CASE REPORT

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Isolated Eosinophilic Myometritis-A Rare Cause of Abnormal Uterine Bleeding in a Peri-menopausal Woman with Review of the Literature

Thotadamane Nagaraja CHANDRASHEKHAR[a], Sateesh S CHAVAN[b], Veena S HEMANT[a], Priyadharshini BARGUNAM[c], Diptanu SARKAR[a]

[a]Department of Pathology, Shimoga Institute of Medical Sciences, Karnataka, India
[b]Department of Pathology, Karnataka Institute of Medical Sciences, Karnataka, India
[c]Department of Pathology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

ABSTRACT This article documents a case of isolated eosinophilic myometritis (IEM) in a peri-menopausal woman presenting with abnormal uterine bleeding with a brief review of the literature. A 48-year-old peri-menopausal woman presented to the gynecology department with easy fatigability, abdominal pain radiating to the back of the leg, irregular cycles, dysmenorrhea, and menorrhagia for the last three months. The present case describes the histopathological findings of an IEM, without any kind of endometrial involvement or pathology in a peri-menopausal woman lacking a history of previous invasive procedure or intervention, allergic manifestation, or systemic disorder. IEM is a cause of abnormal uterine bleeding, which usually represents repair/regeneration-associated changes. Larger case studies are needed to explore the significance of eosinophils in myometrial inflammation or repair and to determine their role in IEM and other non-neoplastic lesions and the contribution of the individual subpopulations of eosinophils.

Keywords: Eosinophil; isolated myometritis; peri-menopausal; abnormal uterine bleeding

Myometritis, inflammation of the myometrium (exclusive), is rare and can be associated with endometritis.[1] Isolated idiopathic eosinophilic myometritis (IEM) is exceptionally rare, with few reported cases.[2,3] This case describes IEM in a peri-menopausal woman without endometrial involvement, invasive procedures, allergies, or systemic disorders. A brief literature review discusses tissue eosinophilia and myometritis mechanisms.

CASE REPORT

A 48-year-old peri-menopausal lady presented to the gynaecology department with easy fatigability, pain abdominal pain radiating to the back of her leg, irregular cycles, dysmenorrhea, and menorrhagia for the last three months. She had a tubal sterilization scar. She was P2L2 (para 2 and living 2) with her last menstrual period 10 days back. There was no history of previous surgical uterine intervention (cesarean section, dilatation, and curettage or endometrial biopsy).

Upon examination, the uterus appeared enlarged (16-18-week size) and anteverted. Speculum examination showed a healthy cervix with no tenderness or bleeding. Ultrasonography revealed a bulky uterus with thickened myometrium. Preoperative investigations, including various tests and screenings like Hemogram, Liver Function Test, Kidney Function Test, Thyroid function Test, serology workup, stool

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Correspondence: Priyadharshini BARGUNAM
Department of Pathology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India
E-mail: priyadharshiniankit@gmail.com

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test, Blood culture, Autoimmune serology, Echocardiogram, Chest X ray, and Chest Computed Tomography, were unremarkable (Table 1). A provisional diagnosis of Abnormal Uterine Bleeding (AUB) was made. Medical management being ineffective, the patient underwent a Pan-hysterectomy with preoperative transfusion.

Pathological Examination: Macroscopically, a specimen of pan-hysterectomy showed a uterus with cervix with bilateral fallopian tubes and ovaries, together measuring 10 cmx7.5 cmx4.2 cm. The cervix measured 3.5 cms in length. On the cut section, uterine cavity was obliterated by hypertrophied myometrium (Figure 1A); the cut surface showed thickened trabeculated myometrium (Figure 1B) and the endometrium was 1.2 cm thick. Ovaries and fallopian tubes were unremarkable.

Microscopically, endometrium was in the secretory phase (Figure 1C) with hypertrophied and hyperplastic myometrium showing foci of dense inflammatory cell infiltrate (Figure 2A) predominantly around smaller blood vessels (Figure 2B), and lymphatics (Figure 2C) sparing medial muscular and large arteries (Figure 2D). The inflammatory infiltrate was predominantly comprised of eosinophils and occasional resident mast cells (Figure 2E). The perivascular inflammation was limited to the inner half of myometrium and was decreasing towards the outer half. Eosinophils releasing their contents by degranulation processes were also noted (Figure 2F). Cervix (Figure 1D), Fallopian Tube (Figure 1E) and Bilateral Ovaries (Figure 1F) were unremarkable. With these findings, a diagnosis of IEM was made, which was an incidental finding in this case. Informed consent was obtained from the patient.

DISCUSSION

Tissue eosinophilia is observed in various human organs and experimental animals, including the spleen, digestive tract, mammary gland, serous membranes, connective tissues, and uterus.[1] Eosinophils, blood granulocytes, have a short half-life of 8 to 18 hours in circulation but can survive up to 2-4 weeks in tissues due to sustained release of factors like interleukin-5.[4]

They are involved in antigen presentation, inflammation via mediator release, responses to parasites, helminths, autoimmune disorders, and malignancies through degranulation and immune reactions.[5]

Eosinophils release their contents through various degranulation processes (Figure 2F) including classical exocytosis, compound exocytosis, piecemeal degranulation, and eosinophil cytolysis, these

TABLE 1: Summary of haemogram and laboratory investigations.

Investigations	Admission workup	Pre-operative day workup	Post-operative workup
Hb %	10.7 gm %	11.5 gm %	12.1 gm %
Total count	8,400 cells/cumm	10,050 cells/cumm	8,500 cells/cumm
Eosinophil count	6%	6.1%	6%
Absolute eosinophil count	512 cells/cumm	613 cells/cumm	510 cells/cumm
Platelet count	3.75 lakhs/cumm	4.79 lakhs/cumm	4.1 lakhs/cumm
Renal function tests	Urea-17 mg/dL, uric acid-3.5 mg/dL, creatinine-0.6 mg/dL		
Thyroid function test	Free T3-120 ng/dL, Free T4-1.2 ng/dL, TSH-2 m IU/L		
Liver function test	Albumin-3.8 g/dL, globulin-2.1 g/dL, total protein-5.9 g/dL, SGOT-12 U/L, SGPT-10 U/L, Alk phosphatase-43 U/L, total bilirubin-0.3 mg/dL		
Ultrasonography	Showed a bulky uterus with normal adnexae, endometrial thickness was normal, and no mass was identified. Fornices free from fluid		
Echocardiography	Normal, no regional wall or valvular abnormalities, ejection fraction-60%		
Serology	HIV, HbsAg, HCV-Neg, Na-141 mEq/L, K-3.8 mEq/L, Cl-101 mEq/L, RBS-124 mg/dL, Anti-nuclear antibody screen-negative		
Stool examination	Negative for ova and cysts of parasites		

HIV: Human immunodeficiency virus; HbsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; Na: Serum sodium; K: Serum potassium; Cl: Serum chloride; RBS: Random blood sugar.

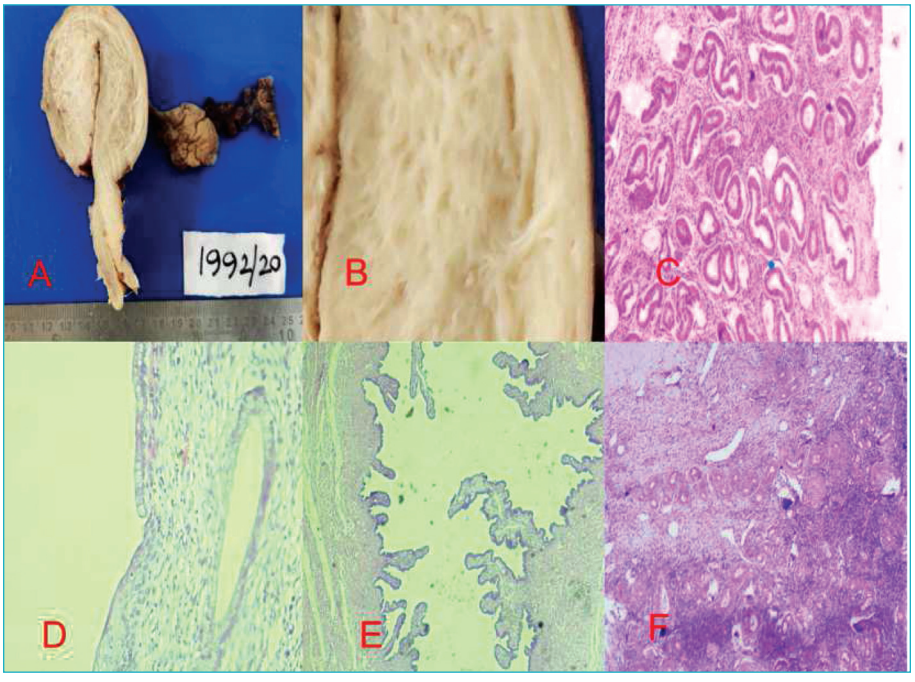

FIGURE 1: Gross specimen of the uterus showing hypertrophied **(A)** thickened trabeculated myometrium **(B)**, endometrium in secretory phase **(C)** [H&E, x10] without inflammation, unremarkable cervix **(D)** [H&E, x40]; unremarkable fallopian tube **(E)** [H&E, x40] unremarkable Ovary **(F)** [H&E, x20] and devoid of inflammation.

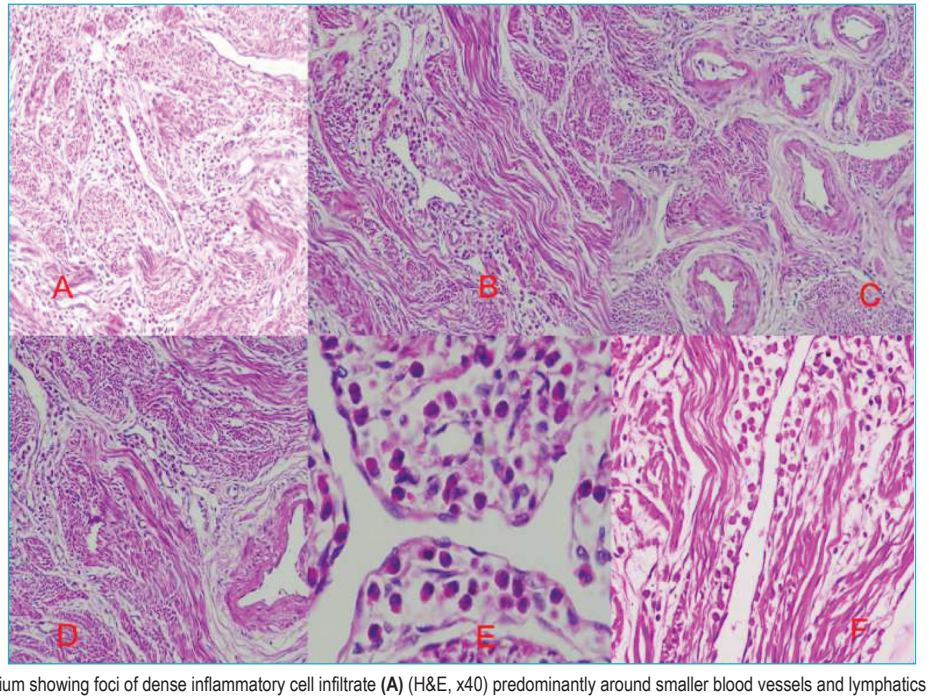

FIGURE 2: Myometrium showing foci of dense inflammatory cell infiltrate **(A)** (H&E, x40) predominantly around smaller blood vessels and lymphatics **(B)** (H&E, x40) sparing medial muscular and large arteries **(C)** (H&E, x40). Inflammatory infiltrate composed of eosinophils and occasional resident mast cells **(D)** (H&E, x40). Myometrium shows large vessels devoid of inflammation **(E)** (H&E, x40). Eosinophils showing degranulation **(F)** (H&E, x40).

processes are highly regulated and coordinated and are still yet to be understood completely.[6] Finally, eosinophils also release DNA nets or traps with intact free granules and this is a regulated pathway of extracellular trap cell death mediated by eosinophils, known as ETosis.[7]

The largest gynecologic uterine specimen series reported eosinophilia in 25 cases out of 2,542 specimens (0.98%) from the Sloane Hospital.[8] Eosinophilic inflammation represents a local allergic response, although highly selective, to the breakdown of tissue due to neoplasia, bacterial inflammation, blood clots, or previous surgical procedures.[8] In the present case, the patient was devoid of any neoplasia, bacterial inflammation, surgical intervention, or systemic, or autoimmune connective tissue disorder.

Our patient had abnormal, irregular excessive bleeding per vaginum with passage of clots which could be the possible trigger for mast cell degranulation and recruitment of eosinophils. The degree of eosinophilic inflammation indicates the response of tissue degradation products. Mast cells are predominantly situated in the mucosal, peri-vascular, and peri-lymphatic region leading to accumulation of eosinophils around these sites (Figure 2A to Figure 2F). Absence of endometrial inflammation can be attributed to shedding and repair of endometrial tissue. The present case also showed a decreasing gradient of eosinophilic inflammation inside out resulting in inflammation limited to the inner half of the myometrium with the outer half of myometrium and serosa devoid of eosinophils (Figure 2A to Figure 2F). Muscular and large arteries were devoid of inflammation as well (Figure 2E) ruling out systemic vasculitis. Eosinophils were found around the smaller blood vessels and lymphatics in our case (Figure 2A to Figure 2E), which could be an eosinophilic vasculitis. However, the lack of systemic complaints or symptoms (related to the cardiovascular system, renal system, gastrointestinal tract, skin, or nervous system) and the lack of evidence of any parasitic infestation or vasculitis, leaves us with the diagnosis of isolated tissue eosinophilia of the myometrium, besides, the endometrium was spared of eosinophils to support the diagnosis.[9] On the follow-up visit after six months, the patient had no postoperative complications or complaints, allergies, or any other system manifestation related to tissue eosinophilic infiltration.

Eosinophils are involved in a wide range of physiologic processes including the normal menstrual cycle and cervical post-labor extracellular matrix remodeling in mice models and further large-scale human studies are needed to determine the eosinophils and their subpopulations (E1 and E2) role. Eosinophil peroxidase (Epx) and major basic protein derived from degranulation play a role in epithelial cell activation and tissue remodeling factor expression.[10]

Similar cases were reported by Nandan et al. and Ghayeb Mohammad et al. in a peri-menopausal patient and a young patient, respectively (Table 2).[2,3]

In the absence of any known cause of tissue eosinophilia, the case can be treated as that of Isolated Eosinophilic Myometritis or Eosinophilic Myometropathy. For patients in whom no underlying disease or hyper-eosinophilic syndrome is found, the term hypereosinophilia of undetermined significance is introduced.[11] It is a rare yet significant cause of abnormal uterine bleeding with bulky uterus in the perimenopausal age group and histopathological examination helps rule out other causes of bulky uterus like fibroids, adenomyosis, and endometrial carcinoma. It is almost impossible to make a pre-operative diagnosis of these conditions as curettage doesn't allow sampling of the myometrium. Biochemical tests and immune-markers are also not specific to make a pre-operative diagnosis of IEM. Hence, targeted medical management and the non-surgical treatment options are not reported in the literature and were not attempted in the current case as well.

Tumor-associated blood eosinophilia is associated with tumor spread and a poor prognosis, whereas, tumour-associated tissue eosinophilia in tumor microenvironment plays an important role in tumor progression and results in better overall survival in certain cancers such as esophageal carcinoma and colorectal cancer and is inversely associated with lymph node metastasis, tumor stage, and lymphatic invasion of cancer.[12-15]

IEM is a cause of AUB, which usually represents repair/regeneration-associated changes. Larger case studies are needed to explore the significance of eosinophils in myometrial inflammation or repair and to determine their role in IEM and other non-neo-

TABLE 2: A summary of published cases of isolated eosinophilic myometritis.

Study	Age (yrs)	Presentation	Duration (months)	Previous uterine intervention	Blood eosinophil count	Systemic diseases
Mohammad et al.[2]	31	Infertility, abnormal uterine bleeding, and dysmenorrhea	--	LSCS-Nil D&C-Nil	Normal	NIL
Nandan et al.[3]	48	Moderate pain in the lower back, and mass in the lower abdomen.	5	LSCS-24 years back D&C-Nil Posterior wall fibroid 6x5x4.7 cms	Normal	NIL
The present case	48	Easy fatigability, abdominal pain radiating to the back of the leg, irregular cycles, dysmenorrhea, and menorrhagia	3	Tubal sterilisation-18 years back. LSCS-NIL D&C/curettage-NIL	Normal	NIL

LSCS: Lower segment caesarean section; D&C: Dilatation and curettage.

plastic lesions and the contribution of the individual subpopulations of eosinophils. Studies are needed to establish a pre-operative diagnosis of this condition and medical management of IEM, hence preventing hysterectomy in these women.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Thotadamane Nagaraja Chandrashekhar, Sateesh S Chavan, Veena S Hemant;* ***Design:*** *Veena S Hemant, Sateesh S Chavan;* ***Control/Supervision:*** *Thotadamane Nagaraja Chandrashekhar, Sateesh S Chavan;* ***Data Collection and/or Processing:*** *Priyadharshini Bargunam, Diptanu Sarkar;* ***Analysis and/or Interpretation:*** *Thotadamane Nagaraja Chandrashekhar, Veena S Hemant;* ***Literature Review:*** *Priyadharshini Bargunam, Diptanu Sarkar;* ***Writing the Article:*** *Thotadamane Nagaraja Chandrashekhar, Priyadharshini Bargunam;* ***Critical Review:*** *Priyadharshini Bargunam, Diptanu Sarkar;* ***References and Fundings:*** *Thotadamane Nagaraja Chandrashekhar, Sateesh S Chava;* ***Materials:*** *Thotadamane Nagaraja Chandrashekhar, Sateesh S Chavan.*

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