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Case Report

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Neuroendocrine Tumors Identified During Laparoscopic Endometriosis Surgery: A Report of 6 Cases

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Abstract

Background: Neuroendocrine tumors (NETs) or carcinoid tumors are rare neoplasms originating from neuroendocrine cells, most commonly found in the appendix. While NETs are often asymptomatic, they may present with abdominal pain, flushing, and diarrhea and are frequently discovered incidentally during surgery for other conditions. Endometriosis has been associated with an increased risk of certain malignancies; however, its relationship with NETs remains unclear. Given the high frequency of laparoscopic surgeries for endometriosis, incidental NET findings pose unique clinical challenges.

Methods: This retrospective case report was conducted at Avicenna Fertility Center, Affiliated to Avicenna Research Institute, Tehran, Iran, from 2016 to 2024. Medical records of six patients (33-55 years old) who underwent laparoscopic surgery for endometriosis, with incidental NETs found in the appendix, were analyzed. Clinical presentation, intraoperative findings, histopathology, and postoperative outcomes were reviewed.

Results: Six women (mean age: 43.7 years) with endometriosis-related symptoms (dysmenorrhea, dyspareunia, and pelvic pain) underwent laparoscopic surgery with appendectomy. The NETs (2–9 *mm*, all G1, Ki-67 <3%) exhibited invasion into the muscularis propria in three cases and into the subserosal fat in one case; lymph nodes were not evaluated, and no metastases were detected. Immunohistochemistry confirmed neuroendocrine differentiation, with positive chromogranin and synaptophysin staining. Follow-up over 1–5 years showed no evidence of recurrence.

Conclusion: Incidental NET detection during endometriosis surgery highlights the need for routine pathological examination of appendectomy specimens. While no direct link exists between NETs and endometriosis, recognizing these tumors may influence surgical decisions and postoperative management, emphasizing the importance of multidisciplinary care.

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Introduction

Neuroendocrine tumors (NETs) are a diverse group of neoplasms originating from neuroendocrine cells, most commonly found in the gastrointestinal tract, particularly in the appendix (1). These tumors exhibit variable biological behavior, ranging from slow-growing benign lesions

to aggressive malignancies (2). While NETs are slightly more prevalent in females than males, their overall incidence has been increasing worldwide due to improved detection methods and heightened awareness (3, 4). Although NET tumors are often nonfunctional and asymptomatic, they can sometimes present with symptoms such as abdominal pain, flushing, and diarrhea, and are occasionally discovered incidentally during surgeries for other conditions (5, 6).

Endometriosis has been linked to an increased risk of certain types of cancers, predominantly ovarian endometrioid and clear cell carcinomas; however, there isn't a well-established direct relationship between endometriosis and NET (7, 8). Incidental NET findings during laparoscopic surgeries for endometriosis, which are common due to the condition's prevalence, pose unique challenges for practitioners, requiring thorough intraoperative assessment and pathological examination to guide surgical decisions and postoperative surveillance (9). Researchers, such as Villaescusa et al. (2021), reported no direct correlation between appendiceal NETs and endometriosis but noted their coincidental occurrence in gynecologic surgeries, with incidences of appendiceal NETs ranging from 0.3–0.9% in appendectomy specimens (7, 8, 10, 11). Similarly, Parra et al. (2020) described a case of coexisting appendiceal NET and endometriosis, emphasizing the need for routine appendectomy during endometriosis surgery to detect such findings (10, 11).

Given the high frequency of laparoscopic surgeries for endometriosis, incidental findings of NETs during these procedures present a unique clinical challenge, necessitating proper intraoperative assessment and postoperative management. In this case series, six patients with endometriosis who underwent laparoscopic surgery and appendectomy are described, with NETs of the appendix subsequently diagnosed based on pathology results. These cases emphasize the importance of thorough pathological examination in gynecologic surgeries, highlighting the need for careful intraoperative evaluation to identify unexpected neoplastic findings.

Case Presentation

This retrospective case report was conducted at Avicenna Fertility Center Affiliated to Avicenna Research Institute, Tehran, Iran, covering the period from 2016 to 2024. Medical records of patients who underwent laparoscopic surgery for endometriosis were reviewed, identifying cases with NET findings in the appendix, confirmed through histopathological examination. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki, ensuring ethical integrity and the protection of patient rights in retrospective research. Informed consent was obtained from all patients for the use of their de-identified data in this study.

Patient selection: Patients included in the study had a confirmed diagnosis of endometriosis, underwent surgery with appendectomy, and had available histopathological confirmation of NETs, along with documented clinical symptoms, intraoperative findings, and follow-up data. Inclusion criteria required complete histopathological reports and at least 12 months of postoperative follow-up.

Data collection: Data collected included demographic details, preoperative imaging findings, surgical observations, and histopathological results, including NET classification, tumor size, mitotic activity, and WHO grading (G1-G3 based on Ki-67 index and mitotic rate).

Case 1: A 35-year-old woman presented with complaints of abdominal pain and menorrhagia. All laboratory data were within normal limits. A transvaginal ultrasound examination for the evaluation of deep infiltrating endometriosis (DIE) (7) revealed tiny follicles measuring up to 8 *mm* in the right ovary, which had adhesions to the uterus and showed polycystic ovary characteristics. The left ovary was normal. Mild adenomyosis was also noted. The patient underwent laparoscopic surgery. During the procedure, both ovaries were found to have adhesions to the uterus and the posterior cul-de-sac. Additionally, bilateral DIE lesions were observed on the uterosacral ligaments, and the appendix was involved. The ovarian adhesions were released on both sides, and the ureters were freed. Endometriosis lesions were excised, and both the pararectal and rectovaginal septa were released. All endometriosis lesions on the rectum and cul-de-sac were removed, and an appendectomy was performed. All specimens were sent to pathology for further investigation The pathology reports identified an appendiceal neuroendocrine tumor located at the tip of the appendix, measuring 9 *mm*, exhibiting fewer than 2 mitoses per 2 mm^2, with subserosal fat invasion, and a Ki-67 index below 3%, as confirmed by chromogranin and Ki-67 immunohistochemical analy

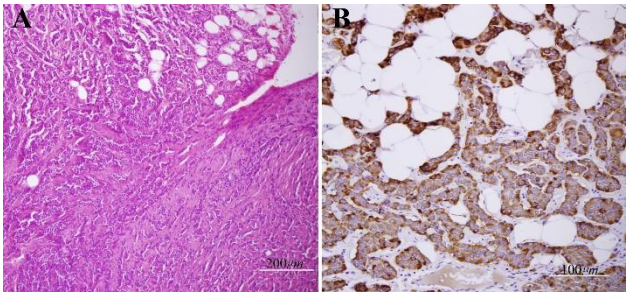

Figure 1. Histopathological features of appendiceal neuroendocrine tumors (Case 1); (A) H&E-stained section showing the neuroendocrine tumor with invasion into the mesoappendix and (B) immunohistochemistry staining for chromogranin, confirming neuroendocrine tumor

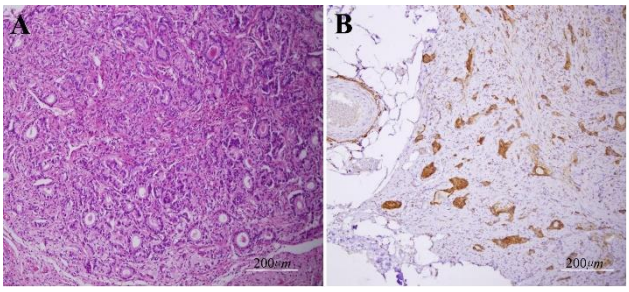

Figure 2. Histopathological features of appendiceal neuroendocrine tumor (Case 2); (A) H&E-stained section showing the neuroendocrine tumor with invasion into the muscularis propria and (B) synaptophysin staining highlighting neuroendocrine differentiation

sis (Figure 1). The tumor was classified as pT3 (pN and pM categories were not applicable).

Case 2: A 45-year-old woman with severe pelvic pain and refractory endometriosis presented for surgical evaluation. Her medical history included diabetes, hypertension, rheumatoid arthritis (RA), managed with methotrexate and prednisolone, and smoking. Laboratory findings showed FBS of 124 *mg/dL*, ALT of 46 *U/L*, and an elevated CA-125 level of 81.33 *U/ml*. Ultrasound revealed a large endometrioma (82×70×60 *mm*) with septations on the left ovary, accompanied by left hematosalpinx. A multiloculated cyst (49×45 *mm*) was observed on the right ovary. DIE (7) was identified in the rectum and rectosigmoid lumen, with obliteration of the posterior cul-de-sac. Multiple gross nodules were noted: 26×7 *mm* in the posterior cul-de-sac, 17×8 *mm* in the right uterosacral ligament, and 30×10 *mm* on the rectal serosa, extending into the mucosal and submucosal layers. An ovarian cyst near the distal left ureter suggested potential adhesion to the serosal surface. Additionally, adenomyosis and multiple myomas were present. The pathology report confirmed a 4 *mm* neuroendocrine tumor in the appendix, with invasion into the muscularis propria. Immunohistochemistry demonstrated strong synaptophysin staining, mild CK20 expression, and negative CK7 staining (Figure 2). The tumor was classified as pT1 (pN and pM categories were not applicable).

Case 3: A 55-year-old woman with severe pelvic pain, dysmenorrhea, dyspareunia, and abnormal uterine bleeding was found to have an enlarged, irregular, myomatous uterus with limited mobility, suggesting adhesions or fibroid-related fixation. During laparoscopic surgery, extensive adhesions were observed between the rectum, adnexa, and posterior uterus, with obliteration of the posterior cul-de-sac. The adnexa were firmly adhered to the pelvic floor and colon, requiring right and left ureterolysis. A bilateral pararectal dissection was performed, and endometriosis lesions on the uterosacral ligaments, posterior cervix, and pelvic wall were excised while preserving the hypogastric nerves. Salpingo-oophorectomy and hysterectomy were completed, with all specimens removed via the vaginal route. Anterior rectal nodules were excised, and an appendectomy was performed by a colorectal surgeon. Pathology analysis identified a neuroendocrine tumor in the distal half of the appendix, with invasion into the muscularis propria. Chromogranin and Ki-67 staining confirmed a neuroendocrine tumor with a mitotic rate of fewer than 2 mitoses *per mm*^{2}. The tumor was classified as pT1(pN and pM categories were not applicable).

Case 4: A 49-year-old woman with chronic pelvic pain, dysmenorrhea, and dyspareunia was found to have uterine enlargement with myomatous changes on examination. She had a history of rheumatoid arthritis, managed with methotrexate and prednisolone. Ultrasound imaging showed normal kidney size, parenchymal thickness, and corticomedullary differentiation, with mild hydronephrosis in the left kidney. During laparoscopic surgery, endometriotic lesions were identified on the uterus, both ovaries, and cervix. A hysterectomy, bilateral salpingo-oophorectomy, and complete resection of deep endometriotic lesions were performed, along with an appendectomy. Pathology analysis revealed a 5 *mm* neuroendocrine tumor in the appendix, with invasion into the muscularis propria and a mitotic rate of fewer than 2 mitoses per *mm*^{2}. The tumor was classified as pT1(pN and pM categories were not applicable).

Case 5: A 33-year-old woman with a history of right ovarian endometriosis, treated with laparoscopic cystectomy a decade ago, presented with abnormal uterine bleeding, dysmenorrhea, dyspareunia, severe pelvic pain, and dyschezia. Given a diagnosis of grade 4 endometriosis, she underwent laparoscopic surgery, which revealed extensive endometriotic lesions affecting both ovaries, the rectum, both cul-de-sacs, and the pouch of Douglas, along with significant adhesions. Complete resection of the lesions was performed, including an appendectomy. Histopathological analysis identified a 2 *mm* neuroendocrine tumor at the tip of the appendix, with no evidence of invasion or mitotic activity. Immunohistochemistry for synaptophysin and Ki67 confirmed the absence of invasion or mitotic activity. The tumor was classified as pT1(pN and pM categories were not applicable).

Case 6: A 45-year-old woman presented with dysmenorrhea, dyspareunia, dyschezia, and severe pelvic pain. Sonographic evaluation revealed ovarian lesions, and her medical history included two prior cesarean sections. During laparoscopic surgery, multiple lesions were identified on the uterus, ovaries, and cervix, prompting an appendectomy as part of the procedure. Histopathological analysis revealed a 6 *mm* neuroendocrine tumor at the tip of the appendix, with invasion into the muscular and subserosa layers. Immunohistochemical analysis revealed a Ki-67 index of less than 3%, and synaptophysin staining confirmed the diagnosis of a neuroendocrine tumor. The tumor was classified as pT1 (pN and pM categories were not applicable).

Follow-up was conducted for all patients who had undergone surgery between 1 and 5 years earlier. Since all tumors measured less than one centimeter, no additional surgical intervention was performed, and all patients were monitored at regular intervals. No cases of recurrence or disease progression were observed.

Discussion

As summarized in table 1, our study presents six cases of incidental NET findings during laparoscopic surgery for endometriosis. These cases illustrate the variability in tumor size, degree of invasion, and histopathological characteristics, reinforcing the need for systematic pathological assessment during gynecologic surgeries. Appendectomies have increasingly been performed during gynecologic procedures aimed at managing endometriosis or chronic pelvic pain (12). Following an appendectomy performed during endometriosis surgery, it is essential that a comprehensive

Table 1. Summary of patient demographics, endometriosis severity, and pathological findings of incidental appendiceal neuroendocrine tumors

Age (years)	Symptoms	Severity of endometriosis	Pathology of neuroendocrine tumor (NET)
35	Abdominal pain, menorrhagia	Bilateral deep infiltrating endometriosis, ovarian adhesions, mild adenomyosis	Tumor located at the tip of the appendix, measuring 9 *mm*, with invasion into the mesoappendix; mitotic rate <2 per 2 mm^2; chromogranin-positive; Ki-67 index <3%
45	Severe pelvic pain, refractory endometriosis	Large endometrioma, hematosalpinx, DIE in rectum, rectosigmoid lumen involvement	Appendiceal NET, 4 *mm*, invading muscularis propria; synaptophysin$^+$, mild CK20$^+$, CK7$^-$
55	Severe pelvic pain, dysmenorrhea, dyspareunia, abnormal uterine bleeding	Extensive adhesions, rectal involvement, hysterectomy and salpingo-oophorectomy	Distal appendix; muscularis propria invasion; <2 mitoses/mm^2; Chromogranin$^+$; Ki-67
49	Chronic pelvic pain, dysmenorrhea, dyspareunia	Uterine enlargement, adenomyosis, bilateral salpingo-oophorectomy	Neuroendocrine tumor of the appendix, 5 *mm*, invading muscularis propria; mitotic rate <2/mm^2
33	Abnormal uterine bleeding, dysmenorrhea, dyspareunia, dyschezia	Grade 4 endometriosis, extensive adhesions	Neuroendocrine tumor of the appendix, 2 *mm*; no invasion or mitotic activity; synaptophysin positive; Ki-67 negative
45	Dysmenorrhea, dyspareunia, dyschezia, severe pelvic pain	Multiple uterine and ovarian lesions, prior C-sections	Neuroendocrine tumor of the appendix, 6 *mm*, invading muscularis and subserosa; Ki-67 <3%; synaptophysin positive

examination of the appendix be conducted by a pathologist, as neuroendocrine tumors may also be detected during this pathological examination (10, 11).

The absence of appendiceal endometriosis in our cases suggests no direct histopathological correlation, but the coincidental finding of NETs underscores the importance of routine appendectomy to detect occult neoplasms that may alter management (7, 8). From an oncologic perspective, all NETs in our series were low-grade (G1, Ki-67 <3%) and classified as T1aN0M0 per TNM staging, indicating small tumors (<1 *cm*) without nodal or distant metastasis (13). This contrasts with advanced cases requiring hemicolectomy or lymphadenectomy, as reported by Altshuler and Schultze (2023) (14).

A study shows similar incidences of appendiceal neuroendocrine tumors and endometriosis, indicating no direct correlation between the two (8). However, incidental NETs may necessitate additional imaging (*e.g.*, octreotide scans) or biochemical tests (*e.g.*, serum chromogranin A) to monitor for recurrence, particularly for tumors with invasion, as seen in four of our cases. Our findings highlight the need for multidisciplinary collaboration, involving gynecologists, colorectal surgeons, oncologists, and pathologists, to optimize surgical planning and postoperative surveillance.

Detecting neuroendocrine tumors during pathological examinations can significantly alter the treatment approach. The presence of NETs may necessitate additional targeted therapies, surgical interventions, or multidisciplinary management involving oncologists and endocrinologists (15).

This discovery can also impact prognosis, follow-up protocols, and overall patient management, emphasizing the importance of thorough pathological evaluations post-appendectomy in endometriosis cases. Unlike our early-stage cases, a study involving five patients reported that hemicolectomy and lymphadenectomy were necessary treatments in two cases after detecting more advanced stages of the disease (14). As mentioned before, there was no correlation between NETs and endometriosis. However, the accidental finding of NETs can significantly change the treatment approach for patients in higher stages of the disease, making appendectomy a crucial step.

Conclusion

Endometriosis is a systemic disease that presents various coincidental complications and challenges. Therefore, it requires the expertise of a multidisciplinary medical team, including gynecologist, urologist, colorectal surgeon, and a pathologist.

Incidental appendiceal neuroendocrine tumors may be encountered during laparoscopic surgery for endometriosis and should be carefully evaluated pathologically. Awareness of this possibility supports appendectomy and appendiceal assessment in patients with advanced endometriosis.

Pathologic findings following appendectomy during endometriosis surgery may change the treatment approach.

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Conflict of Interest

Authors declare no conflict of interest.

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