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Original Research Paper

Pathology

HOW COMMON IS ADENOMYOSIS AND ENDOMETRIOSIS IN SOUTH TAMILNADU. ITS TARGETED THERAPY: ARE WE THERE YET?

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ABSTRACT

Adenomyosis and endometriosis causes similar symptoms and have similar molecular pathogenesis.

Aim: This study was done to evaluate the disease burden in south Tamilnadu. And to review its pathogenesis based on various studies published so far to know if we have reached anywhere near targeted therapy.

Materials and Methods: It is a cross sectional descriptive study carried on for a year from August 2020_21 in the Department of Pathology, Madurai Medical College on 591 hysterectomy cases for the presence of adenomyosis and endometriosis. Age wise stratification, mean age, age wise incidence and symptoms associated with it were analyzed. To understand pathogenesis, review of concerned articles from PubMed site was done.

Results: The incidence of adenomyosis was 15.9% which was higher than that of endometriosis. Peak age incidence of adenomyosis was between 41-45 years and endometriosis was between 25 - 30 years. Age specific incidence was calculated and it was higher in those who were between 36_40 years. Abnormal uterine bleeding _ Leiomyoma (AUB-L) was the most common symptom associated with adenomyosis and abdominal pain was associated with endometriosis. Kirsten rat sarcoma viral oncogene homolog gene (K RAS) mutation and Nuclear factor kappa light chain enhancer of activated B cell (NFkb) activation associated chronic inflammatory status were observed in both. But the dictating pathogenic factor for targeted therapy still eludes.

CONCLUSION: The 15.9% incidence of adenomyosis observed in our study is just a tip of an iceberg, as more number of cases remains undiagnosed or those cases which were diagnosed by other modalities are not confirmed by hysterectomy which is the gold standard. Since target therapy for this condition continues to evade, these females continue to suffer with lifelong morbidity and cyclical unproductive and miserable existence.

KEYWORDS : Chronic inflammation,stem cell, Epithelial mesenchymal transition, Kirsten rat sarcoma viral oncogene homolog gene, Nuclear factor kappa light chain enhancer of activated B cell.

INTRODUCTION

Adenomyosis and endometriosis causes dysmenorrhoea, infertility, menorrhagia and other obstetric complications. [1] Adenomyosis is characterized by benign invasion of endometrium into myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic, nonneoplastic, endometrial glands and stroma surrounded by hypertrophic and hyperplastic myometrium according to Bird et al. [2] Endometriosis is classified into three based on its location- superficial, deep infiltrating and ovarian. It causes similar complication like adenomyosis and both share similar molecular alterations. [3] Matalliotaki et al in their study observed that endometriosis increase the risk of acquiring adenomyosis.[4] Both were identified in peri- and postmenopausal women a decade ago and this scenario changed after the advent of imaging techniques. [5] In the recent past it is being increasingly identified in many young females causing perils of symptoms including psychological distress.

Pathogenesis of both adenomyosis and endometriosis is being studied elaborately in the recent years. Mechanical causes of adenomyosis includes trauma to endometrium-myometrium interphase, local hyper estrogenic state, local hyper and dysperistalsis. In their study Gaetje R, et al. found E cadherin loss is associated with invasion of endometrium in these cases. [6] Loss of cohesiveness of myometrium due to matrix metalloproteinase activation is yet another reason for adenomyosis. [7] Epidermal growth factor induced epidermo –mesenchymal transition [EMT] and loss of fibronectin adhesion was found as a cause of this condition by a study conducted by Chiquet-Ehrismann R, et al. [8] Motility-related molecule cell division control protein 42 analog (Cdc42) expression is higher in those with ovarian endometriosis.[9] All these mechanisms explain the ectopic rest in both adenomyosis and endometriosis. These ectopic endometrial cells activate the interleukins leading on to a chronic inflammatory status. Ultrastructural abnormalities in both endometrial stromal cells and myometrium are noted in a study conducted on those with adenomyosis by Mehasseb MK et al. [10] They observed that there is increase in Golgi apparatus and rough endoplasmic reticulum contribute to myometrial hypertrophy in adenomyosis. Micro vessel density is increased in this condition. Matrix metalloproteinase (MMP)1, 9 expressions and fibroblasts growth factor 1 (FGF1) polymorphism that is noted in both adenomyosis and endometriosis might be reason for neoangiogenesis.

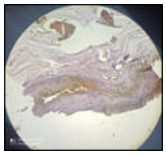
This study was done to find the disease burden, and its clinical characteristics among the urban population attending our referral hospital. And to review the pathogenesis of both to see if we have reached the final destination: that is targeted therapy.

MATERIAL AND METHODS

A cross sectional study was carried out in Madurai Medical College hospital among the patients who had undergone hysterectomy during our one year study period from August 2020 to August 2021 in Madurai Medical College, Department of Pathology. Inclusion criteria include the presence of adenomyosis and/or endometriosis in the hysterectomy specimens. Exclusion criteria include other benign and malignant diagnosis. All the cases were reviewed by our expert pathologist and categorized based on age, symptoms and on the presence of adenomyosis and/ or endometriosis. Adenomyosis was identified in the histopathological sections by the presence of endometrial glands and/or stroma in the myometrium at least one low power below the endometrium myometrial junction [Table/Fig 1].

Table/Fig 1: Endometriotic glands and stroma in the myometrium An adenomyotic foci[40x H&E stain]

An attempt to classify adenomyosis histologically based on depth of invasion, diffuse or local involvement and location of adenomyosis was done in various studies. As correlation between the proposed classification and clinical symptoms were lacking, uniform consensus among the pathologists was not reached. Hence classification of adenomyosis was not done in our study. At least two of the following three features are taken into account while diagnosing endometriosis of the ovary- Presence of endometrial glands, presence of endometrial stroma and evidence of chronic hemorrhage [Table/Fig 2].

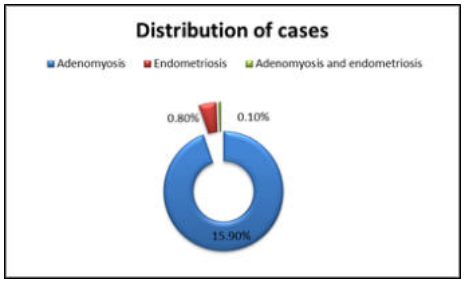


Table/Fig 2: Endometriotic cyst of ovary [10x H&E stain]

Symptomatology associated with both adenomyosis and endometriosis was tabulated. As it is a descriptive study ,mean age group and incidence of those who had adenomyosis and endomeriosis was calculated. For understanding the pathogenesis, diagnostics and treatment of both adenomyosis and endometriosis extensive review of the articles from the PubMed site was done.

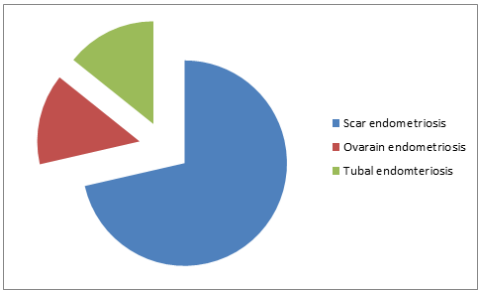
RESULTS

During our study period 591 hysterectomy specimens were received. Among the five ninety one specimens histologically, ninety one had adenomyosis, five had endometriosis and one had both adenomyosis and endometriosis. Among the 97 cases diagnosed as either adenomyosis or endomeriosis histologically, almost equal number of cases was diagnosed as having leiomyoma and adenomyosis, and five were diagnosed as having endometriosis by imaging techniques. The incidence of adenomyosis (15.9%) was more when compared with endometriosis in our study group [Table/Fig: 3].



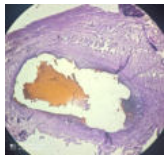
Table/Fig 3: Distribution of cases

We encountered all three types of endometriosis during our study period. Although majority of the endometriosis in our study was scar endometriosis [Table/Fig4].



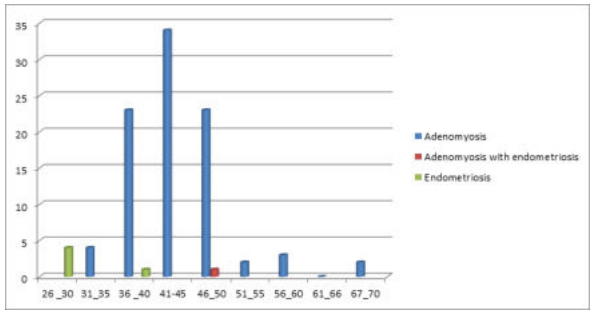
Table/Fig 4: Distribution of Endometriosis in our study population

We came across a case of endometriosis of the fallopian tube as well [Table/Fig 5].



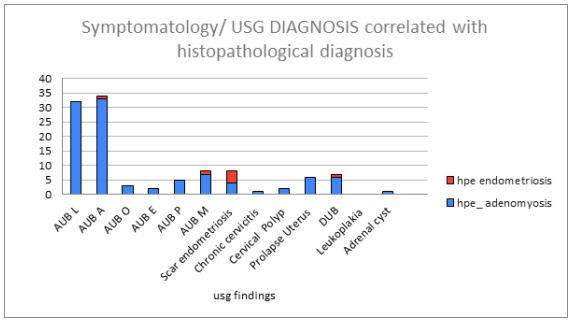
Table/Fig 5: Endometriosis of the fallopian tube [40x H&E stain]

Most of the cases we reported as having adenomyosis were between 41- 45 years of age. Endometriosis was seen in slightly lesser age group and those cases that had both adenomyosis and endometriosis belonged to slightly older age group. [Table/Fig: 6].



Table/Fig 6: Age wise distribution of the cases

Mean age group in our study was 44.9 years. Symptoms include dysmenorrhea, menorrhagia, and abnormal uterine bleeding amongst others. PALM _COEIN category AUB L is most commonly associated with adenomyosis in our study and abdominal pain was associated with endometriosis [Table/Fig: 7].



Table/Fig 7: Distribution of symptoms and ultrasound findings among different age groups

DISCUSSION

Both adenomyosis and endometriosis is defined by the presence of endometriotic tissue outside their physiological sites. Various classifications were proposed for adenomyosis based on depth of myometrium involvement, location of adenomyotic lesions, and whether the myometrial involvement is diffuse or localized. But without clinical significance none of these classifications are valid and hence not universally followed. On the other hand endometriosis has its own classification: 1. superficial when it is seen in the surface or in the subserosal soft tissue of the peritoneum or visceral organs, 2.deep infiltrating when it involves muscular layer of the intestine, bladder wall, diaphragm, or other organs and 3.ovarian when it is presents as a cyst in the ovary. Each has its own clinical features. While the superficial lesions cause less severe symptoms, deep lesions cause pain and organ specific symptoms. Ovarian endometriotic cysts are associated with infertility and carcinomas and its risk factors include Asian origin, prolonged estrogen exposure, increased body mass index and uterine outlet obstruction.[11, 12, 13] Adenomyosis and endometriosis causes severe mental and

physical disability to an individual thereby reducing her working potential. Medical management is there for her rescue with variable results.[14] Surgical management is the last resort for this condition but it is done only in those who have completed the family. This study focuses only on those who had hysterectomy, as it is the gold standard in the diagnosis of adenomyosis and endometriosis.

During our study period we observed that the incidence of adenomyosis in our study population was comparable with various other studies.[2,15] The incidence of endometriosis among hysterectomy cases was 0.8% which is in par with study of Morassutto C et al.[16]. The incidence of adenomyosis was higher when compared with endometriosis. This was similar to the study conducted by Morassutto C,et al.[16] Ovarian endometriosis was commonest in Konrad,et al's study while scar endometriosis were more in number in our study.[17]While calculating the age specific incidence we found that adenomyosis was seen in older age group than endometriosis which was in concordance with Morassutto C, et al's study. [16] Sammour A et al in their study found that dyspareunia, dysmenorrhoea and AUB was associated with number of adenomyotic foci rather than the depth of invasion.[18] Classic symptoms of menorrhagia and dysmenorrhea was seen among the adenomyosis cases in our study whereas asymptomatic patients also had adenomyosis according to the study by Israel SL, et al and Benson RC,et al. [19,20].

Theories about pathogenesis of Adenomyosis

Pathogenesis of adenomyosis is still under debate and specific cause is yet to be identified, but there are several research papers, trials and speculations. In adenomyosis endometrial cells invaginate and invade. Local hyperes togenism causes increased peristalsis at the endometrium myometrial junction leading on to invagination of the endometrial cells, local trauma and chronic inflammatory state at the endometrium myometrial junction leading on to local tissue injury and repair response[TIAR]. Zhou et al in their study had observed that Myostatin, follistatin, transforming transforming growth factor(TGF) β and activinA expression are increased in adenomyotic nodules.[21] Myostatin, TGF β and activinA causes myolysis and invasiveness of the endometrial cells. Estrogen receptor (ER)α and B cell lymphoma (Bcl) 2 gene polymorphism are observed in the adenomyotic foci in the study by Kitawaki.[22]This polymorphism causes these invaginated endometrial cells acquire non-cyclical and anti-apoptotic behavior as seen in basal endometrial glands. As a result they expand into myometrium producing adenomyotic foci. There is also decrease in the progesterone receptor (PR)receptor at the foci and increased p65 immunoreactivity at the adenomyotic site according to the study conducted by Nie, et al.[23]All these factors lead on to local expansion of adenomyotic foci and set up a chronic inflammatory state. Deoxyribonucleic acid methyltransferases 3B (DNMT3B) and class I histone deacetylases 1 and 3 (HDACs) levels are higher in women with adenomyosis and they are associated with the severity of dysmenorrhoea seen in adenomyosis .[24]

Theories about pathogenesis of endometriosis

Several models and theories for the pathogenesis were put forward to understand the pathogenesis of endometriosis so far. Retrograde theory proposed by Sampson holds well for superficial and ovarian endometriosis but not for deep infiltrating type.[25] Endometrial stem cell theory explains all the three types of endometriosis but the precise stem cell that is responsible for the seeding needs further study although there are many candidates including stage specific embryonic antigen 1 (SSEA-1), leucine repeat–containing G protein–coupled receptor 5 (LGR5), N-cadherin and cluster of differentiation (CD)146+, platelet derived growth factor (PDGFR) r-B+ embryonic stem like cells. All these stem cells have a potential to differentiate into both epithelial and stromal component and might be responsible for populating distant sites causing endometriosis. [26-29]Both eutopic and ectopic endometrium is populated by estradiol influenced C_X_C chemokine receptor (CXCR)4 and C_X_C motif chemokine ligand (CXCL)12 expressing bone marrow stem cell according to Singh S et al's study on mouse model which is another theory explaining the ectopic rest in endometriosis. [30] Epithelial mesenchymal transition [EMT] was yet another theory proposed for endometriosis. In their study on chronic inflammatory status observed in endometriosis Bulmer JN et al, concluded that CD45, CD3 and CD8 positive intraepithelial lymphocytes cells were increased in ectopic endometriosis and CD56 cells were significantly less and that does not vary with the menstrual cycle.[31] Significance of these cells on the pathogenesis of endometriosis needs further evaluation. Mutations of KRAS,phosphatidylinositol 4,5 biphosphate 3 kinase catalytic subunits alpha (PIK3CA), AT-rich interactive domain-containing protein 1A (ARID1A), and protein phosphatase 2 scaffold subunit Alpha (PPP2R1A) are observed in endometriotic cells which are also frequently seen mutated in uterine endometrioid carcinomas and endometriosis-related ovarian cancers[32] Inherited polymorphism of a lethal 7 micro ribonuucleic acid (Let-7 miRNA) binding site in KRAS is found in those with endometriosis. [33]It may be a marker of resistance to drug therapy.

Common ground between adenomyosis and endometriosis

K RAS and PIK3CA mutation is seen in normal endometrium as the age advances and parity increases according to the study by Inoue S, et al.[34] In both adenomyosis and endometriosis, KRAS mutation carrying oligoclones rapidly expand and is the earliest change observed.

Both are associated with a chronic inflammatory status due to NFkb activation.[35] Stimulator of interferon gene (STING) is up regulated which in turn activate NFkb and interferon regulatory factor 3 (IRF3) via Cyclic GMP-AMP synthase (cGAS) pathway.[36]Further they also found that the numbers of CD45 cells were increased in both endometriosis and adenomyosis and it correlated with the STING score as well. Chronic inflammatory status and associated increase in intraepithelial lymphocytes are well explained by their study.

Although every possible mechanism of invasiveness, myometrial events, angiogenesis and inflammatory events surrounding adenomyosis and endometriosis were studied extensively by various researchers, concluding evidences that dictate targeted therapy of both these conditions are still elusive.

MRI is more helpful in the diagnosis of both adenomyosis and endometriosis but histopathology is the gold standard. Management of both these condition depend upon age, and patient's need to conserve her fertility. Medical management includes a long list of drugs including progestrins such as norethisterone acetate, vaginal danazol, and dienogest, GNRH antagonists, levonorgestrel-releasing intrauterine system, valproic acid, and anti-platelet therapies. All of these are not without side effects that include therapeutic menopause, irregular bleeding and amenorrhea although they alleviate the symptoms. Minimally invasive procedures like selective vascular occlusion, focused ultrasound/thermal energy without direct tissue dissection and surgical removal of the lesions are also tried. Hysterectomy still remains the final abode when all else fails.

Limitations of our study

This study was done on hysterectomy specimens which is the gold standard. Which of course excludes sonographic

diagnosis and those cases who are under medications. The incidence we have calculated is just a tip of an iceberg.

Future directions

Although there are numerous studies on pathogenesis the clincher marker that would dictate therapy still evades. More research should focus on that aspect for their betterment.

CONCLUSION

Both adenomyosis and endometriosis is associated with dysmenorrhoea, menorrhagia and infertility. Pathogenesis of both is not clearly understood although many studies were being done. Hysterectomy is the last resort and for many youngsters this may not be an option as they want to conserve their fertility, at the cost of bearing cyclical psychological and physical trauma. This study was done to estimate the disease burden in our population and to highlight the need for targeted therapy for those aspiring women who want to conserve her fertility and suffer in silence.

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