

# Epidemiological and clinicopathological aspects of female genital tuberculosis in Antananarivo, Madagascar

## Abstract

Genital tuberculosis constitutes a form of extrapulmonary tuberculosis that remains largely underrecognized, particularly in low-income countries such as Madagascar. In these settings, diagnosis is frequently delayed, despite the potential for severe consequences on women's health, ranging from menstrual disturbances and infertility to malignant transformation.

The aim of this study is to describe the epidemiological, clinical, and morphological characteristics of female genital tuberculosis in the local context, with the aim of improving diagnosis and preventing unnecessary radical treatment, particularly in young patients. This was a retrospective, descriptive study of female genital tuberculosis cases over a five-and-a-half-year period, from July 2019 to December 2024, conducted at the Department of Anatomical Pathology of the Joseph Ravoahangy Andrianavalona University Hospital Center. During the study period, 12 cases were identified. The patients' ages ranged from 17 to 60 years, with a mean age of  $42.2 \pm 15.3$  years. The most common site of involvement was the fallopian tubes, accounting for 50% of cases. In 58.3% of cases, the morphological pattern was typical, consisting of epithelioid granulomas with Langhans-type giant cells centered on caseous necrosis. The lesions were associated with a high-grade squamous intraepithelial lesion (CIN 2), an endometrioid adenocarcinoma of the endometrium, and a bilateral mucinous ovarian adenocarcinoma. From an evolutionary standpoint, the lesions were predominantly observed at a chronic stage, characterized by fibrotic remodeling, extension of the lesions into the abdominal cavity, and instances of malignant transformation. Epithelial alterations with ciliary loss and fusion of tubal fimbriae were also documented. The findings of this study may contribute to the development of more appropriate screening protocols, strengthen the capacities of healthcare professionals, and improve access to specialized care for affected patients. This research therefore aligns with broader efforts to combat tuberculosis and promote reproductive health.

**Keywords:** antananarivo, madagascar, tuberculosis, reproductive health

## Introduction

Despite the progress achieved and ongoing efforts in the fight against tuberculosis, the disease remains a major public health challenge, particularly in low-income countries such as Madagascar. Globally, the World Health Organization estimates that tuberculosis affects more than 10 million people each year, about one-third of whom are women.<sup>1</sup> In countries with low tuberculosis endemicity, such as Western Europe and North America, the prevalence of female genital tuberculosis is very low, generally less than 1% in series of infertile women.<sup>2,3</sup> Conversely, in highly endemic regions, particularly in South Asia and sub-Saharan Africa, female genital tuberculosis is much more common, ranging from 3% to 26% in India<sup>4</sup> to 15% to 21% in sub-Saharan Africa.<sup>5</sup> In Madagascar, a series by Ravelosoa E et al reported 11 cases of female genital tuberculosis in 2007.<sup>6</sup> The present study supplements the one conducted in 2021 at the same institution, in which five cases were documented.<sup>7</sup> Its objective is to describe the epidemiological, clinical, and morphological characteristics of female genital tuberculosis in the local context, with the aim of improving diagnosis and preventing unnecessary radical treatment, particularly in young patients.

## Materials and methods

A retrospective, descriptive study of female genital tuberculosis cases diagnosed at the Paraclinical Training and Research Unit in

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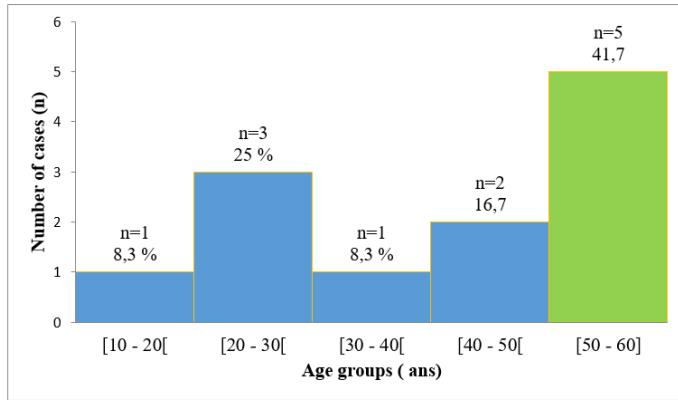
Anatomical and Cytological Pathology of the Joseph Ravoahangy Andrianavalona University Hospital Center was conducted over a sixty six months period, from July 2019 to December 2024. The sampling of patients was exhaustive. All cases of genital tuberculosis in women diagnosed during the study period were included in the study, excluding duplicates, i.e., the same diagnosis for the same patient.

This study has several limitations, including its retrospective design, potential selection bias related to hospital-based recruitment in Antananarivo, probable underestimation of the true prevalence of female genital tuberculosis, limited access to molecular diagnostic tools, and the lack of long-term clinical follow-up.

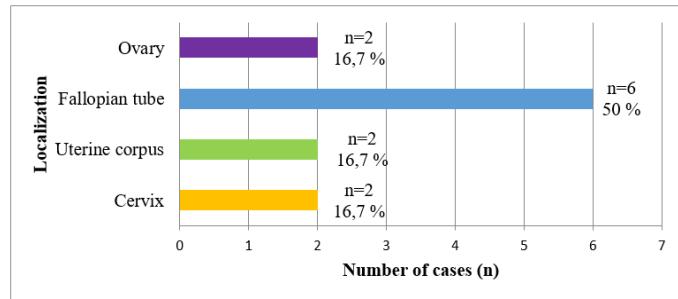
## Results

During the study period, 12 cases were recorded. The patients' ages ranged from 17 to 60 years, with a mean age of  $42.2 \pm 15.3$  years (Figure 1). The fallopian tubes were the most frequent site of involvement, accounting for 50% of cases (Figure 2). Clinical presentation was suggestive in 41.7% of cases (Table 1), and in 58.3% the histological findings were typical, showing epithelioid granulomas and Langhans-type giant cells centered on caseous necrosis. The lesions were associated with a high-grade squamous intraepithelial lesion (CIN 2) in one case, an endometrioid adenocarcinoma of the endometrium in one case, and a bilateral mucinous ovarian adenocarcinoma in another

(Table 2). From an evolutionary standpoint, the lesions were observed at a chronic stage, characterized by fibrotic remodeling, extension of the lesion into the abdominal cavity, and instances of malignant transformation. Epithelial alterations with ciliary loss and fusion of the tubal fimbriae were also noted.



**Figure 1** Distribution of patients according to age groups.



**Figure 2** Distribution of patients according to the site of involvement.

**Table 1** Distribution of patients according to clinical information

Clinical information	Number of cases (n)	Percentage (%)
Suspect mass	5	41,7
Ascites associated with peritoneal granulations or with adhesion to abdominal viscera	4	33,3
Others (hemorrhage, calcification, chronic genital infection)	3	25

**Table 2** Distribution of patients according to the type of lesion and the presence or absence of an associated tumor

Associated tumor/ Lesion type	Yes CIN2	Endométrioide ADK	Mucinous ADK	No
Caseo-follicular tuberculosis (n=7)	1		6	
Follicular tuberculosis (n=5)	1		1	3

## Discussion

In developing countries such as Madagascar, tuberculosis remains a major public health concern. Genital involvement is rare. During the study period, 12 cases were recorded, a number comparable to a previous study conducted at the same institution in 2021,<sup>1</sup> which reported 5 cases over a two-and-a-half-year period. The mean age in the present study was  $42.2 \pm 15.3$  years, higher than that reported

in the earlier study (28.8 years)<sup>1</sup> and also higher than the findings of Hammami B. et al. in Tunisia in 2005, where the mean age was 34 years (range: 18–63 years).<sup>8</sup>

Genital tuberculosis is often secondary to pulmonary tuberculosis. Dissemination occurs via hematogenous or lymphatic routes, or through direct contiguity with an intra-abdominal or peritoneal lesion. In the present series, transmission was attributed in 33.3% of cases to peritoneal tuberculosis extending to the fallopian tube and uterine body. From an anatomopathological perspective, penetration of *Mycobacterium tuberculosis*.

From an anatomopathological standpoint, the entry of *Mycobacterium tuberculosis* into the female genital tract induces an inflammatory reaction initially mediated by humoral immunity, characterized by a nonspecific inflammatory infiltrate predominantly composed of neutrophils. At this stage, the morphological features remain nonspecific, with no distinctive signs suggestive of tuberculosis. Subsequently, more specific lesions develop, enabling clinical suspicion of the diagnosis. On macroscopic examination, certain lesions may already raise suspicion of the diagnosis. Their appearance varies according to the site of involvement and may present as nodular formations or as whitish, millet-seed-like granulations, approximately 1 mm in diameter and evenly distributed. This appearance was observed in two cases, with granulations involving both the peritoneum and the serosal surface of the uterine body.

The lesion may also have a diffuse, poorly demarcated, grayish appearance, which is most commonly seen in myometrial tuberculosis. In this series, the macroscopic appearance of the myometrial case was nonspecific, and the diagnosis was established only through histological examination. A third form is the cavitary type, resulting from fistulization or evacuation of the contents of an encapsulated tuberculous focus.

According to the anatomical site, the morphological lesions and their consequences vary. The most common location of genital tuberculosis is the fallopian tube (95–100%), followed by the endometrium (50–60%), the ovary (20–30%), the cervix (5–15%), and finally the vulva and vagina (1%).<sup>9</sup>

For tubal tuberculosis, the most common form of female genital TB and the initial site of infection. It may occur in isolation or in association with peritoneal involvement, or it may result from the contiguous spread of peritoneal tuberculosis, as observed in 25% of cases in the present study. Tubal involvement accounted for 50% of cases. It was associated with ascites in 16.7%, peritoneal granulations in 8.3%, and adhesion of abdominal organs in 8.3%. Bilateral involvement was observed in 16.7% of cases. According to Mondal KS in India, tuberculous salpingitis represented 21.8% of cases, with 75% being bilateral. In 4.1% of cases, it was associated with HIV co-infection.<sup>10</sup> Histologically, in 16.7% of cases, the tubal fimbriae displayed a normal architecture, although the tubal lumen was reduced due to fibrous thickening of the wall and the presence of tuberculoid granulomas—caseating in one case and non-caseating in the other. The non-caseating granuloma exhibited foci of calcification, raising differential diagnostic concerns with tubal schistosomiasis, particularly in a schistosomiasis-endemic country such as Madagascar. Schistosomal serology was performed and returned negative, thereby supporting the diagnosis of tuberculosis. In the remaining three cases, the tubal lumen was completely obstructed, and the fimbriae were thickened and fused together, harboring tuberculoid granulomas with caseous necrosis. The lesions were already in a chronic phase, characterized by fibro-inflammatory remodeling.

Following chronic, undiagnosed and untreated tuberculous infection, these morphological changes may lead to a significant risk of infertility, ectopic pregnancy, and destruction of ciliated epithelial cells. In uterine tuberculosis, endometrial involvement is more common than myometrial involvement. The uterine mucosa may appear normal or may present ulcerations or granulations. In their series, Mondal KS et al.,<sup>10</sup> and Hammami B et al.,<sup>8</sup> found predominantly endometrial localization in 60% and 40.9% of cases, respectively. They attributed this high frequency to the fact that their patients were recruited during etiological investigations for infertility, which increased the number of diagnostic curettage biopsies. In the present study, uterine tuberculosis accounted for 16.7% of cases, with endometrial and myometrial involvement each representing 50%. In cases of endometrial localization, the macroscopic appearance consisted of a budding mass, without any lesion suggestive of tuberculosis. Histologically, the mass corresponded to a moderately differentiated adenocarcinomatous proliferation infiltrating the cervix, the uterine isthmus, and the uterine body. Notably, tuberculous granulomas with central caseous necrosis were present within the tumor stroma. The iliac-obturator lymph nodes obtained during lymphadenectomy were free of neoplastic involvement but contained similar tuberculous lesions. The coexistence of genital tuberculosis and cancer is exceptional. Only a few studies have been reported in the literature, such as those by Ashraf M et al.,<sup>11</sup> and Gupta A et al.,<sup>12</sup> who each documented 3 cases. Hammami B. et al. also reported one case associated with endometrial adenocarcinoma. From a pathophysiological standpoint, it is difficult to determine whether the carcinoma developed on top of chronic, progressive tuberculosis, or whether cancer-associated cachexia led to reactivation of quiescent tuberculous bacilli. Diagnosis is generally established only after histological examination, which then guides appropriate therapeutic management. In the myometrium, the lesion may present as caseating tubercles or as dense collagenous sclerosis with tuberculous follicles.<sup>13</sup> In the present study, diagnosis was established exclusively on histology, and the lesion was associated with peritoneal tuberculosis.

For cervical uterine tuberculosis, this site is less common. In this series, it accounted for 16.7% of cases. Macroscopically, the uterine cervix may appear normal or enlarged, presenting as a proliferative mass that mimics cervical cancer.<sup>14</sup> This was the case in both patients, where a budding, cancer-like lesion was observed.

The preferred site of involvement is the ectocervix, and it may present in four forms:<sup>14</sup>

- a) **The miliary form**, characterized by yellowish or translucent granulations measuring a few millimeters on the cervical mucosa, set against an inflammatory background.
- b) **The vegetative form**, appearing as a friable, yellowish, bleeding outgrowth that simulates a malignant tumor.
- c) **The ulcerative form** is characterized by one or multiple ulcerations with a grayish base or covered with purulent material. As these lesions coalesce, they form a large ulcer with irregular, elevated margins. The limits of tissue loss are more clearly demarcated than in cervical cancer.
- d) **The interstitial form** presents as a markedly enlarged cervix infiltrated throughout its thickness by tuberculous nodules that may coalesce to form cold abscesses, which can then fistulize into the vagina.

Endocervical involvement may go unnoticed and typically becomes apparent only when the lesions extend to the external cervical os, presenting as a vegetative, and more rarely ulcerative,

lesion.<sup>14</sup> Histologically, multiple tuberculous granulomas are observed, characterized by central caseous necrosis surrounded by epithelioid cells, histiocytes, and multinucleated giant cells, with a peripheral lymphoplasmacytic infiltrate.<sup>15</sup>

In one of the cases in this study, the exocervical epithelium showed a high-grade intraepithelial lesion, while the stroma was fibrous with tuberculous granulomas lacking caseous necrosis. In the other case, the lesion was endocervical, with an ulcerated epithelial lining and a stroma containing tuberculous granulomas with central caseation.

Ovarian Tuberculosis accounted for 16.7% of cases in the present series. Ovarian tuberculosis is a rare but clinically significant condition, as it may mimic an ovarian malignancy clinically, radiologically, and sometimes even macroscopically, particularly in countries with a high prevalence of tuberculosis. This resemblance can lead to unnecessary extensive surgery, especially in young women desiring future fertility. In this series, ovarian tuberculosis affected two postmenopausal women, one of whom presented, in addition to tuberculosis, a bilateral mucinous ovarian adenocarcinoma. Although uncommon, the coexistence of ovarian tuberculosis and ovarian cancer has been reported in the literature. This association may represent a malignancy arising in a previously infected tuberculous organ (the hypothesis of chronic inflammation as a carcinogenic risk factor) or simply a fortuitous coincidence.<sup>16</sup> According to Saini A. et al., tuberculosis may mimic or coexist with ovarian cancer. They reported two clinically suspected cases—one was isolated ovarian tuberculosis, while the other was associated with a dysgerminoma.<sup>17</sup> Aurora et al. emphasized that pelvic tuberculosis should be considered in the differential diagnosis of ovarian malignancy, as this may prevent numerous unnecessary laparotomies.<sup>18</sup> In the present study, one case was initially suspected to be an ovarian tumor but was subsequently identified as tuberculosis following histopathological examination.

## Conclusion

Female genital tuberculosis remains a major challenge, particularly in low-income countries such as Madagascar. The disease often progresses silently and is typically diagnosed at a late stage, with highly variable clinical presentations. In this series, tubal involvement was the most frequent localization. It is therefore essential to consider this condition in patients presenting with chronic pelvic pain or unexplained infertility. This pathology may mimic or coexist with malignancy, necessitating an appropriate diagnostic and therapeutic approach. These observations underscore the need for early detection and the inclusion of tuberculosis in the differential diagnosis of gynecological disorders, especially in endemic areas.

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## Conflicts of interest

The authors declare no conflict of interest related to this publication.

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