

Review Article



Cutaneous Endometriosis

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Abstract

Endometriosis affecting the skin is a very much rare surgical entity encountered almost exclusively in women of childbearing age. It commonly presents as a discolored painful cutaneous swelling, the pain being most commonly a cyclical one occurring during menstrual bleeding. It often needs histopathological examination to arrive at a correct diagnosis. Otherwise, the diagnosis is usually presumptive from typical and atypical presentations and other supportive imaging investigations. Wide surgical excision is the gold standard curative treatment of choice. Nonsurgical treatment includes use of such hormonal agents as danazol or leuprolide, oral contraceptive pills, etc. which can't definitely cure the patient from this nonfatal ailing disease. All other examples of benign and malignant cutaneous swellings like desmoid tumors, fibro-histiocytoma, dermatofibroma protuberans, papilloma, melanoma, visceral malignancies and many other types of fibromatosis are to be included in the differential diagnosis. These patients with cutaneous endometriosis need to be additionally evaluated for endometriosis elsewhere in the body especially in the pelvis and the abdomen proper, though no other tissue like brain, lungs, liver etc. are not immune to it. In women of childbearing age with abdominal or pelvic wall masses or an area of soft-tissue thickening at cross-sectional imaging in or very close to previous surgical scars, endometriosis is to be strongly suspected by the consulting radiologist. Imaging investigations like CT, USG, and especially, MRI may help in the diagnosis of scar endometriosis, but it is only the biopsy that is definitely confirmatory.

Key words: Endometriosis, Hormonal treatment, Wide surgical excision.

Date of received: 03.08.2021

Date of acceptance: 21.11.2021

DOI: <https://doi.org/10.3329/kyamcj.v12i4.58227>

KYAMC January. 2022;12(04): 243-249.

Introduction

Endometriosis is the scientific medical term for the presence of non-tumorous endometrial tissue (endometrial glands and endometrial stroma) outside its normal location of lining the uterine cavity. The most common sites of pelvic endometriosis include the ovaries, the uterosacral ligaments, the ovarian fossa, the pouch of Douglas, the bladder. But no other tissues like the skin, the brain, the lungs, the liver, even the uterine wall itself etc. are immune to endometriosis. Thus, endometriosis may be both endo-pelvic and extra-pelvic (extra-genital), depending on the ectopic endometrial tissue locations.¹⁻⁵

Cutaneous endometriosis falls into the subtype of extra-pelvic endometriosis. Cutaneous endometriosis is very uncommon. It is non-neoplastic endometrial tissue found on or in the skin,

principally involving dermis. Patients usually presents with cyclical pain in affected skin during menstruation, a palpable lump or swelling involving skin, or even very rarely hemorrhage from the affected sites on or in the skin.⁴⁻⁸

The cutaneous endometriosis per se comprises less than one p.c. of all cases of endometriosis. Cutaneous endometriosis, depending on patients' surgical, traumatic and obstetric history is sub-categorized into primary cutaneous endometriosis and secondary cutaneous endometriosis. Primary cutaneous endometriosis is said to develop spontaneously without any surgery or instrumental delivery. Secondary cutaneous endometriosis (sometimes also known as scar endometriosis) is associated with previous known pelvic or abdominal surgery or instrumental delivery. Primary cutaneous endometriosis is less common than secondary cutaneous endometriosis. Only 30%

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patients presenting without a surgical or instrumental trauma history that can explain their primary cutaneous endometriosis. Identifying the patients' past instrumental obstetric or surgical history is crucial to subcategorizing cutaneous endometriosis. Umbilicus is the most common location for both primary and secondary cutaneous endometriosis, comprising 30 to 40 p.c. of all cutaneous endometriosis. Other cutaneous locations include groins, arms, episiotomy scars, appendectomy scars, caesarean scars etc. Scar endometriosis is a variant of secondary cutaneous endometriosis that occurs in or around the surgical scars, and that can be cutaneous or partly subcutaneous in location.⁹⁻¹⁴

Historical Aspects

The discovery and identification of endometriosis have been a subject of intense hot debate over the last decade. There is, however, universal agreement that the American gynecologist Thomas Stephen Cullen during the years 1893 to 1896 was the first to ascertain uterine muscle wall endometriosis and adenomyosis as one disease characterized by the presence of endometrium-like tissue outside the uterine cavity lining. Microscopically endometriosis was first described by Karl von Rokitansky in 1860, though the foremost antecedents may have crawled from the concepts published almost 4 thousand years back. The 'Hippocratic Corpus' had described symptoms simulating those of endometriosis. Similarly, endometriotic clinical features have long been misinterpreted and treated for several thousand years, causing many delays in infallible diagnosis and much indifference to the patients' true pain throughout the 20th and even into the 21st century. Hippocratic doctors were recommending changes in marriage practices because of endometriosis-like illness that implies that this disease was likely common, with prevalence rates higher than 5-15% (the prevalence rate that is often estimated currently). In 1940s, the only available hormonal treatment for endometriosis was high-dose testosterone and high-dose estrogen. In 1948, Karnaky was the first to report high-dose estrogen (diethylstilbestrol) for the treatment of endometriosis. Thereafter pseudopregnancy (by Kistner in the late 1950s), progestogen (in the 1960s and 1970s), Danazol (in 1971s to 1980s), GnRH (Gonadotrophin Releasing Hormone) antagonists (in 1990s) had been widely used for endometriosis. Such oral GnRH antagonists as elagolix were introduced to treat endometriosis in 2018. The very early surgical treatment (Oophorectomy and hysterectomy) is now preferred unanimously in many centers throughout the world.¹³⁻¹⁸

Epidemiology, Incidence and Prevalence

Irrespective of race, ethnicity and parity, endometriosis chiefly can affect any adult woman from pre-menarche to post-menopause. It is difficult to determine the incidence and prevalence exactly because the definitive diagnosis needs surgical intervention. However, depending on the clinical features, surgical assessment, and in some cases on imaging technology, the incidence of endometriosis in women of reproductive age is determined to range from 5% to 15%. The prevalence of cutaneous endometriosis is roughly 0.5% to 1%. The prevalence of primary cutaneous endometriosis is said to be less than 30% in all cases of cutaneous endometriosis. Umbilical endometriosis is about 30% to 40% of all cases of cutaneous endometriosis. Endometriosis within episiotomy scars occurs in about 0.00007% of births. But, this latter incidence is supposed

to be underestimated. Though endometriosis is most commonly diagnosed in their thirties and forties or in accordance to other studies between 25 and 35 years, endometriosis has already been reported in girls as young as 8 to 11 years of age. Endometriosis is said to affect over 19 crore women in their reproductive years. In some studies, the recurrence rate of endometriosis is said to be 40-50% for adult women over a 5-year period. The recurrence rate substantially increases with the time from surgery and is not associated with the stages of the disease, the initial location of disease, the surgical procedure offered and the post-surgical therapy. Another study says that endometriosis is very rare in postmenopausal women. Studies further suggest that endometriosis is most common in taller, lean and thinner women with relatively substantial low BMI (Body Mass Index). Overall incidence of associated pelvic endometriosis in the general population is about 8% to 15%.¹²⁻¹⁵

Theories on the etiopathogenesis of cutaneous endometriosis: Many theories have been put forth to explain endometriosis. Of which, three theories explain the etiopathogenesis of endometriosis well to an acceptable level. One theory (the metaplastic theory or the stem cell theory by Meyer, in 1903) holds that, under suitable conditions, primitive pluripotent stem cells may undergo specialized differentiation or metaplasia to form endometrial cells and stroma at ectopic locations (including skin, subcutaneous and other tissues and organs), which can explain both primary and secondary cutaneous endometriosis. The second theory states that the endometrial cell seeding occurs via lymphatics (described by Halban in 1924) or blood vessels (described by Sampson in 1925) or through other natural routes like fallopian tubes (in the form of retrograde menstruation as by Sampson's theory). These above two theories attempt to explain primary endometriosis well. The third theory is for secondary endometriosis. This third one states that the endometrial cells might have been dislodged and translocated to ectopic locations, particularly during surgical procedures or trauma or instrumental deliveries when the transposed cells get seeded and implanted at new locations especially within any wound, thence within the subsequent scar and adjacent areas. Because the proliferative capacity of endometriotic differentiated cells is limited, transposition of primitive endometrial stem cells into and around the incisions wounds during surgery or trauma is followed by their multiplication at new locations might be an acceptable explanation of scar endometriosis. Some argue that the umbilicus acting as a physiologic scar, like that of secondary scar cutaneous endometriosis harbor endometrial tissue to cause umbilical endometriosis. Many patients of scar endometriosis do not have features of peritoneal endometriosis, which indirectly corroborates the theory of translocation of endometrial cells into the wound during surgery or trauma. However, the most widely accepted hypothesis for the pathophysiology of endometriosis is that endometrial cells are transported and transposed from their native location of uterine cavity lining during menstruation and subsequently get implanted seeded at ectopic locations. Through genetic analytic studies, some researchers had identified a specific gene NPSRI that increases the risk of suffering from endometriosis. Thus, endometriosis may be regarded as an inheritable disease that may be transmitted through the maternal and paternal family lines.^{1,14,16-19}

Pathology

The presence of non-neoplastic endometrial tissue outside its

normal location within the uterine cavity is theoretically defined as endometriosis. Endometriosis is now regarded as a chronic inflammatory disease that causes unusual distressing cyclical pain and many other features, affecting about 2% to 10% of women of reproductive age group. Endometriosis is most commonly detected in the pelvic cavity. It may remain attached to and located within the tissue of any of the female reproductive organs like the uterus, the fallopian tubes, the ovaries, the uterosacral ligaments, the peritoneum, and any of the anatomical spaces amongst the bladder, the uterus, the rectum and the vagina.³⁻⁵

Once implanted on the external aspect of the uterus, the endometrial tissue grows in phases with the monthly menstrual cycles, worsening the symptoms. Endometrial tissue occasionally travels through blood vessels and lymphatics to the lungs, the limbs, the middle ear, the oral cavity, the nose and the brain etc. That is no organ is immune to endometriosis. Very few cases of cerebral and cerebellar endometriosis have been reported so far. Endometriosis can cause low back pain, sciatica, leg pain, gingival pain, earache, intestinal colic in addition to other features. These pains may be of throbbing or stabbing nature, starting a couple of days before their cyclical menstrual bleeding, the peaks being during their bleeding, and stopping once their cyclic bleeding is over. Endometriosis is a dynamic, fluctuating and progressive chronic inflammatory disease process. Without treatment, it usually worsens with time. Early treatment is essential to avoid its potential complications. Women with endometriosis are more prone to abortion, miscarriage, subfertility and infertility.^{16,18-22}

There is no gold standard classification and staging system for endometriosis. A well-organized reproducible classification system is required for the physicians to standardize the optimal treatment strategy. There are many systems of endometriosis classification. The well-known ASRM (American Society for Reproductive Medicine) classification system divides endometriosis into four grades or stages depending on the location, the extent, the number of lesions and the depth of infiltration, presence and severity of adhesions and presence and size of ovarian endometriomas etc. They are minimal [Stage I], mild [Stage II], moderate [Stage III] and severe [Stage IV]. This classification also uses a pointing system to quantify endometriotic severity.²⁰

A diagnosis of endometriosis only confirmed by the presence of endometrial glands and endometrial stroma within the ectopic lesion. Scar endometriosis may have inflammatory cells, surrounding fibrosis, cytogenic chorion and hyperplasia of the tissue (including muscles if any) within which it is contained. Microcysts may be found in gross specimens along with brownish materials at the peripheral zones. Endometrial ducts and glands may be found lined with columnar to cuboidal cells that may be encompassed by areas of chronic inflammation, fibrosis and hemosiderin. Hemosiderin laden macrophages are strongly suggestive of endometriosis.²³

Common Complications of endometriosis in general Abortion, Miscarriage, Subfertility, Infertility. Intractable and Debilitating pain, Adhesions, ovarian cysts and many other complications are related to endometriosis. Though malignant transformation of cutaneous endometriosis (e.g., into endome-

trioid or clear cell adenocarcinoma) had been reported, the exact figure is unknown. And the causes of malignant transformation are unknown and unclear, where genetic, immunologic, and hormonal factors may have implications. Recurrences of cutaneous endometriosis after the treatment is also a complication.^{12,24}

Clinical Features

Early co-existing abdominal endometriosis symptoms include severe, debilitating abdominal cramps, pelvic pain that worsens during menses, long duration of periods, heavy menstrual flow, nausea with or without vomiting, dyspareunia, bowel and urinary disorders including painful bowel movements or urination during menstruation, bleeding in between periods, frequent urination, diarrhea or constipation, painful periods, menorrhagia, polymenorrhoea, etc. Endometriotic patients may be rarely asymptomatic. The diagnostic features include pain and tenderness occurring mostly at the time of menstruation, several centimeter-sized swelling seen in the affected accessible area or in and around the surgical scar, past history of pelvic surgery or trauma or instrumental delivery. Scar endometriosis may be rubbery and multiloculated, with contents similar to that seen in chocolate cysts and classic adnexal region endometriosis. Although these findings are quite variable. Endometriotic women may have dysmenorrhea, recurrent abortion and miscarriage, sub-fertility, infertility with or without menstrual irregularities. Other clinical features are dependent on other its sites of involvement.^{3,4,25}

Differential Diagnosis

Keloid, Dermatofibroma, Dermatofibrosarcoma protuberans, cutaneous metastasis of cancer (e.g., Sister Mary Joseph nodule from visceral malignancies), papilloma, melanoma, desmoid tumors, any other forms of fibromatosis etc.^{15,26}

Diagnosis

Diagnosis is to be ideally made by adequate history taking, physical findings and laboratory aids. The principal diagnostic feature of cutaneous endometriosis is that the symptoms are of cyclical nature, ranging from cyclical pain during menses only to cyclical variation in the size of the swelling in relation to the starting and the ending of the menstrual cycle. Imaging investigations are strongly suggestive, but it is only the histopathologic examination that can confirm it. Immunohistochemistry is not usually required unless there is strong differential diagnosis against it. Endometriosis may be detected by USG (UltraSonoGraphy), CT scans (Computed Tomography Scans) and MRI (Magnetic Resonance Imaging) in symptomatic or asymptomatic patients. Imaging findings combined with clinical history are usually strongly indicative of diagnosis. The appearance of scar endometriosis at USG, CT, and MRI depends on the phase of patients' menstrual cycle, the duration and severity of the disease, the proportion and number of glandular and stromal components, and the amount of hemorrhage and the severity of inflammation and fibrosis. Most scar endometriotic lesions exhibit vascularity at color Doppler USG. Very often, internal vascularity is visible at power Doppler USG. If gray-scale, color, and power Doppler USG findings are not conclusive, the extent and the biologic behavior of the endometriotic lesion should then be further assessed and evaluated by MRI. The use of fine-needle aspiration (FNA) for diagnosis of secondary scar

endometriosis is controversial as this may cause seeding and dissemination of the endometriotic tissue in new areas, causing spread and aggravation of the condition. Thence, wide surgical excision, when done with a safety margin of at least 10 mm away from the solid lesion, will serve for both diagnosis and treatment.²⁷⁻²⁹

Treatment

Endometriosis does not get cured on its own without treatment. Symptomatic patients may get their symptoms worsened without treatment. For mild to moderate pain, Ibuprofen and Naproxen are claimed to be suitable and the best-studied NSAIDs (Nonsteroidal Anti-Inflammatory Drugs). OCPs (Oral Contraceptive Pills) by reducing estrogen which inhibits the growth of endometrial tissue are also effective in alleviating pain. Some women with endometriosis may need both NSAID and OCP to get pain relieved.³⁰

Once the diagnosis cutaneous endometriosis (primary or secondary) is made, the definitive curative treatment is surgical wide excision. Adequate wide surgical excision is essential to prevent recurrence. Many authors advocate and recommend pre-operative or post-operative hormonal therapy. The pre-operative hormonal therapy alleviates patients' discomfort of pain and causes shrinkage of endometriotic lesions to smaller ones that can facilitate easy adequate surgical removal. Post-operative hormonal therapy may prevent recurrence. But no widely available recommended data are there for perioperative hormonal therapy and menstrual interference for cutaneous endometriosis. Regarding the perioperative management of the lesions, the recommendation varies on either performing the surgery at the end of the menstrual cycle, whereby the lesions are smaller in size or initiating preoperative hormonal agents to reduce the size. Postoperative use of hormonal agents can also be done, and the aim is to prevent a recurrence. The combination of hormonal treatment followed by surgical excision may be a better approach for many cases.²²

For those patients who are unwilling to have definite surgical excisional therapy, hormonal agents like GnRH agonists or danazol or leuprolide or OCP may be offered. These hormonal agents act by preventing cyclical proliferative response of the ectopic endometriotic tissues. But there is a very high potential for recurrence. The ectopic endometrial glandular tissue may resume proliferation once the hormonal agents are withdrawn. Hormonal agents definitely cause pain relief and definitely decrease the size of endometriotic nodular mass. The pain may reappear between treatment cycles, if treated with monthly injections of subcutaneous leuprolide. Moreover, hormonal agents are associated with unfavorable side effects. Thence, wide surgical excision is the gold standard treatment. Biopsy and surveillance are essential in any form of treatment that is being given, especially to exclude malignancy. Cutaneous endometriosis may be associated some other endometriotic lesion at other ectopic sites that warrants more detailed clinical and laboratory workup. Ideally, patients with cutaneous endometriosis should have gynecologic consultation especially if they have classical symptoms that includes pain with menstrual bleeding, subfertility, infertility, miscarriage. Menorrhagia, polymenorrhoea, dyspareunia etc. for more detailed exploration and appropriate treatment options.¹⁹

The best fertility treatment options for endometriosis include IUI (Intra-Uterine Insemination) and IVF (In Vitro Fertilization). Generally speaking, IUI is the first line of choice, albeit women with severe endometriosis, older age, or multiple infertility risk factors may opt for IVF first.¹¹

Discussion

Endometriosis has been identified in 15%–44% of women of reproductive age group who had abdomino-pelvic surgery or pelvic trauma or instrumental delivery. Endometriotic swellings may be classified as cystic, solid or mixed, with the cystic type being the most common. Endometrial tissue has been detected in many abdomino-pelvic surgery-related scars, as well as in the skin, the subcutaneous tissues and the abdominal and the pelvic wall musculatures adjacent to the scars, a condition that is often referred to as scar endometriosis. The average time interval between the causative surgical procedures and the onset of symptoms in cases of endometriosis in scar is about 3 to 6 years. Endometriotic tissues within abdomino-pelvic wall scars are an unusual well-explained finding with which imaging interpreters should be familiar very well. Secondary cutaneous scar endometriosis is found to develop most commonly after cesarean deliveries and hysterectomies. They have also been described in laparoscopic tract scars, amniocentesis needle tract scars, episiotomy incision scars, and Bartholin gland excisional areas inside the vulva. Abdomino-pelvic wall endometriotic lesion without prior surgery is fairly uncommon.^{9,13,18}

Cesarean scars are the most common locations of abdomino-pelvic wall endometriosis, that possess an approximate incidence of about 0.03%–0.4% amongst all women. In one study, 94% of cutaneous endometriosis occurred in a pre-existing scar, most commonly in a surgical wound. Nearly 51% of cutaneous endometriosis occurred in caesarean scars. In another series, 57% cases were found within a cesarean scar, and 11% were found with hysterectomy scars. If cesarean section is performed before the onset of spontaneous vaginal delivery, the incidence of scar endometriosis has been found to be higher by 1.1%. Even a higher incidence of scar endometriosis by 1.1% was reported following hysterotomy performed for mid-trimester miscarriage. Another study had reported an even higher incidence by 3.5% of scar endometriosis following incision in a gravid uterus.²⁷

Scar endometriosis may remain isolated within the superficial layers of the abdomino-pelvic wall. But endometriotic tissue often infiltrates through the deeper layers, usually implicating the rectus abdominis muscle. Very occasionally, it may present in the form of a utero-cutaneous fistula. Amongst all cases of scar endometriosis, 14.3%–26% may have concomitant pelvic endometriosis in accordance to one study. An exact diagnosis of scar endometriosis may be made before excisional curative surgery is possible in approximately 20%–50% cases. Clinico-pathological features and the imaging findings are often adequate in pre-operative assessment and evaluation.²⁸ Cutaneous endometriosis usually present with cutaneous or subcutaneous or compound macule or papule or nodular swellings of several cm in diameter. Its color may be dusky, violaceous, blue or brown etc. Patients frequently complain of cyclical pain and a cutaneous swelling, and sometimes hemorrhage corresponding with the bleeding phase of menstrual

cycle. The presence of endometrial glands, ducts and stroma in the dermis with or without involving the subcutaneous tissue are the histopathological hallmarks of diagnosis of cutaneous endometriosis. Preoperative imaging like USG, MRI, CT scan etc. may be required to exclude other differential diagnosis. Distinguishing cutaneous endometriosis from other cutaneous lesions is challenging, especially if there is no history of cyclical pain corresponding with menses.^{29,30}

Patients with a keloid may provide a history of keloid or hypertrophic scars elsewhere in the body. Keloids may appear as well-circumscribed purple-to-pink, firm, smooth nodules or plaques with regular or irregular borders. These may develop at umbilical or other surgical scars, but favorable keloid locations are areas of such increased tension as the shoulders and arms. Occasionally patients of cutaneous endometriosis may have already received intralesional steroids for an erroneous diagnosis of keloid scar. Intralesional steroids can't cure cutaneous endometriosis. Dermatofibromas are benign firm fibro-histiocytic tumors most commonly presenting as asymptomatic masses that dimple down when compressed laterally because of tethering of the epidermis to the underlying nodule (called the nonspecific dimple sign). Dimpling indicates any nonspecific subcutaneous soft tissue swelling tethered to the epidermis and is unknown in cases of cutaneous endometriosis. Dermatofibrosarcoma protuberans is a locally aggressive low-grade soft tissue sarcoma, presenting in early stages as an asymptomatic, indurated plaque that subsequently slowly enlarges. In later stages, it may become raised, firm, and nodular with or without telangiectasia in the surrounding skin. The nodular growth often gets ulcerated with or without bleeding, unlike the classical cutaneous endometriosis.

Biopsy is definitely diagnostic, like cutaneous endometriosis. Sister Mary Joseph's nodule is a palpable nodular umbilical swelling that represents a metastatic cancer from a visceral malignancy, usually typified by its pain, anemia, changes in bowel habits following underlying abdomino-pelvic malignancy. Intra-abdominal malignancy may initially have an occult presentation, that need to be considered even in the absence of obstructive features. Recently, it has been found that the regional lymph node involvement by endometriotic cells is common in women with endometriosis. Endometriotic cells in the regional lymph node are a very potential target for hormonal response following definite surgical excision of the primarily diagnosed lesion. And this lymph node involvement may be a principal cause of recurrence of endometriosis.^{3,13,23}

Pregnancy may temporarily stop the painful episodes and heavy menorrhagia found in patients with endometriosis. Thus, pregnancy provides some form of relief from endometriosis. The benefit may be positively influenced by the increased levels of progesterone of pregnancy. It is noteworthy that most women with endometriosis become pregnant without any medical assistance. For stages III and IV endometriotic patients (severe endometriosis), who desire to get pregnant, about 75% may succeed in having that, two-thirds naturally and one-third with the help of IVF.^{21,28}

Prognosis

Frankly speaking, cutaneous endometriosis is a non-fatal benign disease. The prognosis of cutaneous endometriosis is excellent if exact surgical treatment is offered, unless it is associated with serious non-cutaneous complications of pelvic or some other form of endometriosis. The recurrence rate is low, may be around 9% to 10%, indicating the significance of adequate wide surgical excision. It is to be remembered that endometriosis is a painful chronic disease that commonly interferes with the quality of life, unless adequately treated. And in exceptionally extremely rare situations, endometriosis complications may cause potentially life-endangering conditions. The outlook for fertility following endometriosis surgery is quite positive. Within 45% and 75% of women who undertake surgical treatment are able to get pregnant. Of these pregnancies, many ones are even achieved naturally without therapeutic assistance. Recurrence is seen if there is an incomplete excision.^{7,27,30}

Conclusion

Cutaneous endometriosis is now considered as a primary or ectopic extrauterine presentation or iatrogenic complication of endometriosis. Patients with cutaneous endometriosis should undergo careful history taking for surgery, trauma or instrumental delivery and physical examination to exclude another differential diagnosis especially potential primary or visceral malignancies.^{15,25,30}

Recommendations

Patients of cutaneous endometriosis needs a thorough clinical and imaging workup to evaluate for pelvic and other site endometriosis as many of these patients have associated endometriosis in other locations, especially in the pelvis.⁷ There is no way to prevent cutaneous endometriosis. Careful clinical and histopathological evaluation is essential for any cutaneous lesion. As patients may deem such a lesion for a neoplasm, this can be dealt with an appropriate diagnosis and educating the patient on this treatable lesion.¹⁷ After apparent successful treatment, all patients require regular routine follow up schedules to detect recurrences if any.^{27,30}

Acknowledgment

We are very much grateful to Prof Md Zulfikar Ali of the department of medicine of Khwaja Yunus Ali Medical College, Enayetpur, Sirajganj for his untiring continual inspiration and encouragement in preparing this review article entitled 'Cutaneous Endometriosis' for publication in this esteemed journal.

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