Case Report

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Pathology Section

Co-existent Ovarian Tuberculosis with Borderline Serous Cyst Adenoma in an Infertile Young Female: A Case Report

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ABSTRACT

Genital tuberculosis involving the ovary in young non immunocompromised females is rare, and its coexistence with serous neoplasm makes it even rare and diagnostically challenging. A 32-years-old female patient, presented with primary infertility and abdominal pain. Menstrual history was unremarkable; her Ultrasound (USG) abdomen revealed an anechoic cyst in left ovary with normal right ovary, uterus, and cervix. Serum Carbohydrate Antigen (CA)-125 was 226 IU/mL. Laparotomy with cystectomy was performed, and gross examination revealed a cystic lesion with a small papillaroid growth. Microscopic examination predominantly displayed large coalescing epithelioid granuloma, multinucleate giant cells, and dense inflammation. On careful examination, the sections further revealed areas of irregular glands lined by single layer of cuboidal columnar cells with homogenous chromatin and moderate eosinophilia cytoplasm. These glands were seen infiltrating the ovarian parenchyma. However, the total depth of invasion was not more than 3 mm in any area. Morphological differentials of granulomatous lesion with borderline ovarian tumour or any metastatic adenocarcinoma was made. Further immunohistochemical workup was done and the tumour cells showed strong nuclear positivity for Wilms' Tumor suppressor gene1 (WT1) and Paired-box gene 8 (PAX8), confirming the presence of serous ovarian lesion. As the total depth of invasion was upto 3 mm according to World Health Organisation (WHO) 2020 the lesion was classified as borderline serous neoplasm with microinvasion over shadowed by the tubercular component in the same ovary. Interestingly, both may result infertility in a young female. Above case emphasises on the importance of careful morphological assessment in delineating two different pathologies occurring in same organ which is clinically relevant.

Keywords: Genital tuberculosis, Immunohistochemistry, Serous ovarian neoplasm

CASE REPORT

A 32-year-old female patient, P0+0 with unremarkable menstrual history, presented with inability to conceive even after 2 years of unprotected sex. She also complained of pain in lower abdomen for one year along with off and on burning micturition and dyspareunia. There was no accompanying history of loss of appetite, cough, weight loss, evening rise of temperature, bleeding per vagina or antitubercular treatment given to patient in past. She also reported that she had no family history of tuberculosis or contact with an active tubercular case. Abdominal examination was unremarkable. On per speculum, curdy white discharge was seen. A mass could be palpated through the anterior fornix, which was cystic in consistency, mobile and tender.

On abdominal ultrasound, an anechoic cyst (size: 7.6×7.3 cm and volume 191 cc) was identified in the left ovary. Right ovary was normal in size and echo texture. No free fluid was seen in the cul-de-sac. The uterus was also normal in size, anteverted and antiflexed. Cervix and vagina were normal.

The patient had undergone hysterosalpingography two months back which showed patent lumens with no compromise. Urine examination showed the presence of few red blood cells with few pus cells. Preoperative electrocardiogram, chest X-ray, renal and liver function tests showed the normal result. Serum Carbohydrate Antigen (CA)-125 was raised (226 U/mL), while other ovarian markers were within the normal limit. As the CA-125 was raised, but not in levels of thousands, with radiological correlation, the pre-operative clinical diagnosis of benign cystic lesion with differential of serous or mucinous cystadenoma was made.

Hence, open laparotomy with cystectomy was planned and performed. On laparotomy, abdomen and fallopian tubes were normal preoperatively.

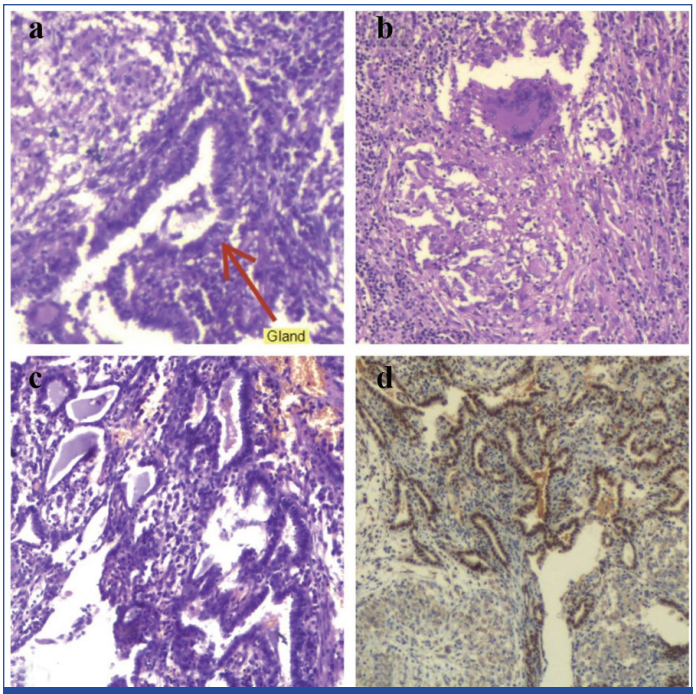
Histological sample: Authors received a single unoriented greyish brown ovary measuring 6×5.5×1.5 cm with attached fallopian tube stump measuring 4 cm. The outer surface was smooth and congested at places. On cutting, the cut surface was predominantly cystic with few solid areas.

Sections showed dense inflammation, well-formed epithelioid granulomas, and multinucleated giant cells along with haemorrhagic areas at places [Table/Fig-1a,b]. Within these dense granulomas, some irregular glands could be appreciated. These glands were lined by cuboidal to low columnar cells with round nuclei, dense homogenous, chromatin, and abundant eosinophilia cytoplasm. In one section a focus of infiltration was identified [Table/Fig-1c]. Overall depth of stromal invasion was found to be 3 mm. Section from attached fallopian tube was largely unremarkable, no granuloma of fibrosis was identified in its wall. The above morphology supports two pathologies:

- First was an infiltrative epithelial tumour which could be either primary ovarian epithelial neoplasm possibly, borderline with microinvasion or a metastatic adenocarcinoma to ovary.
- Second pathology was presence of granulomas which could be either due to tuberculosis, foreign body, etc.

As far as the granulomas were concerned morphologically, they were large and coalescing with central necrosis accompanied by Langham's type giant cells. No foreign body was identified, hence the probability of tuberculosis was considered. To confirm the presence of tubercular bacilli, Ziehl Neelsen staining was performed which was positive for acid fast bacilli.

With respect to the infiltrative epithelial component, the cytoplasm was eosinophilia predominantly; there was no evidence of intracellular or glandular mucin. To confirm that, it was serous tumour WT1 Immunohistochemistry (IHC) was performed. PAX 8 was performed to establish that the tumour was primary ovarian rather than a



[Table/Fig-1]: Haematoxylin and eosin-stained section in scanner view (H&E x40) shows granulomas with central necrosis (a) with infiltrating gland (arrow) the irregular outline of gland can be appreciated once looked carefully. In (b) a well-formed granuloma can be seen with Langhans type giant cell (H&Ex100). In (c) (H&Ex400) irregular glands infiltrating the ovarian stroma are seen; overall infiltrative component was <5 mm. The infiltrative component is highlighted by Wilms Tumor protein 1 (WT1) nuclear expression by serous cells in (d) (DABx200) DAB-3,3'-Diaminobenzidine.

metastatic one. Moreover, WT1 IHC [Table/Fig-1d] highlighted the glandular component so well that the correct depth of invasion could be better determined in IHC slides as compared to haematoxylin and eosin sections. The case was thus diagnosed as borderline serous neoplasm with microinvasion and ovarian tuberculosis.

The surgical excision performed was curative for the patient for borderline serous tumour; so no further management was done in this regard. The patient was started on antitubercular regime two-month course of the drugs rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) and a daily four-month therapy of the drugs rifampicin (R) and isoniazid (H) for her tuberculosis. Her treatment course was uneventful. After complete compliance of her treatment, she is now attending reproductive clinic for conception.

DISCUSSION

Dual pathologies have been reported in the past. They have important pathological and clinical implications as the intermingled pathogenesis affect the patient's treatment. Morphologically, one pathology may be overshadowed by the other. In the above section, the authors have reported a case of ovarian tuberculosis within borderline serous cyst adenocarcinoma in a young female presented in outpatient clinic for treatment of primary infertility.

India harbours high burden of tuberculosis (TB) globally, having an estimated incidence of 100-299/lakh per year in 2020, as per dynamic model estimation [1]. As far as genital TB is concerned, about 12% of women with pulmonary tuberculosis and 15 to 20% of women with Extrapulmonary Tuberculosis (EPTB) are affected [2]. The most typical site of involvement is the fallopian tubes in 90-100%, followed by endometrium (50-80% of the cases), while the ovaries are involved in 20-30% of cases of genital TB [2].

Symptomatology of Genital tuberculosis is not very specific. Approximately 11% of women with genital TB may be asymptomatic. The clinical presentation of genital tuberculosis may be non specific, and few atypical symptoms related to other gynaecological conditions may be predominant like menstrual irregularities, poor general condition, puberty menorrhagia and even symptoms, clinically consistent with malignancy [2].

The determination of the locus of the malignancy in cystic ovarian neoplasm requires histopathological confirmation. However, synchronous occurrence of infection and malignancy in same ovary may present a significant diagnostic challenge. Serous borderline tumour is a non invasive, low grade proliferative serous epithelial neoplasm with stromal invasion less than 5 mm in greatest dimension in a single focus [3].

After an extensive search of the published English literature, the authors found no account of borderline serous cyst adenoma and concomitant tuberculosis infection in the ovary. Chhabra S et al., summarised 11 cases of neoplastic aetiology with concomitant granulomatous pathology. The granulomas may be either due to TB or a T-cell mediated immunological response to cell surface antigens, which occurs due to soluble tumour-related antigen reaching the draining nodes [4]. The reported cases of tuberculosis bacilli with epithelioid granuloma concomitant with ovarian neoplasm are summarised in [Table/Fig-2] [4-11] the findings in these cases suggest that genital TB may be considered for young women with an adnexal mass. Genital tuberculosis usually occurs as a secondary involvement. The transmission usually occurs via lymphatic or haematogenous spread, sexual transmission of genital tuberculosis has also been noted [7-9]. In the present case, no clinical history suggestive of pulmonary tuberculosis was identified neither the patient gave any history of contact with an active tubercular case. Her chest x-ray was largely unremarkable. Computed Tomography (CT) chest was not performed. This was quite unusual; however asymptomatic genital tuberculosis is a known occurrence.

Authors	Number of cases	Findings
Ilhan AH and Durmuşoğlu F [5] 2004	1 case	Ovarian tuberculosis
Chhabra S et al., [4] 2009	11 cases	Authors discussed ovarian stromal granulomas and its pathogenesis and suggested that stromal granulomatous reaction in the absence of tuberculosis represents a T-cell mediated immunological response to cell surface antigens, which occurs due to soluble tumour-related antigen reaching the draining lymphnodes.
Yassaee F and Farzaneh F [2] 2009	3 cases	Ovarian tuberculosis
Rabesalama S et al., [6] 2011	1 case	Isolated ovarian tuberculosis with raised CA-125 levels
Lobo FD and Wong MY [7] 2013	1 case	Ovarian tuberculosis with benign serous cystadenoma
Bhardwaj S et al.,[8] 2017	1 case	Ovarian tuberculosis with struma ovarii with benign serous cyst adenoma
Gudu W, [9] 2018	1 case	Isolated ovarian tuberculosis
Fahmi MN and Harti AP [10] 2019	3 cases	Ovarian tuberculosis
Yang S et al., [11] 2020	1 case	Ovarian tuberculosis with benign serous cystadenofibroma

[Table/Fig-2]: Cases reported in literature of ovarian tuberculosis as well as ovarian tuberculosis with other ovarian neoplasms in past fifteen years.

In cases of Ovarian tuberculosis, two main patterns of involvement are seen:

- Perioophoritis: Most typical form of involvement, the tuberculous process starts from the tube and then involves the ovary resulting in the formation of a tubo-ovarian mass, which frequently adhere to the intestine and omentum.
- Oophoritis: Rare form of involvement, the infection starts from the ovarian stroma through haematogenous route and produces a caseating granuloma within the parenchyma [10]. The latter one seems to be present in the present case. The patient only complained of intermittent dull aching pain in lower abdomen with off and on dyspareunia. In ovarian tuberculosis,

the clinical presentation may mimic ovarian malignancy as well. Radiological findings of ovarian tuberculosis and neoplastic ovarian masses may have overlapping features. Elevated CA-125 has been reported in ovarian tuberculosis. This makes its clinical and radiological differentiation from ovarian neoplasm a diagnostic challenge [11].

In the present case case, radiological and clinical suspicion of malignancy was present with elevated CA-125. Tuberculosis was not suspected. Tuberculosis was the main histological finding. The well-formed epithelioid granulomas and multinucleate giant cells in the background of dense inflammation were concealing the stromal invasion by the irregular serous glands. Follow-up immunohistochemistry was performed to establish invasion. The tumour nuclei were highlighted by WT-1. This was pivotal in diagnosing the lesion to be borderline lesion according to WHO classification 2020 [5].

There have been multiple advances in understanding of molecular pathogenesis of ovarian serous neoplasms. Most critical of them being that though, both High Grade Serous Carcinoma (HGSC) and continuum of borderline serous tumours to low grade serous carcinoma share 'serous' morphology, they have different cellular origin, molecular pathogenesis, and response to treatments. HGSC has been hypothesised to be arising from Serous Tubal Intraepithelial Carcinoma (STIC). Low grade serous neoplasm on the other hand has been shown to be associated with K-ras mutations and increased allelic imbalance of chromosome 5q [12]. Both HGSC and low-grade serous carcinoma can be morphologically differentiated. Currently, Sectioning and Extensively Examining- Functional Independence Measure bria (SEE-FIM) protocol is recommended if an ovarian tumour is diagnosed as HGSC on histology to identify the fimbria lesion.

CONCLUSION(S)

In conclusion, when a granulomatous lesion is associated with a neoplasm, the diagnosis becomes debatable, as the concomitance of the two may be, a mere coincidence. The clinical presentation is also very interesting as both are known to cause infertility. The functional status of the other ovary was found to be unremarkable with adequate follicular count and maturity. The patient is well after surgery and was on oral antitubercular treatment. The patient is undergoing treatment with assisted reproductive facilities provided at our hospital.

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