



Original contribution

Clinicopathologic findings in gynecologic proliferations of the appendix^{☆, ☆ ☆}



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Summary Appendiceal endometriosis, endosalpingiosis, and decidual lesions have received little attention in the pathology literature, meaning their clinicopathologic features remain unclear. We identified 72 cases of appendiceal gynecologic proliferations with available slides. Clinical presentation was recorded when available, and histologic findings were correlated with clinical data. Cases included conventional endometriosis (51), endosalpingiosis (14), and decidual lesions (7). The patients with endosalpingiosis were significantly older (median 45 years) than those with endometriosis (median 34 years, $P = .0085$) or decidual lesions (median 31 years, $P = .0088$). Most endometriosis patients presented with known/suspected endometriosis (20/51, 39%), while acute appendicitis was the most common presentation for patients with endosalpingiosis (5/14, 36%) or a decidual lesion (5/7, 71%). Few patients presenting with appendicitis were ever diagnosed with extra-appendiceal disease. All 51 endometriosis cases showed both glands and stroma, and 18 (35%) had hemosiderin. One case progressed to endometrioid adenocarcinoma. Endosalpingiosis was an incidental finding in all cases, confined to the serosa in 4 and extending intramurally in 10. Four of the 7 patients with a decidual lesion were pregnant, and 2 others were taking oral contraceptives. The cases included florid decidualized endometriosis (5) and deciduosis (2). Two cases spread transmurally and effectively obliterated the appendix. Conventional appendiceal endometriosis can have several clinical presentations. Patients with it who present with acute appendicitis rarely develop it elsewhere. Appendiceal endosalpingiosis is rare and effectively incidental. Decidualized endometriosis may overtake the entire appendix.

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1. Introduction

Appendectomy is the third most common surgical procedure involving the gastrointestinal tract in the United States, following cholecystectomy and colorectal resections [1]. The procedure is most commonly performed for acute appendicitis, which is the most common abdominal emergency [2]. Less commonly, appendectomy is performed for other indications, including interval appendicitis and mass lesion/mucocele.

In addition to intrinsic non-neoplastic and neoplastic processes such as appendicitis, fibrous obliteration, low-grade

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appendiceal mucinous neoplasm (LAMN), and invasive adenocarcinoma, the appendix is at risk of secondary involvement by other processes [3]. This includes processes that may be specific to the gastrointestinal tract, such as inflammatory bowel disease [4], systemic processes such as vasculitis [5], or conditions limited to the peritoneum. Processes in the latter category include gynecologic proliferations such as endometriosis, endosalpingiosis, and decidualosis. These uncommon findings, estimated to occur in fewer than 1% of appendectomy specimens [6], have been described in small case series ($n \leq 6$) in the surgical [7,8] and gynecologic [9] literature but have been little discussed in the pathology literature, outside of inclusion in a review of endometriosis throughout the gastrointestinal tract [10], explorations of endometriosis with intestinal metaplasia mimicking LAMN [11-13], three case reports of appendiceal endosalpingiosis [14-16], and a case series focused on decidual lesions of the appendix [17]. Therefore, their microscopic findings and clinical correlates remain understudied.

2. Materials and methods

With appropriate institutional review board approval, we searched the surgical pathology archives of the University of Rochester Medical Center from 1995 to 2017 for appendix specimens harboring endometriosis, endosalpingiosis, endocervicosis, or a decidual proliferation. Endometriosis was defined as a lesion containing two of the three following histologic features: endometrial-type glands, endometrial-type stroma, and evidence of hemorrhage. Endosalpingiosis was defined as a focus of glandular or cystic structures lined solely by tubal-type epithelium. Decidual proliferations were defined as any stromal lesion, with or without intermixed glands, comprised of large cells with abundant glassy/eosinophilic cytoplasm, generally with bland, rounded nuclei. Available hematoxylin- and eosin-stained slides were reviewed on each identified case to determine the size and mural location of involvement, and whether any additional processes (eg, acute appendicitis) were seen. The presence or absence of glands, stroma, hemosiderin, tubal metaplasia, intestinal metaplasia, and dysplasia/malignancy were noted where appropriate. Gross reports were reviewed to determine whether each lesion was visible grossly. Clinical history was reviewed to determine patient age at time of surgery, symptoms at presentation, and identification of a gynecologic proliferation involving other organs (with radiologic, surgical, or pathologic confirmation).

Presentation type (symptomatic vs. asymptomatic/incidental), involvement of other organs, and histologic findings were compared across three groups (endometriosis, endosalpingiosis, and decidual lesions) using Fisher exact test on 2x2 contingency tables, and patient age was compared using an unpaired *t* test, all in GraphPad Software online (<http://graphpad.com/quickcalcs>, GraphPad Software, San Diego, CA; last accessed 04/18/2019). $P < .05$ was considered statistically significant.

3. Results

Seventy-two cases were identified for inclusion in the study: 51 endometriosis cases, 14 endosalpingiosis cases, and 7 decidual cases. No cases of appendiceal endocervicosis were identified in our archives. Clinicopathologic findings are summarized in the Table.

All patients were women. The patients with endosalpingiosis were significantly older (median, 45 years; range, 19-62 years) than the patients with endometriosis (median, 34 years; range, 13-72 years; $P = .0085$) or with decidual lesions (median, 31 years; range, 19-39 years; $P = .0088$). Ages were similar for the endometriosis and decidual lesion patients ($P = .12$). Endometriosis patients most commonly presented with known/suspected endometriosis (20, 39%), acute appendicitis (9, 18%), or an ovarian mass (9, 18%). Endosalpingiosis patients most commonly presented with acute appendicitis (5, 36%), as did decidualosis patients (5, 71%). The three patient cohorts had varying rates of extra-appendiceal involvement (endometriosis, 37 cases [73%], endosalpingiosis, 5 cases [36%], decidual lesions, 3 cases [43%]), with endometriosis patients significantly more likely to have extra-appendiceal disease than endosalpingiosis patients [$P = .024$]. Appendiceal endometriosis patients presenting with acute appendicitis typically had disease confined to the appendix; only two of the nine (22%) such patients had confirmed endometriosis elsewhere, compared to 35 of 42 (83%) patients presenting with other complaints ($P = .0008$). This relationship was similar in endosalpingiosis patients (0 of 5 [0%] versus 5 of 9 [55%], $P = .086$) and decidual lesion patients (1 of 4 [25%] versus 2 of 2 [100%], $P = .14$).

The size of each lesion was primarily determined based on microscopic findings, as only 20 cases (28%) had grossly visible disease. The decidual lesions had a median size of 1.2 cm, with a range of 0.1 to 2.0 cm. This was significantly larger than the cases of endometriosis (median, 0.5 cm; range, 0.05-2.4 cm, $P = .0026$) and the cases of endosalpingiosis (median, 0.13 cm; range, 0.05-1.0 cm; $P = .0006$); the sizes of the endometriosis and endosalpingiosis cases did not significantly differ ($P = .052$).

Endometriosis most commonly involved the muscularis propria of the appendix (42 cases, 82%). Eleven cases (22%) showed serosal involvement, and only 2 (4%) showed mucosal involvement. Endosalpingiosis had a similar distribution, with no cases involving mucosa, 10 (71%) involving muscularis propria, and 4 (29%) involving serosa. However, decidual lesions strongly favored the serosa, with 6 cases (86%) involving it. This was significantly more common than for the endometriosis ($P = .0018$) and endosalpingiosis ($P = .0237$) cases. The decidual lesions less commonly involved the mucosa (2 cases, 29%) and the muscularis propria (4 cases, 57%).

Histologically, endometriosis always demonstrated both glands and stroma (Fig. 1A). Hemosiderin was present in 18 (35%) cases (Fig. 1B), which was significantly higher than the endosalpingiosis cases (0 of 14, $P = .007$) and also higher

Table Clinicopathologic features of 72 appendiceal gynecologic proliferations

	Endometriosis (n = 51)	Endosalpingiosis (n = 14)	Decidual lesions (n = 7)
Patient age, years (median; range)	34 (13–72)	45 (19–62)	31 (19–39)
Patient presentation	Endometriosis (20, 39%) Acute appendicitis (9, 18%) Ovarian mass (9, 18%) Pelvic pain (5, 10%) Intestinal mass (3, 6%) Other complaints (5, 10%)	Acute appendicitis (5, 36%) Intestinal mass (3, 21%) Pelvic mass (2, 14%) Pelvic pain (1, 7%) Endometriosis (1, 7%) Other complaints (2, 14%)	Acute appendicitis (5, 71%) Endometriosis (2, 29%)
Lesion grossly visible	16 (31%)	0 (0%)	4 (57%)
Lesion size, cm (median; range)	0.5 (0.05–2.4)	0.13 (0.05–1.0)	1.2 cm (0.1–2.0)
Histologic findings	Glands: 51 (100%) Stroma: 51 (100%) Hemosiderin: 18 (35%) Tubal metaplasia: 28 (55%) Intestinal metaplasia: 0 (0%)	Glands: 14 (100%) Stroma: 0 (0%) Hemosiderin: 0 (0%) Tubal metaplasia: n/a Intestinal metaplasia: 0 (0%)	Glands: 5 (71%) Stroma: 7 (100%) Hemosiderin: 2 (29%) Tubal metaplasia: 1 (14%) Intestinal metaplasia: 0 (0%)
Layer of appendix wall involved (some individual cases involved multiple layers)	Mucosa: 2 (4%) Muscularis propria: 42 (82%) Subserosa/serosa: 11 (22%)	Mucosa: 0 (0%) Muscularis propria: 10 (71%) Subserosa/serosa: 4 (29%)	Mucosa: 2 (29%) Muscularis propria: 4 (57%) Subserosa/serosa: 6 (88%)
Extra-appendiceal disease	37 (73%)	5 (36%)	3 (43%)

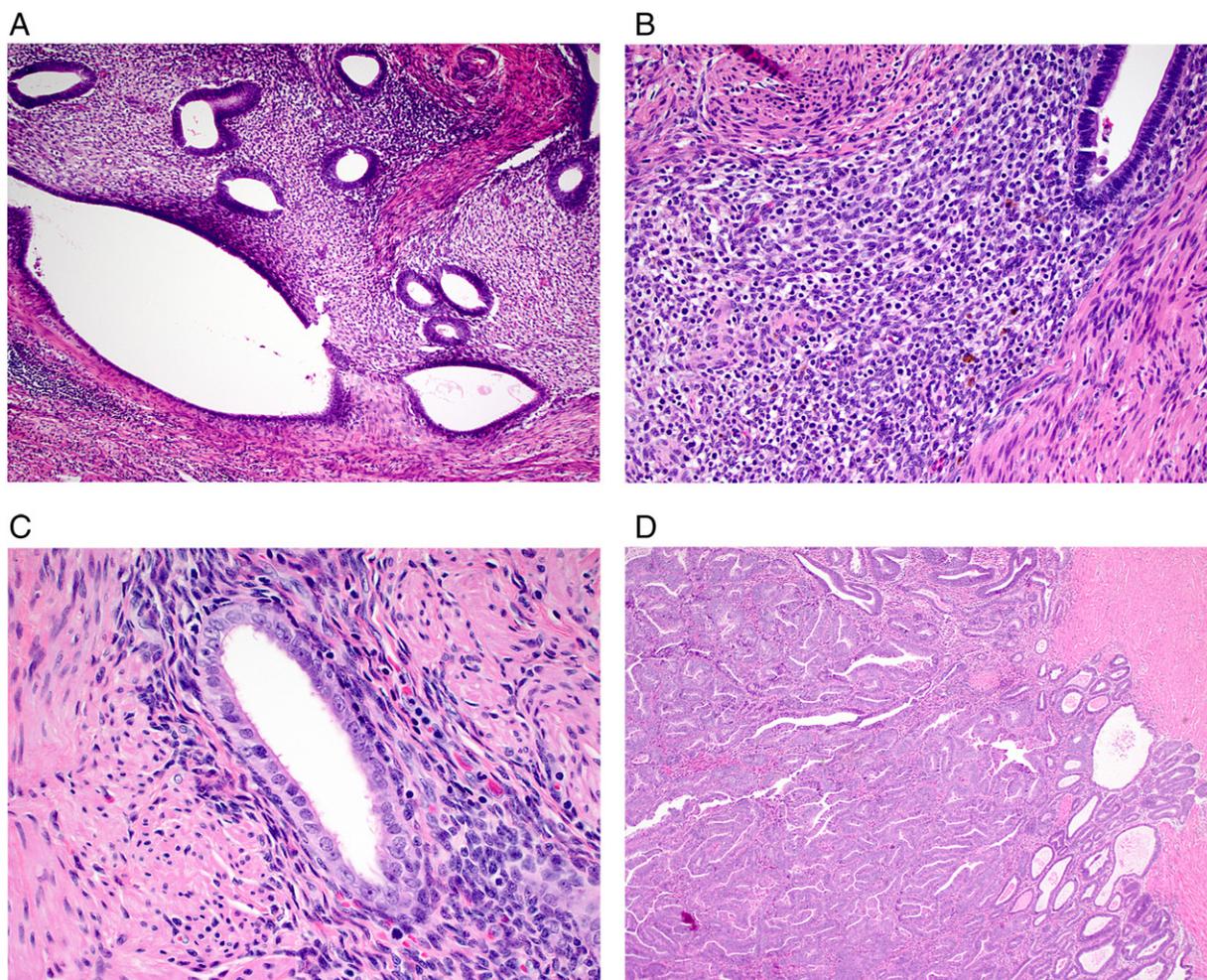


Fig. 1 A, Endometriosis involving the appendix, with glands and stroma both readily visible. B, Hemosiderin was generally present within endometriosis, but it was usually sparse and subtle. C, Tubal metaplasia was not uncommon in appendiceal endometriosis, though no cases in this study showed intestinal metaplasia. D, One case of appendiceal endometriosis progressed to well-differentiated endometrioid adenocarcinoma.

than the decidual cases (2 of 7 [29%], $P = .10$). Tubal metaplasia was identified in 28 cases (55%) (Fig. 1C), whereas intestinal metaplasia was not identified in any cases in this study. One case of endometriosis progressed to endometrioid adenocarcinoma of the appendix (Fig. 1D).

Endosalpingiosis was typically minute and somewhat difficult to detect (Fig. 2A), though lesions were occasionally larger (Fig. 2B). All cases had glands without stroma, by definition; hemosiderin was always absent, as above. Intestinal metaplasia was never seen.

Decidual lesions always contained stroma and were subclassified as decidualized endometriosis if glands were present (5 cases, 71%) and decidualosis if no glands were present (2 cases, 29%). The serosa was always involved, and three cases were solely localized there (Fig. 2C). Two cases, in contrast, spread transmurally and effectively obliterated the appendix (Fig. 2D). One case showed tubal metaplasia, but none showed intestinal metaplasia. Four patients with decidualized

endometriosis were pregnant, including the two with obliterative appendiceal disease. Of the three other patients, two were taking oral contraceptive medication and one had no known source of hormonal alteration.

Background changes in the appendixes included fibrous obliteration (41 cases, 60%) acute appendicitis (12 cases, 17%, including 11 of the 19 presenting as acute appendicitis), and acute serositis (2 cases, 3%).

4. Discussion

Involvement of the gastrointestinal tract has been reported in 5% to 32% of patients with endometriosis [18,19]. The appendix is the second most common site of involvement, after the rectosigmoid [20]. Still, endometriosis involving the appendix is uncommon and can present with variable symptoms,

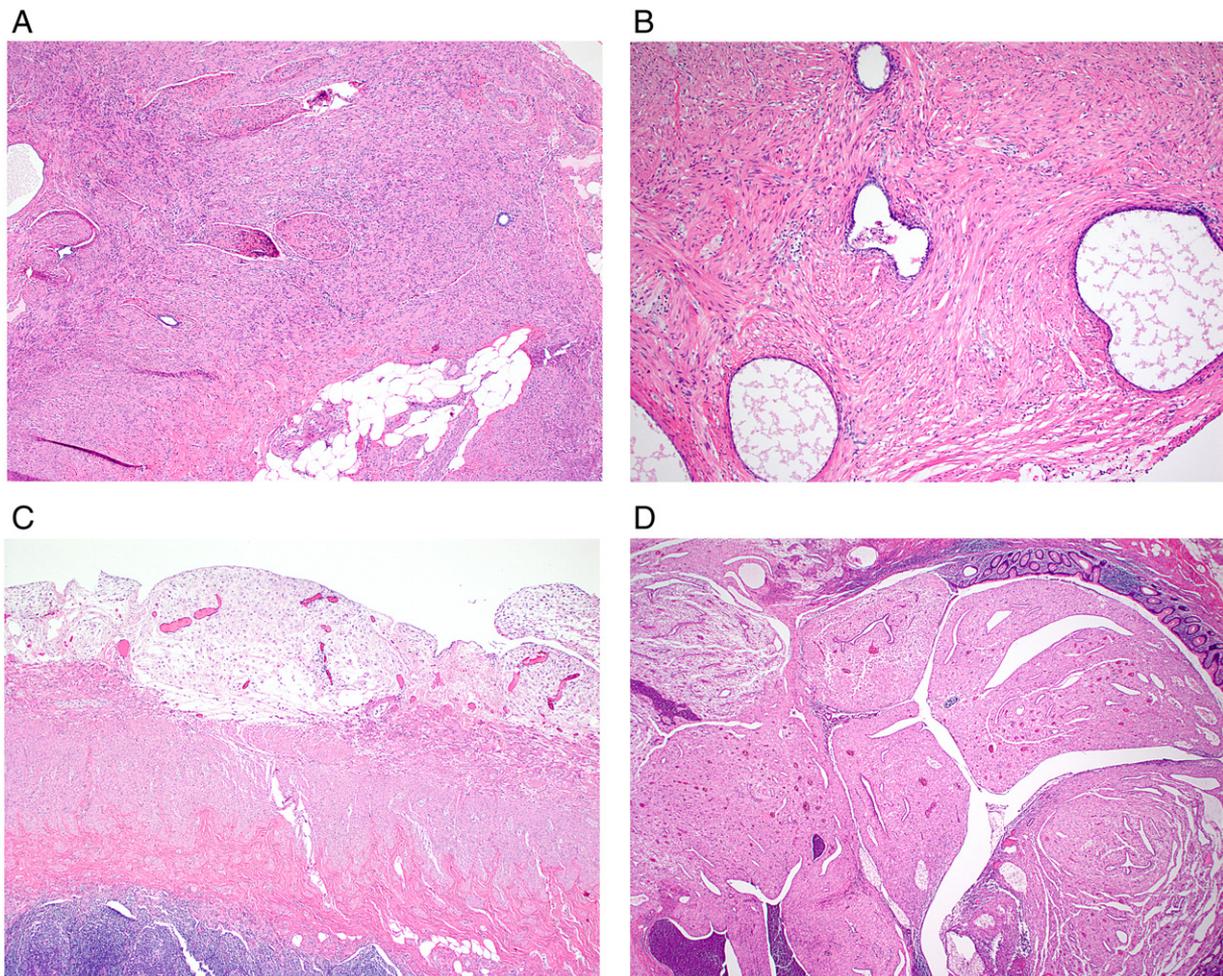


Fig. 2 A, Appendiceal endosalpingiosis typically consisted of small discrete glands. This low-power view shows two glands of endosalpingiosis involving an appendix with fibrous obliteration. B, Even when larger and more tightly arranged, endosalpingiosis showed individual glands rather than a confluent aggregate. C, Decidualized lesions were uncommon in the appendix and took a variety of forms. This case consisted primarily of serosal decidualosis, without mural involvement or a glandular component. D, Larger examples of decidualized endometriosis often formed mass lesions obliterating the appendiceal lumen and overtaking the organ, spanning mucosa to serosa.

often making accurate preoperative diagnosis difficult. In a 1951 study of 50 000 appendectomy specimens, endometriosis was observed in only 0.054% [21]. Other studies have reported rates of 0.3% [22] and 0.80% [23], but overall endometriosis appears to occur in fewer than 1% of appendices overall [24]. Patients with known endometriosis, however, have rates of appendiceal involvement ranging from 4% to 22% [9,25,26]. Appendiceal endometriosis may be asymptomatic [19], but patients may present with chronic right lower quadrant pain [27], acute appendicitis [28,29], perforated appendicitis [30], intussusception of the appendix [6], and massive lower gastrointestinal bleeding [31].

Our findings echo those reported in the literature. Patients presented with a variety of symptoms, including acute appendicitis, pelvic pain, ovarian or intestinal mass, and bowel obstruction. Interestingly, few of the patients presenting as acute appendicitis ever developed extra-appendiceal endometriosis; this finding was also true for the endosalpingiosis and decidual lesion patients. Only 39% were suspected of having appendiceal endometriosis preoperatively. While both glands and stroma are not always readily observed in endometriosis involving gynecologic organs [32], they were both always clearly present in our cohort, making the diagnosis relatively straightforward. Roughly one-third showed hemosiderin, a common finding in gynecologic samples [32]. The muscularis propria was by far the most common site of involvement; mucosal and serosal involvement was relatively rare. The exact mechanism by which endometriosis can involve the appendix is unclear; the theory that peritoneal endometriosis results from retrograde menstruation of steroid hormone-sensitive endometrial cells and tissues [33] would generally suggest that serosal involvement should be more common.

Malignant transformation of endometriosis is rare, occurring in approximately 1% of cases of ovarian endometriosis [34]. It has been previously reported in the gastrointestinal tract, and our cohort included one appendiceal example.

Endosalpingiosis involves the gastrointestinal tract less commonly than endometriosis, and to our knowledge, no large-cohort study has been reported. Appendiceal endosalpingiosis has been even more rarely reported, with only a few dozen cases mentioned in the literature [16,35-38]. Three of these are pathology case reports, of cystic lesions measuring 0.5 cm [14], 0.35 cm [15], and 0.8 cm [16]. In contrast, the median size of our 14 cases was 0.13 cm. The endosalpingiosis typically appeared as small, scattered glands within the wall of the appendix, usually not forming a large, discrete mass. The lack of a stromal component aided the distinction from endometriosis. About one-third of patients presented with symptoms mimicking acute appendicitis, only two of whom showed acute appendicitis histologically. A retrospective study by Keltz [39] of 51 laparoscopies for pelvic pain found six cases of endosalpingiosis in locations associated with the patient's pelvic pain, and all obtained relief after surgery, suggesting that endosalpingiosis may not be an incidental finding in cases of pelvic pain [40].

The most unusual, and least common, category of gynecologic proliferations we studied was decidual lesions. Decidualization is a physiologic process during pregnancy, caused by the influence of ovarian and placental steroid hormones [41]. Accordingly, four of our seven patients with decidual lesions were pregnant, and two others were taking exogenous hormones. Representing only 10% of the cases in this series, the decidual lesions were on average larger (median size 1.2 cm) than the endometriosis or endosalpingiosis lesions, and they sometimes markedly obliterated the entire wall of the appendix. Other cases, however, remained confined to the serosal surface, as previously described [17]. Two cases contained no glands and were designated deciduosis. The other five demonstrated glands, suggesting they represented decidual change in existing endometriosis [42]. This included both of the transmural lesions; no non-decidualized endometriosis cases showed transmural involvement, suggesting that the decidual change (or its physiologic driver) played a part in the lesions' notable proliferation. Indeed, decidual lesions have been reported as florid in the past, sometimes causing diffuse omental deciduosis [43], perforating the appendix [44], or mimicking gastrointestinal malignancy [45].

Compared to the decidual lesions, the endometriosis and endosalpingiosis cases were relatively small; in fact, 12 of the 65 cases (18%) measured ≤ 0.1 cm, and two of those presented as acute appendicitis without any histologic evidence of background inflammation. Therefore, while the diagnosis of endometriosis or endosalpingiosis is generally straightforward, pathologists should be aware of their potential small size and should search carefully for such lesions in female patients with otherwise unexplained acute appendicitis.

One gynecologic proliferation we did not encounter in the appendix is endocervicosis. This uncommon benign lesion typically occurs in the urinary bladder as a mass composed of haphazard, cystically dilated endocervical-type glands that measure up to 5 cm [46]. To our knowledge, it has not been reported in the gastrointestinal tract.

In summary, our large case series demonstrates that appendiceal endometriosis can cause a variety of symptoms. It may masquerade clinically as acute appendicitis; in this scenario, patients uncommonly develop endometriosis elsewhere. Appendiceal endosalpingiosis is rare and may also cause symptoms of acute appendicitis, despite its small size. Decidual lesions typically involve the serosa but may in some cases overtake the entire appendix. These entities may not be suspected preoperatively, though they do not generally involve a pathologic diagnostic dilemma.

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