumor location, and cell type. Because of the rarity of primary appendiceal cancer, issues regarding diagnosis, surgical management, and adjuvant chemotherapy are not well established, although aggressive resection and treatment should be offered to young patients with ovarian metastasis, as this generally confers a 5-year survival advantage of 20-30%[12].

Managing a pelvic mass is one of the common problems for gynecologists; unfortunately, there is no reliable method to distinguish between benign and malignant ovarian tumors. Gynecologists as well as radiologists should consider carcinoma of the appendix in the differential diagnosis of pelvic mass. Both of our cases were presented with elevation of CEA levels preoperatively, but their studies of barium enema and colonoscopy were normal. This might be a clue for us to make the diagnosis of metastatic ovarian tumor from GI tract. Abnormal elevation of CEA level is less common in early stages of primary ovarian cancer. On the other hand, in patients with colorectal cancer, it is associated with all stages of the disease. Some reports suggest that ovarian metastasis from colorectal origin should be consider in any patient whose CA-125/CEA ration is less than 25[14]. In our cases, the CA-125/CEA ration were 0.6 and 5.3 respectively.

Recent studies reveal Human Epididymis Protein 4 (HE4) is superior to distinguish benign ovarian tumors from primary ovarian malignancies[15]. Whether HE4 can be used to identify the primary ovarian cancer from metastatic tumors might need further evaluation. We suggest that the CEA and HE4 tests should be offered to patients with suspected ovarian tumors to assist in making preliminary diagnosis before surgery, especially those with primary sites that are difficult to determine.

Since primary appendiceal adenocarcinoma is rare, these cases remind gynecological surgeons to be familiar with primary appendiceal tumors and to inspect the appendix when the initial exploration surgery

is to be performed. The clinical picture can be misleading and the differential diagnoses of primary appendiceal cancer should be considered when preoperative workup is planned.

Declarations

Ethics approval and consent to participate

Statement: The IRB reviewed and determined that it is expedited review according to Case research or cases treated or diagnosed by clinical routines.

Ethic committee: Chang Gung Medical Foundation Institutional Review Board

Consent for publication

Consents have been obtained from the patients.

Availability of data and materials

The data describe during the current study are not publicly available due patient’s privacy but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The authors received no specific funding for this work.

Authors' contributions

Ko-Chao Lee and Hong-Hwa Chen performed colectomy and postoperative adjuvant chemotherapy for patients and recorded their clinical courses. Kung-Chuan Cheng was a major contributor in writing the manuscript. Yu-Che Ou contributed to the conception of this issue and literature review.

Acknowledgements

Not applicable

Abbreviations

KT: Krukenberg tumor

CT: Computed tomography

CEA: carcinoembryonic antigen

CK: cytokeratin

5-FU: fluorouracil

References

1. Young RH. From krukenberg to today: the ever present problems posed by metastatic tumors in the ovary: part I. Historical perspective, general principles, mucinous tumors including the krukenberg tumor. Adv Anat Pathol. 2006;13(5):205-227. doi:10.1097/01.pap.0000213038.85704.e4
2. Al-Agha OM, Nicastri AD. An in-depth look at Krukenberg tumor: an overview. Arch Pathol Lab Med. 2006;130(11):1725-1730. doi:10.1043/1543-2165(2006)130[1725:AILAKT]2.0.CO;2
3. Jiang R, Tang J, Cheng X, Zang RY. Surgical treatment for patients with different origins of Krukenberg tumors: outcomes and prognostic factors. Eur J Surg Oncol. 2009;35(1):92-97. doi:10.1016/j.ejso.2008.05.006
4. Agnes A, Biondi A, Ricci R, Gallotta V, D'Ugo D, Persiani R. Krukenberg tumors: Seed, route and soil. Surg Oncol. 2017;26(4):438-445. doi:10.1016/j.suronc.2017.09.001
5. Romeo M, Quer A, Tarrats A, Molina C, Radua J, Manzano JL. Appendiceal mixed adenoneuroendocrine carcinomas, a rare entity that can present as a Krukenberg tumor: case report and review of the literature. World J Surg Oncol. 2015;13:325. doi:10.1186/s12957-015-0740-1
6. Wilfred D C, Mysorekar V V, Kamath S, Singla S. Appendiceal Carcinoma with Krukenberg's Tumour Mimicking Primary Ovarian Cancer. J Clin Diagn Res. 2013;7(8):1747-1749. doi:10.7860/JCDR/2013/5478.3252
7. Wu F, Zhao X, Mi B, et al. Clinical characteristics and prognostic analysis of Krukenberg tumor. Mol Clin Oncol. 2015;3(6):1323-1328. doi:10.3892/mco.2015.634
8. Zhang W, Tan C, Xu M, Wu X. Primary appendiceal mucinous neoplasm: Gynecological manifestations, management, and prognosis. Gynecol Oncol. 2020;156(2):357-362. doi:10.1016/j.ygyno.2019.11.030
9. Ojo J, De Silva S, Han E, et al. Krukenberg tumors from colorectal cancer: presentation, treatment and outcomes. Am Surg. 2011;77(10):1381-1385.
10. Tsai HW, Chen YJ, Twu NF*, et al.* Primary appendiceal malignancy mimicking advanced stage ovarian cancer. *Taiwan J Obstet Gynecol*. 2007;46(3):304-7.
11. Hart WR. Diagnostic challenge of secondary (metastatic) ovarian tumors simulating primary endometrioid and mucinous neoplasms. Pathol Int. 2005;55(5):231-243. doi:10.1111/j.1440-1827.2005.01819.x
12. Dietrich CS 3rd, Desimone CP, Modesitt SC, et al. Primary appendiceal cancer: gynecologic manifestations and treatment options. Gynecol Oncol. 2007;104(3):602-606. doi:10.1016/j.ygyno.2006.09.014

13. Beşe T, Kösebay D, Kaleli S, Oz AU, Demirkiran F, Gezer A. Appendectomy in the surgical staging of ovarian carcinoma. Int J Gynaecol Obstet. 1996;53(3):249-252. doi:10.1016/0020-7292(96)02665-3
14. Lee KC, Lin H, ChangChien CC, et al. Difficulty in diagnosis and different prognoses between colorectal cancer with ovarian metastasis and advanced ovarian cancer: An empirical study of different surgical adoptions. *Taiwan J Obstet Gynecol*. 2017;56(1):62-67. doi:10.1016/j.tjog.2015.02.009
15. Kondalsamy-Chennakesavan S, Hackethal A, Bowtell D; Australian Ovarian Cancer Study Group, Obermair A. Differentiating stage 1 epithelial ovarian cancer from benign ovarian tumours using a combination of tumour markers HE4, CA125, and CEA and patient's age. Gynecol Oncol. 2013;129(3):467-471. doi:10.1016/j.ygyno.2013.03.001

Figures

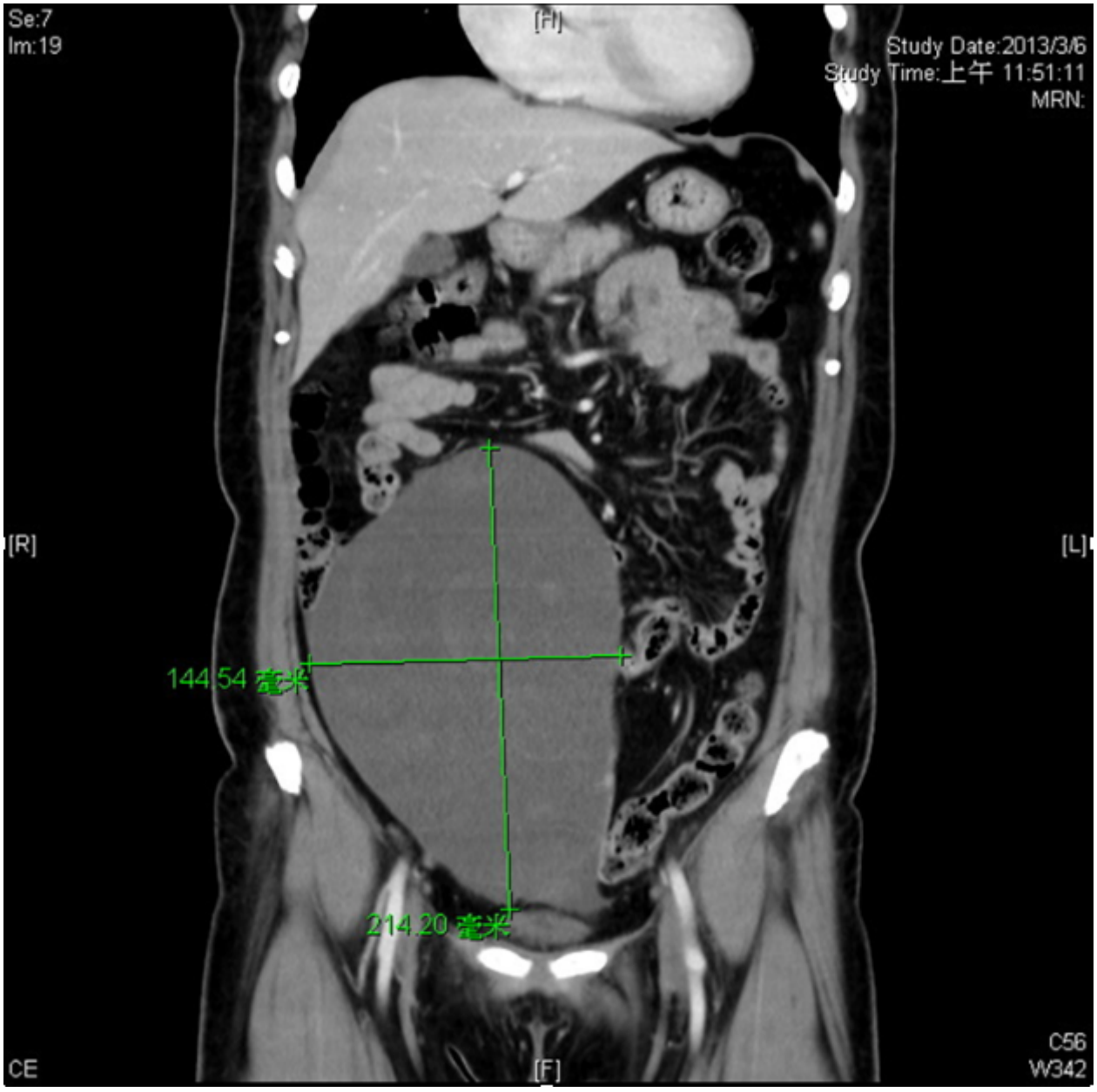

Figure 1

Contrast-enhanced computed tomography scan reveals a 21.4x14.4cm heterogeneous mass, which evidences a metastatic ovarian tumor.

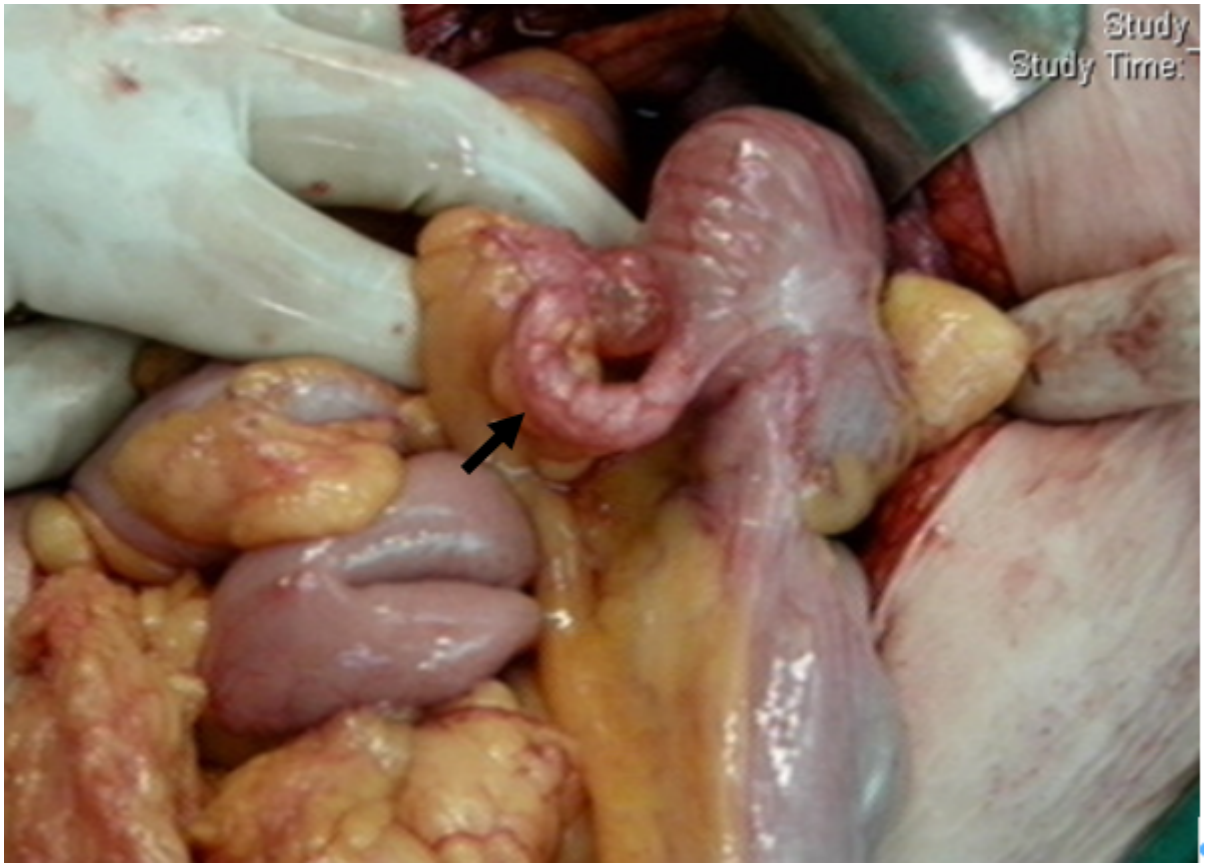

Figure 2

A black arrowhead indicates a swollen appendix with mucinous content tumor of about 2 x 2 cm in the tip of appendix.

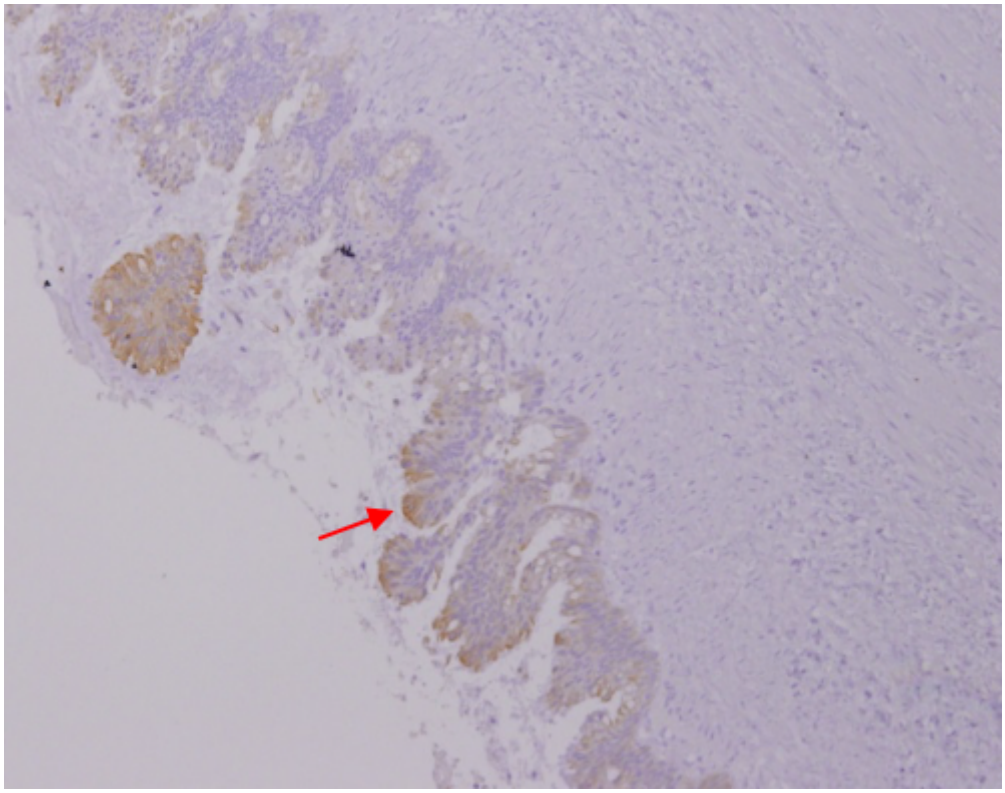

Figure 3

A red arrowhead shows CK20 in appendiceal primary adenocarcinoma (IHC stain).

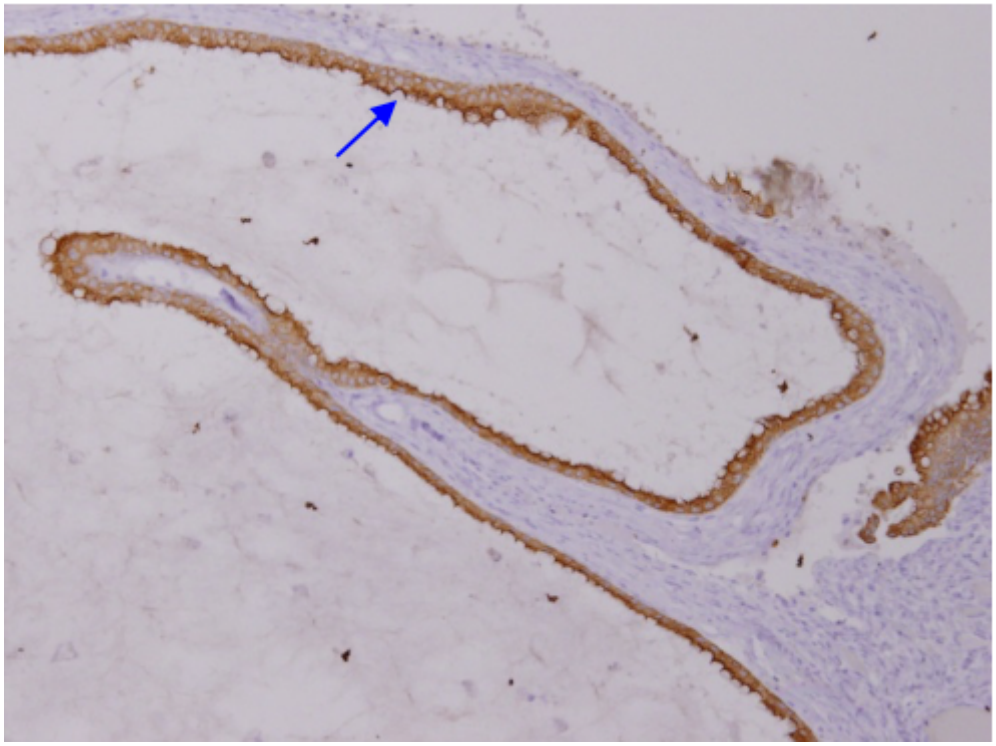

Figure 4

A blue arrowhead shows CK20 in ovarian metastatic tumor (IHC stain).