

## Appendix cancer mimicking ovarian cancer

P. A. GEHRIG\*, J. F. BOGGESS\*, D. W. OLLILA<sup>†</sup>, P. A. GROBEN<sup>‡</sup> & L. VAN LE\*

\*Division of Gynecologic Oncology, Department of Obstetrics and Gynecology; <sup>†</sup>Division of Surgical Oncology, Department of Surgery, <sup>‡</sup>Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

**Abstract.** Gehrig PA, Boggess JF, Ollila DW, Groben PA, Van Le L. Appendix cancer mimicking ovarian cancer. *Int J Gynecol Cancer* 2002;12:768-772.

Appendiceal adenocarcinoma is a rare malignancy for which there is no characteristic clinical presentation. We describe five women who presented with signs and symptoms characteristic of advanced ovarian cancer but whose final diagnosis was stage IV appendiceal cancer. Between 1998 and 1999, five women treated for presumed ovarian cancer were identified as having primary appendiceal cancer. Medical records and pathology were retrospectively reviewed. The median age was 47 years (range 36-61 years). All had elevated preoperative CA125 levels with a median value of 171  $\mu$ /ml (range 46-383). Four women underwent right hemicolectomy with two requiring radical surgical tumor debulking to render them optimally debulked. Four had postoperative chemotherapy, the most common agent used was 5-fluorouracil. Median survival was 6.75 months (range 19 days-11 months). Primary adenocarcinoma of the appendix is rare; therefore, the clinical utility of radical tumor debulking and chemotherapy is not well described. Given the poor survival in our series, all efforts should be considered palliative. Although this disease process is uncommon, it should be entertained by gynecologic oncologists in the differential diagnosis of an intra-abdominal mass and ascites. The ability to make the correct diagnosis and differentiate between an ovarian and appendiceal primary is critical as the treatment modalities vary.

KEYWORDS: appendiceal carcinoma, cancer antigen-125, carcinoembryonic antigen, ovarian carcinoma

Primary appendiceal tumors are rare with the most common being carcinoid. Primary appendiceal adenocarcinoma accounts for less than 0.5% of all gastrointestinal tumors and 5% of primary appendiceal neoplasms. To date, there have been approximately 450

cases of primary appendiceal carcinoma reported in the literature<sup>(1)</sup>. The most common clinical presentation of primary appendiceal adenocarcinoma is a palpable mass or acute appendicitis<sup>(2-5)</sup>. Rarely is the diagnosis of a primary appendiceal adenocarcinoma made preoperatively as neither abdominal ultrasound or computed tomography (CT) can differentiate between this and other more common malignancies, including ovarian carcinoma<sup>(2,4-7)</sup>.

There are approximately 23,000 cases of ovarian car-

Address correspondence and reprint requests to: Paola A. Gehrig, MD, CB# 7570 MacNider Building, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599. E-mail: pam68@med.unc.edu.

cinoma diagnosed in the United States annually. Most ovarian cancers are epithelial in origin, with serous papillary being the most common. The preoperative diagnosis of ovarian carcinoma is based on clinical presentation, physical examination, tumor markers, and radiographic studies. Despite advances in chemotherapy, surgical debulking remains the mainstay in the primary treatment of ovarian carcinoma. Intraoperatively, the goal of ovarian cancer surgery is optimal tumor debulking, defined as removal of all tumor masses greater than 2 cm. Studies have shown that patients who are optimally debulked have a significant survival benefit over those patients with bulky residual tumor<sup>(8,9)</sup>. In contrast, in colorectal surgery, the benefit of optimal surgical debulking is controversial<sup>(3,5,7,10,11)</sup>.

There are few reports in the literature of advanced appendiceal carcinoma. In a study of 15 patients on the management and prognosis of appendiceal adenocarcinoma, the author described three patients with primary appendiceal carcinoma who preoperatively were felt to have disease consistent with advanced ovarian carcinoma. These authors observed that the absence of carcinomatosis was a favorable prognostic factor<sup>(1)</sup>. In our study, we present five women with clinical presentations suggestive of advanced ovarian carcinoma who upon surgical resection and pathologic review had metastatic appendiceal carcinoma. Appendiceal malignancies should be considered in the differential diagnosis of a pelvic mass and the appendix should be evaluated in all patients undergoing surgical exploration for an ovarian neoplasm.

### Patients and methods

Five women with the preoperative diagnosis of advanced stage ovarian carcinoma, who on final pathology had Dukes stage D (any T, any N, M1) primary appendiceal adenocarcinoma, were surgically explored by the Gynecologic Oncology service at the University of North Carolina at Chapel Hill from 1998 to 1999. Clinical records were abstracted for patient history, physical examination, preoperative evaluation, surgical procedures, pathology reports, stage at the time of diagnosis, adjuvant therapy, and outcomes. As there is no formal staging for appendiceal neoplasm, staging was based on the Astler-Coller modifications of the Dukes staging system. This study met the exclusion criteria as set forth by the Institutional Review Board.

The study pathologist (PAG) reviewed all histologic specimens. The pathologic diagnosis of primary ap-

pendiceal carcinoma was based on the presence of extensive replacement of the appendiceal mucosa by tumor, which in several cases was more concentrated towards the luminal surface than the serosal surface. Cytokeratin (CK) 7 and CK 20 immunohistochemistry were also performed to assist in the pathologic distinction between a primary gastrointestinal and primary gynecologic malignancy<sup>(12)</sup>.

### Results

The median age of the five study patients was 47 years (range 36–61 years). All five women were referred to the gynecologic oncology service with the presumptive diagnosis of ovarian carcinoma based on physical symptoms, physical examination, and radiographic and biochemical studies and were offered surgical exploration (Fig. 1). All the women had an elevated CA-125 with a median value of 171 U/ml (range 46–383). Carcinoembryonic antigen (CEA) was available for four out of five women; two had a normal CEA (0.6 ng/ml, 1.5 ng/ml) and two had elevated values (9.2 ng/ml, 343.7 ng/ml).

All women underwent exploratory laparotomy. Four of the five women underwent a right hemicolectomy with primary anastomosis after the appendix was noted to be abnormal. The appendix was removed at the time of initial surgery in all five cases for either an abnormal appearing appendix or a palpable cecal mass. Intraoperative frozen section was performed on a removed ovary in three cases and was diagnostic of an adenocarcinoma with signet ring cell features. The ovaries were grossly involved with tumor in all cases, however, were removed in only four. The right ovary was always enlarged varying from 6.5 to 17 cm in size and was generally larger than the left ovary. Based on the surgical findings of an appendiceal or cecal mass, the frozen section results and the foreshortening on the small bowel mesentery, the diagnosis of an appendiceal primary was made in four women. In the last case, it was not made, though suspected, as there was no identifiable appendix secondary to complete replacement by tumor.

Adenocarcinoma, with at least focal signet ring appearance, was found in the appendix in all five cases, although in one case the appendix was not separately identified because it was adherent to the right ovary and essentially obliterated by tumor. In another, the signet ring pattern was admixed with a prominent glandular mucinous pattern with goblet cells (Figs. 2A and 2B). Small foci of glandular differentiation with goblet cells were seen in two additional cases. An ap-

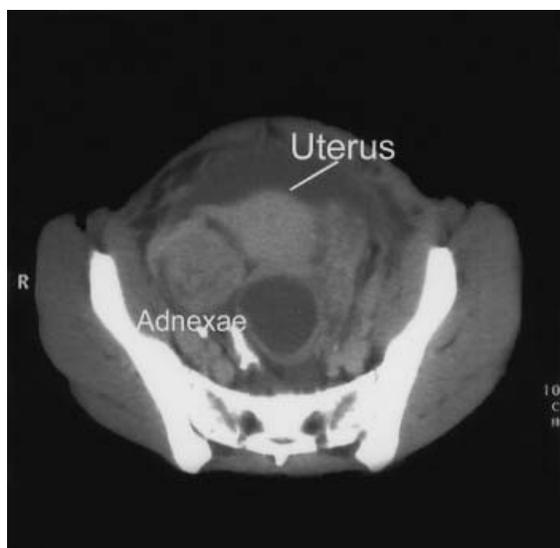


Fig. 1. Representative CT scan.

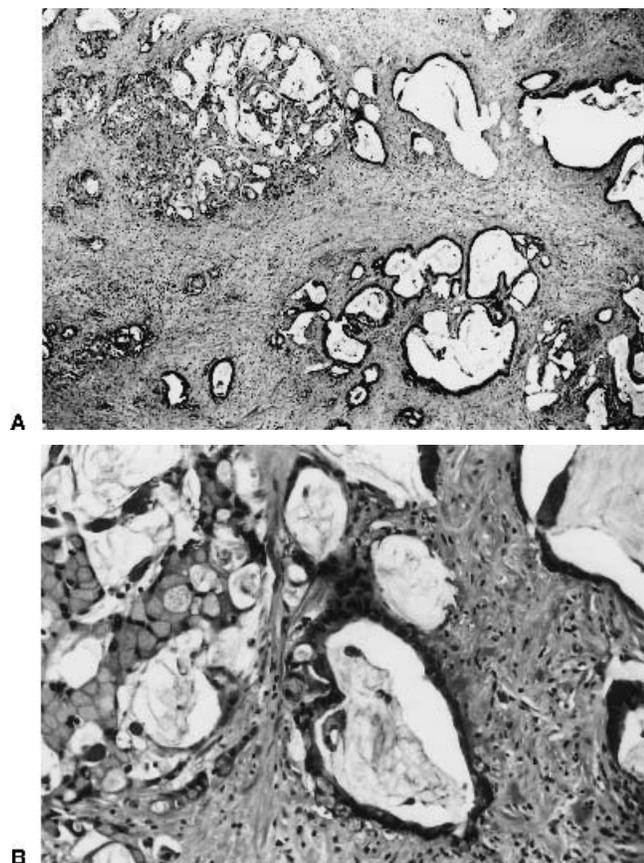


Fig. 2. (A) and (B). Appendiceal primary adenocarcinoma with prominent glandular pattern (2A) and focal signet ring pattern (2B), original magnification 10 $\times$  (2A) and 100 $\times$  (2B).

pendiceal adenoma was not seen in any of the surgical specimens. A signet ring cell adenocarcinoma pattern was found in all four of the ovarian tumors and was similar in both ovaries (Fig. 3). The signet ring pattern

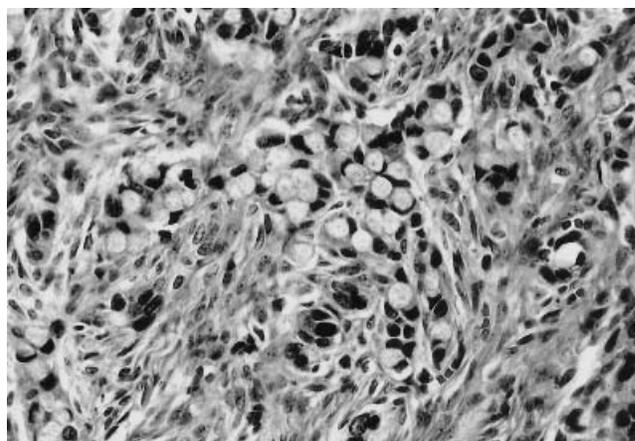


Fig. 3. Ovarian metastasis with signet ring cell pattern and cellular stroma consistent with Krukenberg tumor. Original magnification 100 $\times$ .

was accompanied by a cellular stroma in two cases consistent with a Krukenberg tumor. In the lesion with prominent glandular differentiation in the appendix, a similar pattern was seen in the ovary and was accompanied by pseudomyxoma ovarii (Fig. 4). Pseudomyxoma peritonei was not clinically apparent at the time of any of the surgeries. CK 7 and CK 20 immunostaining was performed in part for all cases (Table 1). Figure 5 shows a representative staining of metastatic foci in an ovary.

Four women underwent adjuvant therapy with chemotherapy, with the most common agent being intravenous continuous infusion 5-fluorouracil. None of the women were rendered disease free despite surgery and chemotherapy. The median survival was 6.75 months (range 19 days-11 months). One woman died on postoperative day 19, if she is excluded, the median survival was 8.25 months (range 2-11 months), with no woman living beyond 11 months.

## Discussion

Primary adenocarcinomas of the appendix are rare therefore issues regarding diagnosis, operative management, and adjuvant therapy are not well described. There have been approximately 450 reported cases of primary appendiceal adenocarcinoma described in the literature<sup>(1)</sup>. In a recent study, which described 15 cases of adenocarcinoma of the appendix, three (23%) were felt preoperatively to be ovarian carcinoma<sup>(1)</sup>. In another study, 13 patients presented with symptoms related to a pelvic or adnexal mass<sup>(12)</sup>. Other diagnoses which were considered included metastatic adenocarcinoma of unknown primary, ruptured appendix, adenocarcinoma of the ileocecum or sigmoid

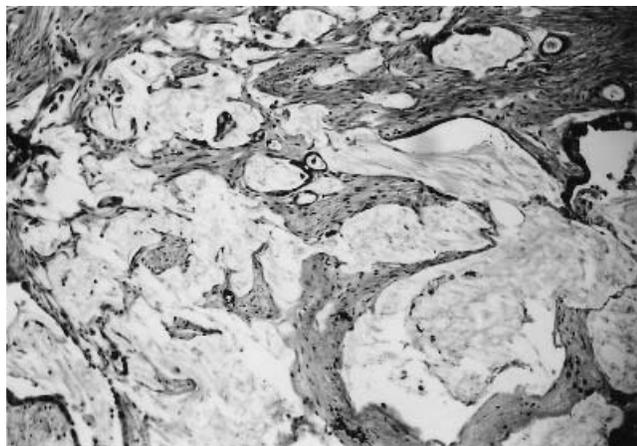


Fig. 4. Ovarian metastasis with extensive mucin extravasation – pseudomyxoma ovarii, original magnification 25 $\times$ .

Table 1. Cytokeratin staining results (study)

	Ovary		Appendix	
	CK 7	CK 20	CK 7	CK 20
Patient 1	Negative	Positive	Negative	Positive
Patient 2	Negative	Positive	Negative	Positive
Patient 3	Negative	Positive	Not available	
Patient 4	Positive	Positive	Positive	Positive
Patient 5	Not available		Positive	Negative

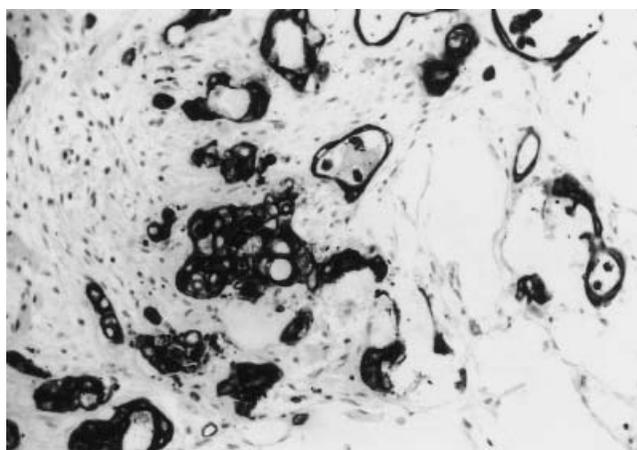


Fig. 5. Strong diffuse staining with CK 20 in an ovarian metastasis. Original magnification 50 $\times$ .

colon, or a hernia. Most patients with appendiceal cancer present with signs and symptoms of acute appendicitis or a right lower quadrant mass<sup>(2-5)</sup>. Overall, the preoperative diagnosis of an appendiceal adenocarcinoma is rarely made. In fact, the diagnosis is considered intraoperatively only 32% of the time<sup>(1)</sup>. In our study, the diagnosis was correctly made intraoperatively in four of five patients and in the other case was suspected and not made because there was no identifiable appendix as it was completely obliterated with

tumor. In two women, the diagnosis was suspected immediately at the time of laparotomy secondary to the foreshortening of the small bowel mesentery from carcinoma and a palpable mass in the area of the appendix.

Histologically, the signet ring cell pattern was seen in all five cases, the most common histologic finding, followed by mixed, intestinal, and colorectal types<sup>(12)</sup>. CK 7 and CK 20 immunostaining was performed on both the appendiceal and ovarian specimens in three cases. CK 20 positivity is consistent with gastrointestinal origin while CK 7 is generally attributed to tumors of gynecological origin. However, appendiceal carcinomas can be CK 7 positive in 50% of cases (Table 2)<sup>(12)</sup>. In the cases with both appendiceal and ovarian specimens, the cytokeratin results were concordant between the appendix and ovaries (Table 1). Two were CK7 negative and CK 20 positive and another showed the reverse pattern. In patient 3, the appendix could not be isolated, however, the ovarian cytokeratin pattern was consistent with gastrointestinal origin. The cytokeratin staining pattern for patient 5 was not typical despite histologic confirmation of a signet ring cell adenocarcinoma in the appendix.

Four women were offered postoperative chemotherapy, the most common regimen involved the use of 5-FU. One woman was referred for hyperthermic intra-abdominal therapy with mitomycin-C. Despite surgery and chemotherapy, none of the women were rendered disease free. The median survival in our study was 6.75 months. Two of the women were optimally debulked and three were suboptimally debulked. As the numbers in this study are too small for statistical analysis, determination of the benefit of aggressive debulking for metastatic appendiceal carcinoma cannot be made; however, there did not appear to be a difference in quality of life or overall survival between the two groups. Of the women who were optimally debulked, one survived 2 months and the other survived 10 months, as compared to 19 days, 11 months and 10 months in those suboptimally debulked.

It is well known that appendiceal neoplasms can metastasize to the ovaries and our finding that all five patients had ovarian metastases is consistent with previous reports. One study showed ovarian metastases in seven of eight patients (87.5%)<sup>(3)</sup>. In a larger study, 57% of women had ovarian metastases<sup>(5)</sup>. Such reports have led many authors to recommend bilateral oophorectomy in postmenopausal women with gastrointestinal neoplasms, as it may change a patients' stage and eliminate possible residual sites of metastasis<sup>(3,5)</sup>. In addition, the presence of ovarian metastases may contribute to an inaccurate preoperative diagnosis.

**Table 2.** Cytokeratin staining results (literature)<sup>12</sup>

Cell type	CK7	CK20
Mucinous ovarian primary	Almost always positive	Almost always positive
Appendiceal primary	50% positive	Almost always positive
Colorectal primary	Almost always negative	Almost always positive

At our institution, we had five cases of advanced appendiceal adenocarcinoma presenting as advanced ovarian cancer. There are several other similar cases reported in the literature, however the majority of the patients reported in the literature were not initially felt to have ovarian carcinoma<sup>(1,12)</sup>. While there is one other case report in the gynecologic oncology literature of three patients who presented in a fashion similar to our cohort, they did not comment on preoperative tumor markers, CK staining, or outcomes<sup>(13)</sup>. Obtaining a frozen section of either the ovarian tumor or the appendiceal lesion appears to be reliable as in our series when a frozen section was performed, the correct diagnosis of a signet ring carcinoma was made in all cases. At the time of permanent histopathologic evaluation, CK 7 and 20 staining is helpful in confirming a metastatic gastrointestinal primary if the tumor is CK 20 positive and CK 7 negative. Since other patterns of staining may represent either a primary ovarian neoplasm or a metastasis from the appendix, it is imperative that the appendix be examined histologically.

As primary appendiceal adenocarcinoma is so rare, the clinical utility of radical tumor debulking and chemotherapy is not well described. However, given the poor survival rates in our series despite aggressive surgical and adjuvant therapy, all efforts should be considered palliative, especially in patients presenting with carcinomatosis. Though uncommon, it should be a diagnosis considered by all gynecologic oncologists and supports that the appendix should be evaluated carefully at the time of all laparotomies for suspected ovarian carcinoma.

## References

- 1 Cortina R, McCormick J, Kolm P, Perry RR. Management and prognosis of adenocarcinoma of the appendix. *Dis Colon Rectum* 1995;**38**:848–52.
- 2 Andersson A, Bergdahl L, Boquist L. Primary carcinoma of the appendix. *Ann Surg* 1976;**183**:53–7.
- 3 Conte CC, Petrelli NJ, Stulc J, Herrera L, Mittelman A. Adenocarcinoma of the appendix. *Surg Gynecol Obstet* 1988;**166**:451–3.
- 4 Ozakyol AH, Saricam T, Kabukcuoglu S, Caga T, Erenoglu E. Primary appendiceal adenocarcinoma. *Am J Clin Oncol* 1999;**22**:458–9.
- 5 Nitecki SS, Wolff BG, Schlinkert R, Sarr MG. The natural history of surgically treated primary adenocarcinoma of the appendix. *Ann Surg* 1994;**219**:51–7.
- 6 Foshager MC, Hood LL, Walsh JW. Masses simulating gynecologic diseases at CT and MR imaging. *Radiographics* 1996;**16**:1085–99.
- 7 Rutledge RH, Alexander JW. Primary appendiceal malignancies: rare but important. *Surgery* 1992;**111**:244–50.
- 8 Hoskins WJ. Epithelial ovarian carcinoma. principles of primary surgery. *Gynecol Oncol* 1994;**55**:S91–6.
- 9 Hoskins WJ, Bundy BN, Thigpen JT, Omura GA. The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume stage III epithelial ovarian cancer: a gynecologic oncology group study. *Gynecol Oncol* 1992;**47**:159–66.
- 10 Sugarbaker PH, Kern K, Lack E. Malignant pseudomyxoma peritonei of colonic origin. *Dis Colon Rectum* 1987;**30**:772–9.
- 11 Herrera LO, Ledesma EJ, Natarajan N, Lopez GE, Tsukada Y, Mittelman A. Metachronous ovarian metastases from adenocarcinoma of the colon and rectum. *Surg Gynecol Obstet* 1982;**154**:531–3.
- 12 Ronnett BM, Kurman RJ, Shmookler BM, Sugarbaker PH, Young RH. The morphologic spectrum of ovarian metastases of appendiceal adenocarcinomas. *Am J Surg Pathol* 1997;**21**:1144–55.
- 13 McBroom JW, Parker MF, Krivak TC, Rose GS, Crothers B. Primary appendiceal malignancy mimicking advanced stage ovarian carcinoma: a case series. *Gynecol Oncol* 2000;**78**:388–90.

Accepted for publication June 1, 2002.