CASE REPORT

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# Low Grade Mucinous Appendiceal Neoplasia Presenting as Ovarian Tumor; A Rare Case Report

## Over Tümörü Olarak Ortaya Çıkan Düşük Dereceli Müsinöz Apendiks Neoplazisi; Nadir Bir Olgu Raporu

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**ABSTRACT**

It can be difficult to distinguish between primary and metastases in ovarian mucinous neoplasms, both clinically and histopathologically. Especially in mucinous type ovarian neoplasia, the possibility of metastasis of a mucinous neoplasia originating from the appendix or colon should be kept in mind due to its close proximity to the ovary. Considered to be of primary ovarian origin with clinical and radiological findings; however, we present a rare case that we detected as a mucinous neoplasia metastasis originating from the appendix by histopathological and molecular analysis. Although intraoperative histopathological evaluation is important in ovarian neoplasia, a more accurate diagnosis can be made with immunohistochemical and molecular additional diagnostic methods, especially in cases with mucinous type ovarian neoplasia.

**Keywords:** Appendiceal mucinous neoplasm, ovary, diagnosis, molecular

**ÖZ**

Over müsinöz neoplazilerinde primer ve metastaz ayrımını yapmak hem klinik hem de histopatolojik olarak zor olabilir. Özellikle müsinöz tip over neoplazilerinde overe yakın komşulukları nedeniyle apendiks veya kolon kaynaklı bir müsinöz neoplazinin metastaz yapmış olma olasılığı akılda tutulmalıdır. Klinik ve radyolojik bulgular ile primer over kaynaklı olduğu düşünülen; ancak histopatolojik ve moleküler analiz ile apendiks kaynaklı bir müsinöz neoplazi metastazı olarak saptadığımız nadir bir olguyu sunuyoruz. Over neoplazilerinde intraoperatif histopatolojik değerlendirme önemli olmakla birlikte özellikle müsinöz tip over neoplazi olan olgularda ameliyat sonrasında immünohistokimyasal ve moleküler ek tanı yöntemleri ile daha doğru tanı konulabilmektedir.

**Anahtar Kelimeler:** Apendiks müsinöz neoplazmı, over, tanı, moleküler

## Introduction

Mucinous appendiceal neoplasms are rare, sometimes found incidentally, during follow-up, or during surgery for other reasons, and histopathologically classified as low-grade mucinous appendiceal neoplasms (LAMNs), high-grade mucinous appendiceal neoplasms, and mucinous adenocarcinomas (MA) (1).

Up to 23 cases of appendiceal mucinous neoplasia have been reported till date in English medical literature. When the literature is reviewed, our case is an uniq case of primary LAMN causing ovarian metastasis and pseudomyxoma peritonei (PMP).

## Case Report

Our patient, 45 years old female, was admitted to the hospital with abdominal pain and swelling. The tumor markers cancer antigen 125 (CA-125), cancer antigen 19-9 (CA 19-99) and carcinoembriyonic antigen levels rose slightly (71.5 U/mL, 48.3 ng/mL and 48.7 ng/mL, respectively). On ultrasonography (USG) imaging, a 110x105 mm multicystic mass was observed in the right ovary. A small amount of acid was detected.

Right ovarian mass was excised with laparotomy and sent to pathology for frozen study. In the macroscopic examination, a ruptured multicystic mass of 11x11x3 cm in size with mucoid material and a solid area of 4 cm in

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the cyst were observed. A borderline mucinous tumor was diagnosed on microscopic examination. With this result; the operation was terminated by appendectomy, bilateral salpingo-oophorectomy, hysterectomy, lymphadenectomy, omentectomy and peritoneal implant excision. Microscopically (Figure 1), the surface of the ovarian and appendiceal tumors was lined with mucinous epithelium with low-grade dysplasia. Acellular mucin was in the omentum and peritoneal tissues, and mucinous epithelium was observed in the stroma. Lymph node metastasis was not observed.

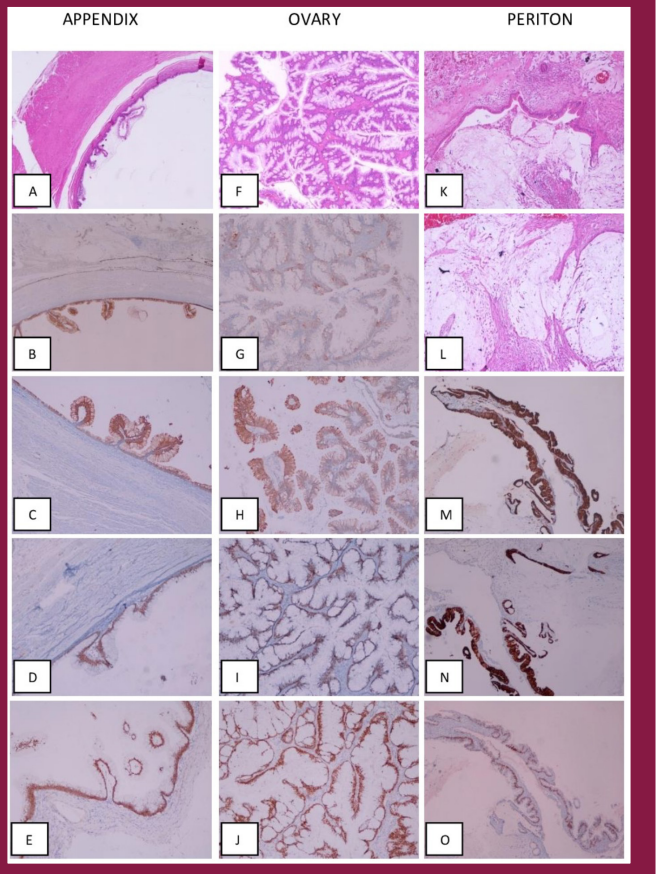


**Figure 1. A-E.** Low-grade appendiceal mucinous neoplasm. **(A)** Villous and flat proliferation of mucinous epithelial cells lining the appendiceal mucosa in LAMN (HX&Ex 40). Immunohistochemical positivity of CK7 **(B)**, CK20 **(C)**, CDX2 **(D)** and SATB2 **(E)** in tumor cells of the appendix mucinous neoplasm (x100). **F-J.** Low-grade appendiceal mucinous neoplasm involving the ovary. **(F)** The mucinous glands have a complex anastomosing architectural pattern (HX&Ex 40). Immunohistochemical focal positivity of CK7 **(G)** and CK20 **(H)**, diffuse positivity of CDX2 **(I)** and SATB2 **(J)** in tumor cells of the ovary (x100). **K-O.** Pseudomyxoma peritonei, low grade. **(K)** Lakes of mucin and epithelial cells (HX&E×100). **(L)** Acellular mucin in the fibrous tissue (HX&E×100). Immunohistochemical positivity of CK7 **(M)**, CK20 **(N)**, and CDX2 **(O)** in tumor cells of the periton (x100)
*LAMN: Low-grade mucinous appendiceal neoplasm*

### Immunohistochemistry

In order to understand the origin of the tumor, 4 µm thick sections were made from the blocks of the appendix, ovary and omentum, and immunohistochemical studies were performed. The tissue was separated from paraffin with xylene and rehydrated with ethanol. Monoclonal cytokeratin 7 (CK7) (dilution 1:100), cytokeratin 20 (CK20) (dilution 1:100), CDX2 (dilution 1:250), PAX-8 (prediluted), CA-125 (dilution 1:100), and Specific AT-rich sequence binding protein 2 (SATB2) (dilution 1:100) antibodies were applied to the slides. While CK7 and CK20 stained focal positively in tumor cells of ovary, CDX2, PAX-8 and SATB2 antibodies showed diffuse nuclear positivity. On the other hand; diffuse strong positive staining was observed with CK7, CK20, CDX2 and SATB2 in the sections of tumor samples in the appendix and omentum (Figure 1).

### GNAS Mutation Analysis

GNAS mutation analyzes were performed in both appendiceal and ovarian tumor tissues (Figure 2). Hotspot sites for pathogenic mutations in exons 8 and 9 of the *GNAS* gene were analyzed by polymerase chain reaction (PCR)-based direct sequencing. Tumor targets (>90% viable tumor) were manually microdissected from 10 mm thick unstained histological sections. Sections were deparaffinized. DNA was then isolated using the QIAamp DNA FFPE Tissue Kit (50) (catalog #56404) (QIAGEN, Hilden, Germany). The primers used in the amplification process are as follows: Exon 8-Forward: 5'ACTGTTTCGGTTGGCTTTGGTGA'3, exon 8-Reverse: 5'AGGGACTGGGGTGAATGTCAAGA'3, exon 9-Forward: 5'TTGACATTCACCCCAGTCCC'3, exon 9-Reverse: 5 'ACAAACACAGAAGCAAAAGCGCAAAAGCG.

The purified PCR products were submitted to direct sequencing in both directions (forward and reverse) by applying reagents from the Big Dye Terminatorv3.1 Cycle Sequencing kit. After the precipitation of alcohol, the products were run on an automatic sequencer. Bidirectional sequence traces were analyzed with SeqScape Software v3.0 and manually reviewed with the reference sequence of the *GNAS* gene.

As a result, GNAS exon 8 c.602G>A (p.R201H) mutation was identified in both appendix and ovary tumor tissues (Figure 2), while GNAS exon 9 mutation was not detected.

### Follow-up

No problem was detected in the controls of the patient and he was discharged in good health. Follow-up was performed using computed tomography, USG imaging and tumor markers. No recurrence/residual tumor was detected in the first 2 years of follow-up.

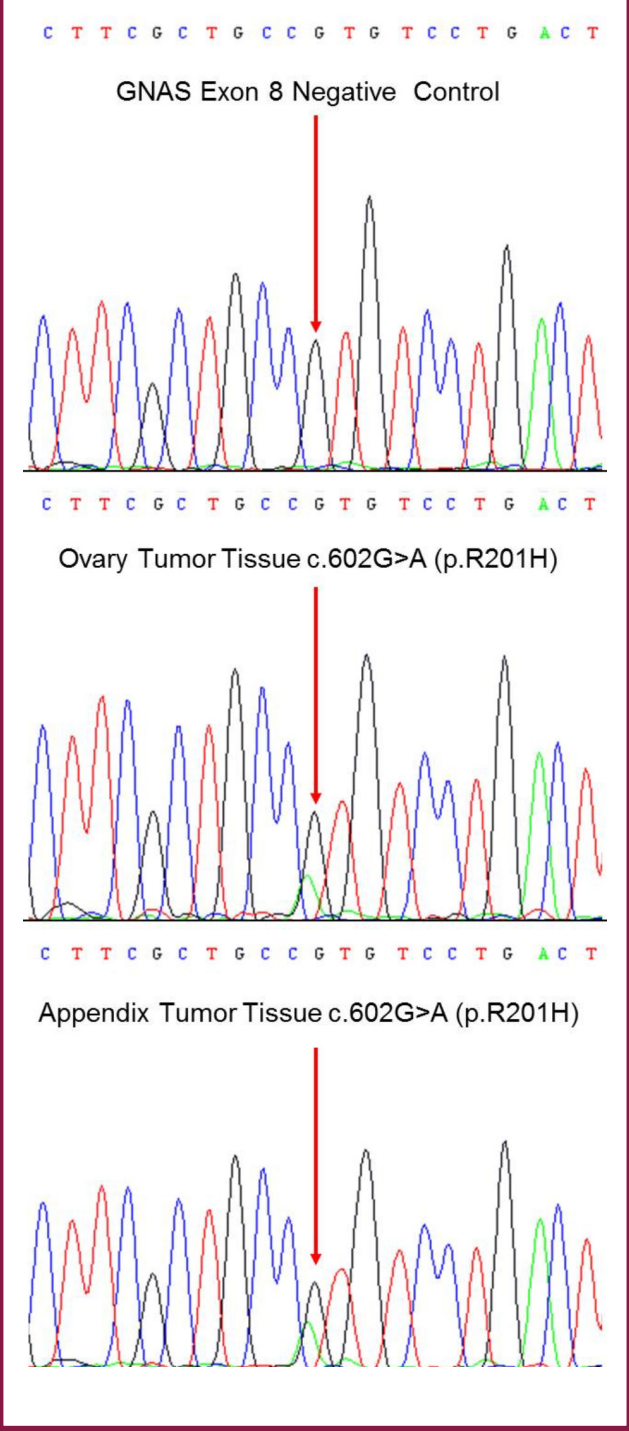


**Figure 2.** Representative sequencing forward electropherograms of GNAS exon 8 c.602G>A (p.R201H) mutation in both appendix and ovary tumor tissues while corresponding region of the IVS-000 polyclonal control DNA's reference sequence is shown in upper lane

## Discussion

The primary/metastasis differentiation of appendiceal and ovarian mucinous neoplasms can be difficult. Only histopathological examination is not sufficient, pathological additional diagnostic methods should be applied.

Most ovarian tumors express CK7 and are CK20 negative, while tumors of colon and appendix are CK20 positive but CK7 negative. In some tumors, CDX2 will be required to exclude tumors originating from other gastrointestinal and pancreato-biliary systems.

A newly recognized marker proposed for primary/metastasis differentiation of mucinous neoplasms in the ovary is SATB2 (2). The SATB2 antibody indicates the origin of colorectal or appendiceal cancer of the lower gastrointestinal tract. Schmoeckel et al. (2) reported 7 cases of LAMN that had ovarian metastasis or caused PMP. They applied an immunohistochemical panel including SATB2 to these cases, and SATB2 showed diffuse and strong positive expression in all of them. On the other hand, it was determined that immunohistochemical SATB2 negative 40 cases had ovarian mucinous borderline tumor or ovarian mucinous carcinoma. According to this finding, SATB2 antibody can be used in the differential diagnosis of mucinous neoplasia originating from the ovary and appendix.

In the presence of 2 or more tumors in different anatomical regions, DNA sequencing can be used as a more specific indicator than immunohistochemistry for the differentiation of metastases or primary tumors (3). This approach may be useful in genetically stable tumors such as LAMN. Since genetic variants associated with LAMN are primarily confined to a few hotspot regions in GNAS, it would be appropriate to work with Sanger sequencing.

This case is the rare one in the literature with a diagnosis of LAMN metastasizing to the ovary (4) and causing low-grade PMP, and is the second one (5) without PMP. Also our case is the 4$^{th}$ one with simultaneous appendiceal and ovarian mass, indicating primary appendix. If we look at the other 3 literature (Table 1) from the past to the present, Klein and Rosen (6) diagnosed a postmenopausal female patient with vaginal bleeding after the operation with MA and mucinous carcinoma in bilateral ovaries. Mandai et al. (7) diagnosed appendiceal adenocarcinoid and bilateral Krukenberg tumors after the operation in a young premenopausal female patient who presented with a lower abdominal mass. Toffaha et al. (4) detected a 21 cm right adnexal complex cyst on USG imaging in a postmenopausal female patient who presented with minimal vaginal bleeding. They detected the appendix adjacent to the ovary

during the operation and considered it as primary ovarian carcinoma. As a result of histopathological examinations, it was diagnosed as primary LAMN and ovarian metastasis, as in our case.

Borges et al. (8) presented a case diagnosed LAMN by post-operative histopathological examination in a postmenopausal female patient who presented with an adnexal mass. They did not detect any other mass in the ovaries or abdomen in this patient. They searched literature in PubMed, asking if there was a case similar to this case and found 23 similar literature. Mucocele in the appendix in 9 cases, LAMN in 7 cases, mucinous cystadenoma in 6 cases

**Table 1. Literature review: pre-op adnexal mass, intra-op abnormal appendix and ovary, origin in appendix[a]**

| Report[b] | Age (y) | Examination | Surgery | Macr. find | Micr. find | Follow-up/rec |
|---|---|---|---|---|---|---|
| **Current case** | 45 | 21x11x3 cm | L, right adn. | Large mobile | Appendix: LAMN | No rec, 1 y |
| | | Ruptured cystic | Mass | thin walled | ROV: LAMN met., | |
| | | Mass of the | Excision | multi locular | periton, omentum: PMP | |
| | | right ovary, | with (frozen) | cystic mass | | |
| | | normal uterus, | TAH with USO, | arising from R OV., | | |
| | | perforated | AP and periton, | N Lt OV., and U., | | |
| | | appendix, | om., LAD | perforated appendix, | | |
| | | peritoneal and | | peritoneal and omental | | |
| | | omental imp. | | mass/mucus | | |
| **Toffaha A 2020** | 58 | Soft Abd, no | L, TAH with | Large mobile thin | | No Rec 3 y |
| | | tenderness/ | BSO and AP | walled multi locular | ROV: LAMN met | |
| | | guarding; mobile | | mass arising from R OV., | | |
| | | non-tender | | N. Lt OV and U., | | |
| | | 15x10 cm mass; | | Small and large bowel | | |
| | | bulky U, fullness | | adhesions, appendix | | |
| | | around adnexa | | adherent to ovary, mucus | | |
| | | | | extruding through its tip | | |
| **Mandai M. 2000** | 35 | Lower abdominal | 1st Op: L, TAH, | 1st Op: Large | ACC with Bil. | Died 24 m after |
| | | mass | Lt SO, partial | Lov, N ROV. | Krukenberg | diagnosis |
| | | | Resection of | 2nd Op: ROV | Tumor | |
| | | | R OV. 2nd Op: | slightly large | | |
| | | | RSO, AP, Om, | and hard | | |
| | | | Res of colonic | | | |
| | | | nodule, P& | | | |
| | | | para-A Lad | | | |
| **Klein E. 1996** | 66 | NR | L, TAH with | Partly exophytic | AMC, both | Death after 20 m |
| | | | BSO and | Lt OV mass, | OV involved | |
| | | | modified R H, | 4 cm, distending | (ROV microscopic) | |
| | | | biopsy of peritoneal | the cecum, suspicious | | |
| | | | nodules | nodule in cul-de-sac | | |

[a] Evidence based on case report, [b]For space considerations, only the first author is cited, AAC: Appendiceal adenocarcinoid, Abd: Abdominal, AMC: Appendiceal mucinous carcinoid, AP: Appendectomy, Bil: Bilateral, BSO: Bilateral salpingo-oophorectomy, L: Laparotomy, Lad: Lymphadenectomy, Lt: Left, Macr. find.: Macroscopic finding, Micr. find.: Microscopic finding, m: Month, N: Normal, NR: Not reported, Om: Omentectomy, Op: Operation, OV: Ovary/s P: Pelvic, Para-A: Para-aortic, R: Right, Rec: Recurrence, Res: Resection, SO: Salpingo-oophorectomy, TAH: Total abdominal hysterectomy, U: Uterus, y: Years

and MA in 1 case of these literatures was found. No tumor was detected in any other focus in any of these cases.

It is difficult to understand the origin of mucinous tumors because the ovary and appendix are close to each other anatomically, there are no specific serum markers for cancers originating from these organs, and mucinous tumors originating from the appendix can metastasize to the ovary (9).

## Conclusion

Our case showed how we can distinguish between metastasis from primary appendix or ovary in a case of LAMN. Surgeons should provide the pathologist with more information about the clinical, radiological and laboratory characteristics of patients. We also found that performing frozen sections during the operation was significantly important for helping the pathologist diagnose the definitive one. In addition, the presence of PMP indicated that mucinous neoplasms of the appendix should be considered. Based on our results, a more accurate diagnosis can be made in patients with mucinous ovarian neoplasm with the diagnosis of frozen during the operation and with immunohistochemical and molecular additional diagnostic methods after the operation.

### Ethics

**Informed Consent:** Informed consent was obtained.

**Peer-review:** Internally and externally peer-reviewed.

**Financial Disclosure:** The author declared that this study received no financial support.

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