CASE REPORT ARTICLE
Volume - 10 | Issue - 10 | October - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

NEUROMUSCULAR AND VASCULAR HAMARTOMA SECONDARY TO ENDOMETRIOSIS AT APPENDICEAL TIP MISDIAGNOSED AS APPENDICEAL NEOPLASM: AN EXTREMELY RARE CASE REPORT WITH LITERATURE REVIEW

Medicine

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ABSTRACT

Background: Endometriosis of the appendix is reported to be 1 to 3 % of the total endometriosis. Neuromuscular and vascular hamartoma (NMVH) is a rare lesion with only 27 cases reported in intestine since its initial description in 1982 and only one reported case in the appendix until now. **Case presentation:** We present a 52-year-old Omani female patient complaining of chronic intermitted abdominal pain. On CT scan (computed tomography scan), there was appendiceal lesion near the tip suggestive of mucinous cystadenoma. Diagnostic laparoscopy with appendectomy was conducted. There was a well-defined lesion with central fatty area at appendiceal tip focally merge with the outer muscle layer and mostly embedded in the mesoappendix. Microscopic examination showed focal area of endometriosis at the outer longitudinal muscle layer of the appendix. This focally merge with a well-defined mass like lesion that is embedded in the mesoappendix. The lesion composed of benign random arranged smooth muscle fibers, scattered nerve bundles, some of which showed ganglionic cells including degenerated one, adipose tissue, thin and thick-walled small blood vessels. Features were consistent with NMVH that appeared secondary to the nearby endometriosis. **Conclusion:** Endometriosis of bowel should be suspected in female with longstanding intermitted abdominal pain. NMVH is extremely rare in appendix, thus clinical and radiological suggestion of such diagnosis is difficult. Secondary neuromuscular hamartoma is reported in association with Crohn's disease as a consequence of the chronic inflammation and thus could be suspected secondary to endometriosis.

KEYWORDS

endometriosis, appendix tip, neuromuscular and vascular hamartoma, chronic inflammation.

INTRODUCTION

Endometriosis affects the intestinal tract in 15-30% of patients with pelvic endometriosis, mostly involves sigmoid and rectum and rarely involving the appendix. Appendiceal endometriosis is reported to be 1 to 3 % of the total endometriosis cases (1).

Neuromuscular and vascular hamartoma (NMVH), also known as neuromesenchymal hamartoma, (2), is a rare lesion of the intestine, with only 27 cases reported since its initial description by Fernando and McGovern in 1982 including only one reported case at appendix (3). NMVH is consist of proliferation of benign nerves, smooth muscle and blood vessels in the intestine. NMVH may represent an abnormal histologic consequence of chronic inflammation as inflammatory bowel disease, especially Crohn's disease that was described in 3 out of the 27 previous diagnosed cases. Other authors suggest that NMVH is a rare separate entity as most of the patients in the previous reports (24 out of 27 reported cases) did not have any chronic inflammatory intestinal disease (4).

Appendiceal endometriosis could show symptoms that mimic acute appendicitis with sudden onset of right-side lower abdomen pain that worsens with movement. Other symptoms include constipation or diarrhea, loss of appetite, nausea, vomiting, abdominal bloating, and fever. However, unlike acute appendicitis, endometriosis of the appendix usually causes intermittent and recurrent abdominal pain (5). NMVH also mostly presented by longstanding abdominal pain (3).

The correct diagnosis is often delayed because intestinal endometriosis and NMVH may misdiagnosed clinically as regional enteritis, ischemic enteritis or colitis, diverticulitis or neoplasms (1).

In this study, we present an extremely rare case of NMVH, secondary to localized appendiceal endometriosis at the tip diagnosed after appendectomy and diagnostic laparoscopy due to longstanding history of unexplained recurrent abdominal pain along with CT scan showed appendiceal lesion suggestive of neoplasia.

Case Presentation

We present a 52-year-old female Omani patient who was initially seen overseas as she had long history of intermitted abdominal pain since 2 to 3 years sometimes associated with nausea, vomiting and change in bowel habits, sometimes loose motion and sometimes constipation with one week before surgery, she was presented by loose motion with no blood or mucous. The pain was mostly at the right and the left iliac fossa. The pain was intermitted, colicky and sometimes burning in nature, respond partially to medications and herbal. She had past history of hysterectomy 11 years back, but she did not know her pathological diagnosis and no reports available with her. There was no fever, chills, weight loss, night sweats, bleeding from any sites, pallor, cyanosis, jaundice, lower limb edema, chest or heart abnormalities and there was soft floppy non distended abdomen with no organomegaly. Patient did upper endoscopy, colonoscopy and CT scan abdomen since time and all came normal. Stool examination ruled out any parasitic infestation. Recently, at our Armed Forces Hospital, she did new CT scan that showed well-defined low attenuated cystic appearing lesion measuring about 13x10 mm, just proximal to the appendiceal tip with rim of enhancement with no significant interval changes suggestive of mucocele most likely mucinous cystadenoma **(Figure. 1A and B).** However differential as mucinous cystadenocarcinoma or carcinoid cannot be ruled out. Mild omental stranding that may represent doubtful significance and may represent mild panniculitis was also noted.

Patient was admitted for diagnostic laparoscopy along with appendectomy. Intraoperative findings: Thickening at appendiceal tip with no gross mass lesion and small omental adhesion to anterior abdominal wall were found. Examination of pelvic and abdominal wall along with the organs revealed no appreciated lesions.

Appendix was received formalin fixed. It was measuring 5 cm in length and 1 cm across and showed amalgamated yellow to dark brownish hemorrhagic mesoappendiceal fat extending about 4 cm from the tip of the appendix and was about 1.5 cm across. Surgical margin of mesoappendix was measuring about 3×2 cm. On inspection, there was no gross perforation or any mass seen before cutting. Palpation of the mesoapendiceal fat near the tip revealed query firm nodule. Mesoappendiceal resection margin was inked yellow, appendiceal proximal resection margin was inked green and outer serosal surface was inked black. The cut section at appendiceal tip showed well-defined small oval nodule / lesion whitish to greyish brown with central fatty area measuring about 1×0.7 × 0.6 cm that appeared focally adherent to / merge with the outer muscle layer and mostly embedded at the mesoappendiceal fat. It was away from nearest outer serosal surface by less than 1 mm. It was far away from mesoappendiceal and appendiceal proximal resection margins. The lumen and the inner

appendiceal wall appeared dark brownish hemorrhagic **(Figure 2A, B, C and D).** Representative sections were taken including submission of the whole lesion with the nearby appendiceal wall, representative from the appendiceal wall away from the lesion and the resections margins (peeled).

Microscopic examination of the appendix at the gross appreciated lesion showed focal endometriosis affecting the outer longitudinal muscle layer, near from appendiceal tip composed of small, mild elongated and few mild dilated endometrial glands lined by endometrium and ciliated epithelium, some surrounded by rim of endometrial stromal cells along with some lymphocytes, histiocytes and scattered eosinophils **(Figure 3 A and B).** This associated with a well-defined lesion composed of proliferating random arranged bundles of smooth muscle fibers that merge focally with the outer appendiceal muscle layer at area of the endometriosis amidst some hyalinized collagen bands intermingled with many nerve bundles / ganglia (some nerve bundles showed ganglionic cells, some of which appeared degenerated) associated with scattered small thin and thick-walled blood vessels and fatty areas with no appreciated endometrial glands and stroma within the mass lesion consistent with secondary NMVH / neuro-mesenchymal hamartoma **(Figure 4 A, B, C, D, E and F).** The appendiceal wall showed hemorrhagic atrophic mucosa with crypt loss replaced by granulation tissue with active fibroblastic proliferation. The submucosa also showed fibrosis interrupting the inner muscle layer. The muscle layer showed mild eosinophils and some chronic inflammatory cells with no appreciated neutrophils. Serosa showed prominent fibrosis with few appreciated mesoappendiceal fibrotic bands along with congested blood vessels, some showed mild peri-vascular chronic inflammatory cells (features of chronic appendicitis) **(Figure 3 C and D).**

Thus, the case was diagnosis as localized appendiceal endometriosis at the tip associated with secondary neuromuscular and vascular hamartoma along with chronic appendicitis. Pain is improved after removal of the appendix.

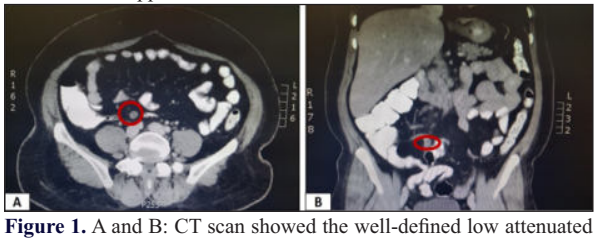

Figure 1. A and B: CT scan showed the well-defined low attenuated possible cystic appendiceal lesion at its tip associated with rim of enhancement (within the red circle).

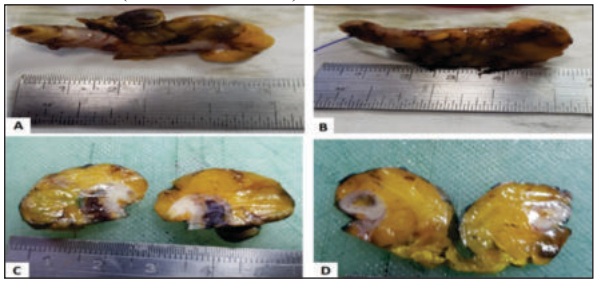

Figure 2. Gross appearance of the appendix, A and B: Appendix with amalgamated yellowish to brownish hemorrhagic mesoappendiceal fat. C: Tip showed small whitish nodule merge with the outer muscle layer along with dark brownish hemorrhagic appendiceal lumen and inner wall. D: At mesoappendiceal fat, nodule is larger, well-defined nodule with outer whitish to greyish brown rim and central fatty area.

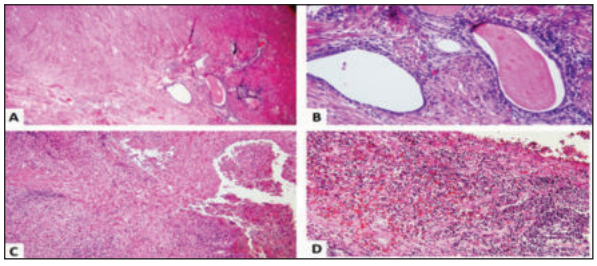

Figure 3. Endometriosis of appendix along with features of chronic appendicitis. A and B: Endometrial glands and stroma at outer muscle layer with benign endometrial lining in (A) merging with the outgrowth of smooth muscle fibers H&E, x 40, x200 respectively. C: appendiceal mucosa is hemorrhagic with crypt loss associated with active fibroblastic proliferation, D: Mucosal granulation tissue formation H&E, x100, x200 respectively.

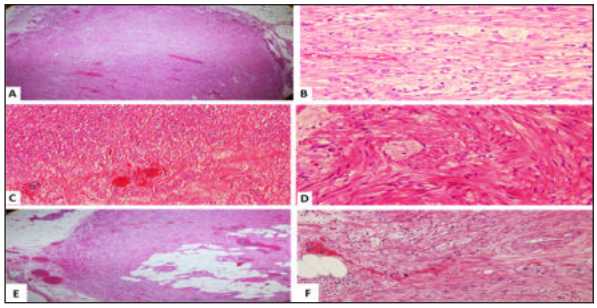

Figure 4. NMVH: A: The nodule appeared well defined composed of proliferating spindle cells / smooth muscle noted, H&E x40. B: The proliferating benign smooth muscle fibers intermingled with nerve bundles that showed degenerated looking ganglionic cells, H&E x200 C: Thin-walled blood vessels along with fibrosis with hyalinosis. H&E x200 D: Smooth muscle fibers are randomly arranged associated with scattered nerve bundles H&E x400. E: Mature fatty areas present within the lesion, H&E, x40. F: All components of smooth muscle fibers, fatty tissue, nerve bundles and thin with thick-walled blood vessels, H&E x200.

DISCUSSION

Endometriosis is an important cause of lower abdominal pain. Its incidence is reported to be 15% but appendix rarely involved in only 1 to 3% of the cases (1).

Incomplete excision of endometriosis, lead to recurrent abdominal pain after hysterectomy, is one of the most frustrating events that can happen to the patient. It is reported that the type of hysterectomy affects the recurrent symptoms mainly by impacting the extent of excision of the lesion (6). Bowel is the commonest site for recurrence / persistent endometriosis, especially the rectum and sigmoid colon (7). This is in concordance with our presenting case, as our patient had hysterectomy 10 years back but with no available report, thus no available diagnosis and had bowel endometriosis after hysterectomy. In our case, appendix which is a rare site for bowel endometriosis was involved rather than the rectum and the sigmoid colon which are the commonest sites, but in view of left iliac fossa pain, the possibility of microscopic endometriotic foci deep embedded in rectum or sigmoid colon wall that were not apparent on radiology and laparoscopy may be suggested. Thus, patient is under follow up to assess pain recurrence and / or radiologically new appreciated pelvic lesion.

The mean patient age for NVMH is 53.7 (12–91) years, and it is more reported in females. This is in agreement with our case who was female patient aged 52 years. Most of the patients complained of abdominal pain, and 3 patients had Crohn's disease as a comorbidity (3). The case presented here showed endometriosis along with appendiceal fibrosis thus, it is suggested to represent secondary reactive process induced by chronic inflammation. Endometriosis can cause mass like lesion in the bowel wall from mucosa till serosa but composed of endometrial glands and stroma with hemorrhage, hemosiderin laden macrophages, fibrosis and could be associated with concentric muscle and nerve hyperplasia and hypertrophy that may lead to bowel obstruction (7). Shepherd NA and Jass JR (8) suggested that NMVH may represent an abnormal histologic consequence of chronic inflammation and in their study, it was related to inflammatory bowel disease (Crohn's disease). Also, Caruso ML et al (9), suggested that NMVH was exacerbated by recurrent hemorrhage and diffuse ulceration in their studied case at jejunum, secondary to the use of non-steroid anti-inflammatory drugs (10). Similarly, our case also showed diffuse mucosal ulceration and hemorrhage along with features of chronic inflammation and thus, our NMVH is suggested to be a secondary event.

Common symptom in both endometriosis and NMVH is longstanding abdominal pain and non-specific mild swelling of the appendix on CT imaging. In our case and in the other reported cases, the preoperative diagnosis was less likely to be a progressive disease such as cancer or carcinoid, instead the possibility of benign neoplasm as mucinous

cystadenoma was considered because of the longstanding non progressive symptoms or mass lesion for years since the condition started. For this reason, diagnostic laparoscopy and only appendectomy was conducted for therapeutic purposes in our case and mostly in other reported cases. There is no clear explanation for the abdominal pain that associate the NMVH, but authors suggested that rising in the internal pressure of the appendix could be a possibility. In our case, this is not a suggested cause, as our case showed out-growth of the NMVH in the mesoappendiceal fat rather than the inward growth toward the appendiceal lumen which mostly found in the previous reported NMVH cases. Thus, in our case, the endometriosis is suggested to be the main cause of the abdominal pain but we suggest that NMVH may increase the pain due to the prominent proliferating nerve bundles (11).

Endometriosis and NMVH posed a diagnostic challenge for clinicians and surgical treatment should provide definitive resolution (9). Medical treatment by hormones as progesterone (and others) is another possible choice as long as the patient is not seeking conception and there are no features of intestinal obstruction (12). In the presenting case, there was clinical and radiological diagnostic challenge that was solved after appendectomy with histopathological examination. At histopathological level, the differential diagnosis of glands extending into muscle was adenocarcinoma but the benign cytologic features of glandular epithelium, the appreciated ciliated epithelium, the appreciated endometrial stromal cells and the absence of desmoplastic stromal reaction confirm the endometriotic nature of the glands. Regarding the NMVH, the differential diagnosis was neoplastic benign spindle cell lesion as leiomyoma or gastrointestinal stromal tumor but the intermingling of the proliferating smooth muscle fibers with many nerve bundles/ganglia and mature fatty areas as well as its site that was adherent to the endometriotic lesion, makes the neoplastic process un-favored and raises the possibility of reactive process of hamartomatous / disorganized proliferating benign appendiceal tissue as abnormal consequence of chronic inflammation in similar way to what described for Crohn's disease (8).

Our patient is under regular visits for follow up every 6 months or if she develops any new complain, with multidisciplinary team composed of the operating surgeon and a gynecologist. She is informed about the possibility of medical treatment (hormonal/progesterone) if she gets recurrent intermittent abdominal pain again along with sonographic follow up to assess any new lesion and its progression. In addition, other investigations could be implicated according to the patient complain.

CONCLUSION

Endometriosis of appendix is rare and could be associated with an extremely rare secondary neuromuscular and vascular hamartoma / neuromesenchymal hamartoma as abnormal histologic consequence to chronic inflammation. Clinical and radiological suggestion is difficult, but this study highlighted its importance in the differential diagnosis with any female patient complain of longstanding intermitted right lower abdominal pain along with suggested neoplastic lesion on CT scan. Bowel is the commonest site of recurrent / persistent endometriosis after hysterectomy.

Ethical Considerations

Ethical issues (including plagiarism, data fabrication or double publication) have been completely observed by authors. The patient gave the consent to publish as a case report.

Conflicts Of Interest: No conflicts of interest.

Funding Resources: None.

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