ORIGINAL RESEARCH

Granulomas of the Female Genital Tract: A Case Series with Review of Literature

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Received: 22 December, 2023

Accepted: 14 January, 2024

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The extensive family of granulomatous diseases all share the histological characteristic of granuloma. A granuloma is a form of chronic inflammation characterized by the collection of activated macrophages and T lymphocytes, with or without necrosis. It typically develops as a result of the persistence of an offending agent and active cellmediated hypersensitivity. Invading organisms or protracted antigenemia, a Th1 cell response, macrophage activity, B cell overactivity, and a wide range of biological mediators all interact in intricate ways in the formation of a granuloma.¹

Granulomatous conditions in the female genital tract are quite uncommon. The causes can be infectious and non-infectious. The infectious causes are Tuberculosis, atypical mycobacteria, actinomycosis, fungal infections, cytomegalovirus, and parasitic infections. The non-infectious causes are surgical procedures/instrumentation, foreign bodies, systemic disorders such as sarcoidosis, giant cell arteritis and other systemic vasculitis Crohn's disease, medications, lymphoma, and other neoplastic conditions.^{2,3} In some cases, it is cryptogenic.^{2,3} Granulomas in the ovary and fallopian tube are more frequently encountered. Very rarely malakoplakia of the fallopian tube causes granulomatous granulomas inflammation.⁴ The Uterine are uncommon and often incidental findings in histopathological examination.² Granulomatous lesions occurring in the cervix is rare.5

We reported eight cases over a period of 2 years from August 2021 to July 2023 in Bangalore Medical College and Research Institute; two cases of granulomatous salpingitis, two cases of Tuberculous salpingo-oophoritis, two cases of granulomatous endometritis, a case of granulomatous cervicitis and a case of Tuberculous vulval ulcer in the Department of Pathology, Bangalore medical college and research institute.

CASE 1

A 24 year old nulligravida presented with infertility since one year and lower abdominal pain since two months. Per abdominal and per speculum examination did not yield any significant findings. Ultrasonogram revealed features of hydrosalpinx. Salpingectomy was done after a course of antibiotics, and the specimen sent for histopathological examination. Grossly the fallopian tube measured 5 cm in length. External surface was dilated and congested. Microscopic examination of the sections showed structure of fallopian tube with dense lymphocytic infiltrate, histiocytes and epithelioid cells forming granulomas with few multinucleated giant cells. Focal area of necrosis identified. Ziehl Neelsen Stain (ZN stain) for Acid Fast Bacilli (AFB) was negative. Final impression was given as Granulomatous salpingitis. Subsequently, Xpert® MTB/RIF assay (CBNAAT-Cartridge Based Nucleic Acid Amplification testing) was performed on tissue extracted from formalin fixed paraffin embedded blocks (FFPE). M. tuberculosis (MTB) was not detected in the test. The patient followed up after 3 weeks, symptomatically improved, not taking antituberculosis treatment.

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Figure 1: Structure of fallopian tube showing well-formed granulomas in the muscularis (10x). High power view of the granuloma composed of epithelioid cells. Numerous giant cells can be seen (blue arrows). Area of necrosis(black arrow)

A 27 year old female complaining of fatigue and weight loss since 6 months, presented to the casualty with acute abdominal pain. Exploratory laparotomy and salpingectomy done in view of clinical suspicion of tubal ectopic gestation. Patient's grand father had history of Tuberculosis (TB) 2 years back and patient was residing in the same home with him. Fallopian tube sent for histopathological examination. Grossly the fallopian tube appeared dilated and enlarged, measuring 4 cm in length. Rupture site along with blood clot noted on the external surface. On serial sectioning, extensive areas of hemorrhage seen, no gestational sac identified. Microscopic examination of multiple sections revealed structure of fallopian tube with complex branching architecture of tubal plicae with fusion of plicae. Many epithelioid cell granulomas are noted in the fibrovascular core of the papillae. Focally large areas of hemorrhage with presence of chorionic villi lined by trophoblastic cells are noted. Plicae are lined by single layer of columnar epithelium with pseudostratification. ZN stain for AFB was negative. Final histopathological diagnosis was Tubal ectopic gestation with granulomatous salpingitis showing evidence of complex tubal hyperplasia without atypia. FFPE tissue was sent for, Xpert® MTB/RIF assay, MTB not detected in the test. On follow-up after 4 weeks, the patient is not on antituberculosis treatment, symptomatically improved.



Figure 2: Fallopian tube showing muscular layer and complex branching tubal plicae with well-defined granulomas. Chorionic villi are seen amidst extensive areas of hemorrhage (bottom left figure).

A 45 year old female presented with abdominal pain, amenorrhea and weight loss since 4 months. Ultrasonography revealed right complex ovarian cyst. Intra operatively, a solid cystic tubo-ovarian mass identified on the right side. Total abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy done and sent for HPE. Received cyst wall, uterus cervix with attached left fallopian tube and ovary, separately sent right ovary and omentum. Uterus cervix measures 10x5x3cm, external and cut surface of both uterus and cervix appeared unremarkable. Endometrial thickness was within the normal limits. Left ovary measure 1.5x1.0x0.5 cm, external and cut surface appeared unremarkable. Left fallopian tube measures 3 cm in length, and appears unremarkable. The right ovary is enlarged, appears globular, and measures 8x4x2 cm. Cut surface of the

ovary is grey-white with central necrotic area. The cyst wall is received in multiple grey-brown bits varying in size from 1.5x1x1 cm to 0.5x0.5 cm. Omentum measures 3x2x1 cm, grossly appearing unremarkable. On microscopic examination, the right ovary and cyst wall showed ovarian stroma with dense inflammatory cell infiltrate composed of lymphocytes and histiocytes. Multiple well-formed epithelioid granulomas are noted. At places, there are areas of caseous necrosis. Sections from the uterus appeared normal with endometrium in proliferative phase. The cervix showed nonspecific chronic inflammation with squamous metaplasia and Nabothian cyst. The left ovary and fallopian tube are unremarkable. Sections from the omentum showed focal panniculitis. No granuloma seen in the omentum. The stain for AFB was Positive in the sections from tubo-ovarian mass.



Figure 3: Ovarian tissue showing multiple well formed granulomas- 4x (Top right). Low power view of a granuloma showing epithelioid cells and lymphocyte cuffing (Top left). High power view of a granuloma. Caseous necrosis- low power view (Bottomleft)

25 year old nulligravida presented to the (Out Patient Department) OPD with irregular menstrual cycles, menorrhagia and dysmenorrhea since around 6 months. Patient's mother had history of pulmonary Tuberculosis, which is treated and cured 2 years back. Clinical examination revealed left forniceal fullness. Ultrasonography revealed a solid cystic mass in the left pelvis measuring 10x3.5x1cm, adhering to the left fallopian tube and ovary. The Right adnexa, uterus and cervix appears to be normal. There is minimal free fluid in the Puch of Douglas. Exploratory laparotomy, left salpingo-oopherectomy done and specimen sent for histopathological examination. Here at the laboratory, we received endometrial biopsy and tubo-ovarian mass. The tubo-ovarian mass measures 10x3.5x1cm, solid and cystic on the external surface with adherent fimbrial end of the fallopian tube. External surface of the cyst appears shaggy and grey white. On cut section of the mass show grey-white to grey brown solid areas with necrotic material and secondary cystic degeneration, adjacent ovarian

parenchyma is made out, showing multiple small follicles largest measuring 0.5x0.5 cm. The fallopian tube measures 1.2 cm in length and grossly appear unremarkable. Microscopic examination of sections from the tubo-ovarian mass show ovarian tissue with presence of epithelioid cell granulomas showing epithelioid cells, histiocytes, lymphocytes and giant cells. Cortical surface also shows epithelioid granulomas. Sections from Fallopian tube is unremarkable. ZN satin stain for AFB did not identify any bacilli. The endometrial biopsy show tubular glands and stroma with maintained gland to stromal ratio (proliferative phase). No granulomas or atypia seen. The diagnosis given as Granulomatous oophoritis with unremarkable Fallopian tube and endometrium in proliferative phase. The endometrial biopsy and sputum sent for CBNAAT did not detect any bacilli. The patient is followed up for 2 months. She is given anti tubercular therapy (ATT) on clinical and radiological suspicion, immediately after surgey. Patient has symptomatically improved after starting ATT.



Figure 4: Ovarian tissue showing multiple well formed granulomas- 4x (Top and lower right). High powerview of a granuloma showing epithelioid histiocytes (blue arrow), and Langhan's giant cells (red arrow).

A 29-year-old female presented with secondary amenorrhea and secondary infertility since two years. On per-abdominal and bimanual examination, the uterus appeared bulky (16 weeks size) with irregular contours. The cervix and vagina were healthy on per-speculum examination.

Mantoux test showed a response of 40 mm (Positive). The Ultrasonogram revealed bulky uterus with multiple uterine fibroids; the largest in the sub-serosal location. A cystic lesion identified in the left ovary, measuring 3.3x2.4 cm. Right ovary was not visualized. Pouch of Douglas was clear. HPE of endometrial curettage showed fragmented endometrial tissue with tubular and endometrial glands and

compact stroma. Multiple well defined epithelioid cell granulomas with epithelioid cells, histiocytes, multinucleated giant cells, lymphocytes and a small focus of necrosis. No atypical cells seen. A small fragment of endocervical tissue noted. Stain for AFB was negative and CBNAAT did not detect M.tuberculosis. On strong clinical suspicion of tuberculosis, a rebiopsy was sent which revealed granulomatous endometritis with AFB stain being positive. Xpert[®] MTB/RIF assay detected Mycobacterium tuberculosis resistant to Rifampicin. On follow up at 6 weeks, and at 5 months the patient is being treated for Tuberculosis with first line drugs, not resumed menstruation.



Figure 5: The endometrial biopsy showing endometrial tissue, composed of endometrial glands and stroma. Granuloma and Langhan's giant cells are highlighted with blue and red arrows respectively. A cystically dilated endometrial gland is also seen (top right figure). Also seen is a small focus of necrosis and Langhan's giantcells. (Top left figure)

A 23 year old female P1L1, complaining of abdominal pain, fatigue and weight loss and post coital bleeding since 6 months. No history of dyspareunia. She has regular menstrual cycles, associated with dysmenorrhea. On examination, Patient is poorly nourished and has anemia, speculum examination revealed minimal bleed noted through the cervical os (Day 3 of menstrual cycle). No other significant abnormalities noted. Ultrasonographic findings of abdomen and pelvis are as follows; Right ovary enlarged in size. Endometrial thickness is increased to16.5 cm. Right adnexa shows ill defined echogenic area measuring 3.4x3.3 cm. The plane between the lesion and fundus of uterus is ill defined. Left ovary is enlarged, shows an ill defined cystic lesion measuring 4.0x3.0 cm with thin septations within. Minimal free fluid noted in the pouch of Douglas with internal echoes. There was mild hepatosplenomegaly. CT abdomen and pelvis revealed tubular and cystic enhancing lesions with septations in bilateral adnexa, mild ascites with nodular enhancing peritoneum. Diffuse thickening of omentum and mesentery noted with multiple tiny enhancing nodules. There is mild dilatation of proximal and mid thirds of transverse colon with pericolonic fat stranding. On clinical suspicion of tuberculosis, Mantoux test was done, which gave a positive result with 20mm area of induration and erythema. Endometrial biopsy was sent for histopathological examination and Xpert® MTB/RIF assay. Histopathological examination revealed segment of endometrial tissue with epithelioid cell granuloma showing epithelioid cells, foreign body and Langhan's type of giant cells, histiocytes and lymphocytes. Small focus of necrosis in some of the granulomas are showing neutrophils. Endometrial

glands appear tubular and elongated with some of the glands showing infoldings and outpouchings. Few glands show clear cell change. Stroma appear compact with thin-walled blood vessels. Gland to stromal ratio is maintained. Stain for AFB is Negative. Xpert® MTB/RIF assay of endometrial biopsy did not detect MTB. Culture for M. tuberculosis yielded no growth even after 6 weeks. On follow up after 3 weeks, patient has started ATT on high clinical suspicion, and improved symptomatically in terms of reduction in pain and fatigue and weight gain.



Figure 6: The endometrial biopsy showing endometrial tissue, composed of endometrial glands and stroma.Granulomas are highlighted with blue arrows, foreign body type giant cells are also seen (orange arrow). Endometrial glands showing infoldings and outpouchings (red arrow) is also seen (bottom right figure). Well-formed epithelioid cell granuloma (bottom left figure)

CASE 7

A 44 year old female, P1L1 with the history of previous Lower Segment Cesarian Section (LSCS), postmenopausal status since 2 years and Type 2 diabetes mellitus presented with foul-smelling vaginal discharge and clinically diagnosed as atrophic endometritic pyometra. HPE of the endometrial curetting sent revealed endocervical tissue lined by a single layer of columnar epithelium. Endocervical stroma shows many epithelioid cell granulomas, Langhan's giant cells, histiocytes and lymphocytes. Stain for AFB is negative. Further information could not be retrieved as patient lost for follow up.



Figure 7: The low power(100X) view of the biopsy showing endocervical tissue lined by a single layer of columnar epithelium containing mucin. The stroma shows multiple well-defined granulomas (black arrows) and Langhan's giant cells (red arrow). A high power view (400X) showing well-formed granuloma composed of epithelioid cells, histiocytes, multinucleated giant cells and lymphocyte cuffing.

A 36 year old female patient presented with loss of consciousness secondary to hypoglycemia. On clinical examination, she had a vulval ulcer, right axillary and inguinal lymphadenopathy. Ultrasonogram revealed multiple matted lymph nodes in the axillary and inguinal region with necrosis and loss of fatty hilum. Bilateral breasts appeared normal. Edge biopsy from the vulval ulcer was taken and sent for histopathological examination. The microscopic examination of ulcer edge biopsy revealed skin with

stratified squamous epithelium showing acanthosis. Sub epithelium showed numerous well-defined granulomas composed of epithelioid cells, Langhan's giant cells and lymphocytes. Dense lymphocytic infiltrate all over the dermis is noted. Stain for AFB was Positive. Final histopathological diagnosis made as vulval granulomatous lesion of Tubercular origin. FFPE tissue was sent for Xpert® MTB/RIF assay and MTB was not detected. Patient was followed up after 4 months. She started anti tubercular therapy and is symptomatically improved.



Figure 8: Ulcer edge biopsy showing stratified squamous epithelium thinned out and eroded with subepitheliumshowing dense lymphocytic infiltration and granulomas. Acanthosis is evident (bottom left figure). High power view of granuloma in the dermis (bottom right figure).

DISCUSSION

Female genital tract granulomas can be localized or diffuse. While diffuse granulomas can be caused by infections, systemic disorders, or occasionally idiopathic causes, focused granulomas are more frequently the result of prior surgical intervention or instrumentation.²

The most prevalent cause of female genital tract disease is TB.⁶ The highest - risk factor to contract genital TB is regarded to be the reproductive age group.⁷ Amenorrhea, irregular menstrual cycles, infertility, vaginal discharge, and postmenopausal bleeding are frequent presentations of tuberculosis of the female genital tract.⁷ 90–100% of tuberculous pelvic infections in India occur in the fallopian tube, and 50–80% of these infections extend to the uterine endometrium. Less frequently, between 20 and 30 percent of the time, microorganisms may be found in the ovary, cervix, vagina, and vulva.^{6, 7} The most common mode of spread is hematogenous, although

there is also evidence of direct dissemination from other abdominal organs, and the peritoneum, and ascending infection from the vulva and perineum.⁷ According to Turkmen et al, infertility resulting from genital tuberculosis is predominantly due to the endometrial involvement, thus resulting in impairment in implantation.⁷

As stated before, the most common location of female genital tuberculosis is the fallopian tube. In ovarian tuberculosis, peri-oophoritis and oophoritis are the two patterns that are seen. The infection in peri-oophoritis progressed from the fallopian tube to the tunica and ultimately the ovarian parenchyma. As a result, often a tubo-ovarian mass is formed adhering to the omentum and intestines. Rarely, ovarian parenchyma can become infected with tubercle bacilli through hematogenous dissemination, resulting in oophoritis.⁸

Tuberculous salpingitis is usually composed of noncaseating granulomas. In later stages, single or numerous confluent granulomas in the lamina propria can be seen. The microscopic features of tuberculous oophoritis are cortical non-caseating granulomas (peri-oophoritis pattern).⁹ The diagnosis of tuberculosis is confirmed when AFB is found using Ziehl-Neelson staining, Nucleic Acid Amplification Tests, or culture.^{8,9}

Most of the time, the gross characteristics of tuberculous endometrium are near normal, most likely as a result of the monthly shedding. In cases of severe involvement, lesions that are ulcerative, granular, or fungating may be present, or intrauterine adhesions may completely obliterate the endometrial cavity. The macroscopic appearance can occasionally resemble cancer.⁹

Although TB of the endometrium is similar to TB in other tissues, the classical features of caseation and late features such as fibrosis and calcification are rarely seen during reproductive age. 7,9 The noncaseating granuloma, which is made up of lymphocytes, Langhans giant cells, and epithelioid cells, is the typical lesion in tuberculous endometritis. While present throughout the endometrium, these granulomata are more prevalent in the layers that are closer to the surface and fundus. On rare occasions, they pierce into the gland lumina, producing an acute inflammatory response and the formation of microabscesses.

Granulomatous endometrial glands may not show secretory activity or they may get compressed, giving them a pseudo-adenomatous appearance. The cycle days 24-26 or the first 12 hours within the start of menstruation are typically the ideal times to detect the granulomatous lesions. ^{9,10}

Granulomatous cervicitis is mostly caused by tuberculosis in India⁵ whereas in the western countries, it is mostly after previous surgery or instrumentation.⁷ The incidence of cervical involvement in female genital tract TB is 5–15%.¹⁰ Systemic granulomatous or vasculitic disorders can also cause uterine or cervical granulomas.^{2, 11} Other organisms, such as fungi and Schistosoma, may result in uterine or cervical granulomas.¹² Rarely, granulomatous inflammation of the cervix has been attributed to chlamydia infection.⁴

The gross appearance of the tuberculous cervix is highly variable. It can be ulcerative, papillary, miliary, interstitial, velvety, endocervical, or polypoid forms and at times show no visible gross features.^{7,9} Most commonly seen are ulcerative lesions.⁹ In some cases, the lesions may mimic malignancy.⁹ Histopathologic examination reveals granulomatous inflammation sometimes associated with marked reactive atypia and mucosal hyperplasia. Caseation may be seen. Endocervical involvement is common and usually results in an increased secretion of mucin.⁹ Tuberculosis can be diagnosed in cytopathological examination (PAP smear) as well. The cytological features of cervical TB are clusters of histiocytes, epithelioid cells, and multinucleated giant cells simulating the appearance of the granuloma. There may be associated reactive epithelial atypia.⁹ Bacteriological examination can be done on tissue specimens, cytological specimens as well as cervical mucin.⁷ Previous diathermy to the endometrium or the cervix can result in granulomatous inflammation, the granulomas typically contain central necrobiotic material, mostly associated with brown or black pigment, surrounded by histiocytes and giant cells.⁵

The gross features of cervical sarcoidosis are erosions. In the majority of cases, it is diagnosed by endometrial or endocervical curettage, but it has also been detected by examination of polypectomy, hysterectomy, and autopsy specimens. Nonnecrotizing granulomas are the characteristic pathologic finding of sarcoidosis.¹¹

In females, the cervix is the most common site of infection by S. haematobium. Infection manifest as granulomatous cervicitis. Detecting schistosome eggs in cervical tissue by any of the methods such as cytological examination of a cervical smear, histopathological examination of a cervical biopsy, and direct examination of cervical tissue obtained by quantitative compressed biopsy technique (QCBT) confirms the diagnosis.¹²

Postmenopausal pyometra occurs due to cervical canal stenosis which mostly occurs at the internal os. The causes are infection, neoplasia and factors such as prior surgeries or radiation therapy.¹³

In the second case discussed above, we got endocervical curetting instead of the intended endometrial biopsy, indicating cervical stenosis. The superficial location of multiple granulomas and the presence of Langhan's giant cells in the granuloma favor tuberculosis which has to be confirmed by bacteriological or molecular tests. Since the patient had a prior intervention, the granulomatous response elicited by the prior surgery to be ruled out.

Of all forms of tuberculosis of female genital tract, lesions of vulva are the least frequent (1-2%).^{6,7,14} The clinical and gross features can be quite variable and a vulval tubercular ulcer may be misdiagnosed as sexually transmitted disease like syphilis or chancroid.¹⁴ Other differential diagnoses of granuloma in the vulva are granulomatous vulvitis associated with Chrons disease, sarcoidosis.^{15,16} A case of Superficial granulomatous pyoderma is reported in a patient receiving rituximab for lymphoma.¹⁷

ZN stain helps to detect Acid Fast Bacilli in tissues and smears. It is simple, economical, and fast. A positive ZN test requires greater than 106 bacteria/gram tissue, so it is of limited diagnostic value in the majority of pauci-bacillary samples. Polymerase Chain Reaction (PCR)-based assays such as CBNAAT have been found to be more helpful in ruling in rather than ruling out a diagnosis of tuberculosis.¹⁸

The Xpert® MTB/RIF assay (United States) is an automated real time PCR in which sample lysis, DNA

extraction, amplification and detection happens within a single plastic cartridge. The assay takes about 2 hours and detects the presence of the M. tuberculosis complex and rifampicin resistance.¹⁹

A study published in 2017 by Polepole et al. found Xpert® MTB/RIF assay is useful for the diagnosis of tuberculosis in FFPE tissues. However, the sensitivity was found to be too low in both lymph nodal and non-lymph nodal tissues (30% and 35% respectively) when compared with histology. ²⁰

A study published in 2019 found that the sensitivity of ZN staining was 20.3% and the sensitivity of the Xpert® MTB/RIF assay was 53.2% in FFPE tissues considering histopathological diagnosis as the gold standard. The quality of DNA is also likely to have been reduced due to the untoward effects of formalin

fixation.18

DNA extraction from FFPE tissues is a sophisticated procedure that relies on differential solubility to purify DNA. The quality and quantity of the extracted DNA and the success of further DNA amplification are dependent on a number of parameters before, during, and after extraction. These include, but are not limited to the type of fixative used, the duration of fixation, type and amount of tissue, age of the block and storage conditions, also the length of the DNA segment to be amplified. ²¹

The low sensitivity of Xpert® MTB/RIF assay compared to the ZN stain observed in our cases could be attributed to the above-said factors which might have affected the DNA extraction at least in some of the cases.

LIST	OF ABBRE	VIATIONS

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Conflict of Interest: None Funding Source: Nil

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2233-5188 · eISSN 2233-5196

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