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Case Report

Cervical Tuberculosis Mimicking Cervical Cancer in a Postmenopausal Woman: A Case Report

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Abstract: Cervical tuberculosis is a rare form of genital tuberculosis. A case of a 73-year-old woman who presented with cervical wall thickening on magnetic resonance imaging, suggesting an invasive malignant neoplasm, is documented. Cervical cone excision was performed for histopathological study. Microscopy showed epithelioid granulomas, without appreciable caseous necrosis, in the wall of the uterine cervix, associated with erosion of the overlying cervical mucosa. Histochemical stains for microorganisms (Ziehl–Neelsen, Grocott, and Warthin–Starry) were negative. Immunohistochemistry for *Treponema pallidum* revealed scarce, spiral-shaped bacilli, which raised the diagnostic possibility of secondary syphilis. The serological study for syphilis was negative, however. Polymerase chain reaction (PCR) tests for *Mycobacterium tuberculosis* and *Treponema pallidum* were performed in the formaldehyde-fixed, paraffin embedded tissue and resulted positive for *Mycobacterium tuberculosis* and negative for *Treponema pallidum*, confirming the diagnosis of cervical tuberculosis. Our objective was to report a rare case of cervical tuberculosis, discussing the advantages and limitations of complementary techniques used in the pathological diagnosis of infectious agents and highlighting diagnostic pitfalls. In conclusion, correct microbiological diagnosis requires the implementation of integrated workflows employing complementary techniques in a multidisciplinary setting to improve the accuracy of histopathological examination in infectious diseases.

Keywords: cervix; *Mycobacterium tuberculosis*; *Treponema pallidum*; immunohistochemistry; PCR

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1. Introduction

Tuberculosis (TB) remains one of the world's leading causes of death from a single infectious agent. According to the World Health Organization (WHO), there were 7.5 million new TB cases worldwide in 2022, leading to 1.3 million deaths. The highest reported incidences are in Southeast Asia, Africa, and the Western Pacific [1]. In Europe, TB incidence is generally lower compared to high-incidence regions, with an overall 7.4 cases per

100,000 people, as reported by the European Centre for Disease Control (ECDC) in 2021. There is significant variation between countries, however, with higher rates reported in Eastern European countries, namely Romania, Lithuania, and Latvia [2]. In the West, Portugal has one of the highest TB incidence rates, nearly double the European average. Interestingly, within the country, this is also heterogeneous, with some high-risk municipalities showing notification rates exceeding 20 cases per 100,000 people [3].

TB is a multisystemic disease that can affect any organ or tissue, excluding only the hair and nails. Although it is traditionally considered a pulmonary disease, it is estimated that between 15% and 40% of new patients present with extrapulmonary disease on diagnosis. Of these extrapulmonary TB cases, 30–40% correspond to urogenital TB, which includes both urinary and genital tract involvement [4–7]. This is particularly important among women of reproductive age, for whom genital tuberculosis constitutes a significant proportion of extrapulmonary TB cases. In fact, it is a recognized cause of infertility, especially in high-prevalence regions [8]. Studies suggest that genital tract TB accounts for approximately 9% of extrapulmonary TB cases in endemic areas [7,8] and that in certain developing countries, the incidence of genital TB among women presenting with infertility can range between 3% and over 16% [8,9]. Numerous case reports have highlighted the varied presentations of genital TB, emphasizing the importance of considering it in differential diagnoses [9–11].

Among these, TB of the cervix is a rare manifestation, and overall, it comprises less than 1% of all reported TB cases [9,11]. These patients can present with mass-forming lesions, mimicking neoplasms, clinically and on imaging. A correct and timely diagnosis is essential to enable adequate treatment and avoid unnecessary surgery, which remains the staple of treatment for these more common HPV-related lesions [12].

2. Case Report

A 73-year-old woman with a clinical history of hypertension and laparoscopic cholecystectomy due to biliary cholelithiasis presented with anorexia, weight loss, asthenia, and anemia. She denied fever, night sweats, and respiratory or gynecological complaints, namely vaginal bleeding or discharge. Laboratory evaluation revealed elevated plasma levels of CA15-3 = 41.8 U/mL (<30 U/mL) and CA-125 = 392 U/mL (0–35 U/mL). These laboratory results raised the suspicion of pelvic neoplasia, and the patient was referred to the gynecology department. Gynecological examination revealed no visible tumor, and no lesions were palpable on bimanual examination. A Pap smear test was negative for malignancy, and colposcopy was inconclusive. Pelvic magnetic resonance imaging (MRI) was performed. The MRI revealed a heterogeneous mass in the cervix, measuring up to 37 mm in diameter, highly suggestive of malignancy (Figure 1).

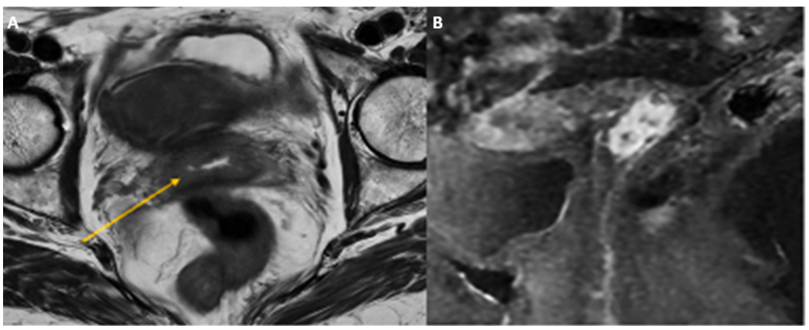

Figure 1. Axial T2W (**A**) shows irregular hyperintense circumferential thickening and loss of normal low signal intensity of the cervix (yellow arrow), with heterogeneous enhancement in the post-contrast sagittal T1W (**B**), representing cervix mass. There is no apparent involvement of the vaginal walls or parametrium.

Cervical curettage and biopsy for histopathologic study of the lesion showed a nonspecific inflammatory reaction with epithelial erosion. Due to imaging-histological discordance, a large loop excision of the cervix was performed. Microscopic examination showed an extensive granulomatous inflammatory process affecting the entire thickness of the uterine cervix. Granulomas were epithelioid, sometimes confluent with perivascular distribution, without appreciable caseous necrosis (Figures 2 and 3).

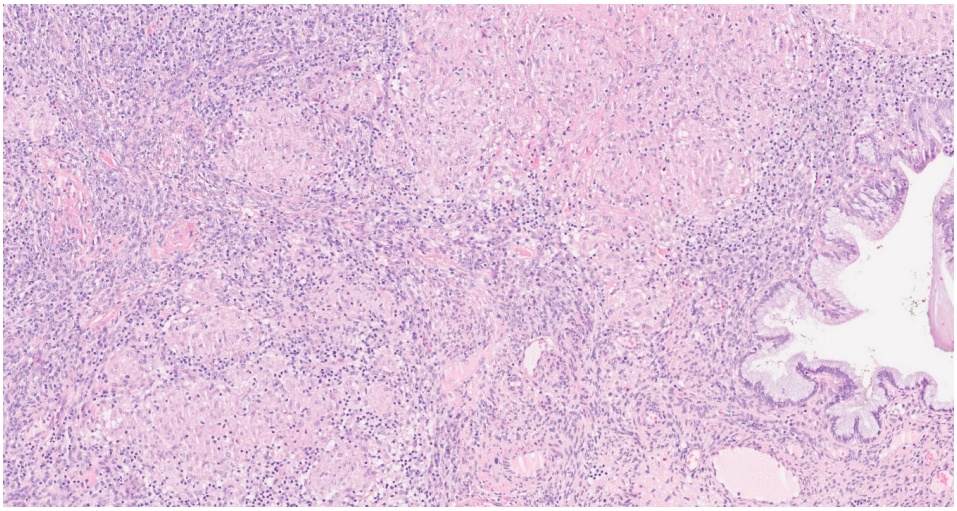

Figure 2. Granulomatous inflammatory process affecting the entire thickness of the uterine cervix wall. Epithelioid granulomas were sometimes confluent—H&E stain.

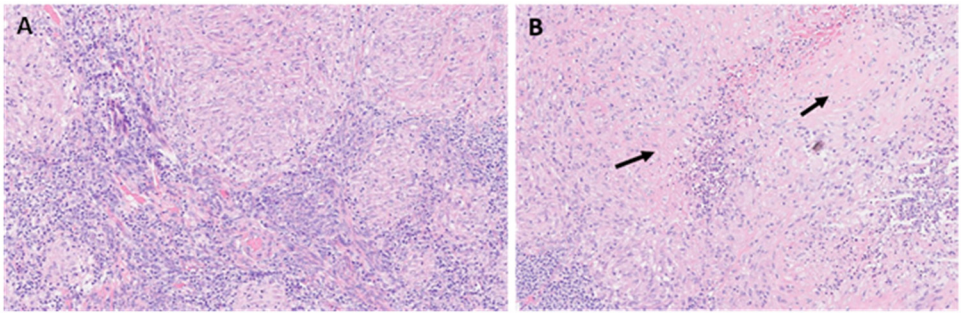

Figure 3. Epithelioid granulomas without appreciable caseous necrosis (**A**) associated with fibrinoid and suppurative necrosis (**B**) (arrows)—H&E stain.

On the mucosal surface of the endocervix, there were foci of erosion with fibrinoid and suppurative necrosis, as detailed in Figure 3. Histochemical stains for microorganisms (Ziehl–Neelsen [ZN], Grocott, and Warthin–Starry [WS]) were applied, but the results were negative. These special stains, with adequate controls, were evaluated by three pathologists.

Immunohistochemistry (IHC) for *Treponema pallidum* (rabbit anti-human *Treponema pallidum* antibody—polyclonal, MAD-000624QD–3, Vitro master diagnóstica®, Sevilla, Spain; Optiview-DAB, Benchmark Ultra, Roche, Basel, Switzerland) revealed the presence of scarce, focally spiral-shaped bacillary forms in the lesion, which raised the diagnostic possibility of secondary syphilis (Figure 4).

The IHC was evaluated by three pathologists and recorded with collegial agreement.

However, serological studies were negative for syphilis (Abbot ARCHITECT Syphilis TP test—8D06-32; 8D06-42, Abbot®, Amadora, Portugal). Given these results, after multidisciplinary discussion, it was decided to perform polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* and *Treponema pallidum* on the formalin-fixed, paraffin-embedded

(FFPE) tissue blocks, as well as microbiological culture for *Mycobacterium tuberculosis* prepared from a fresh tissue sample.

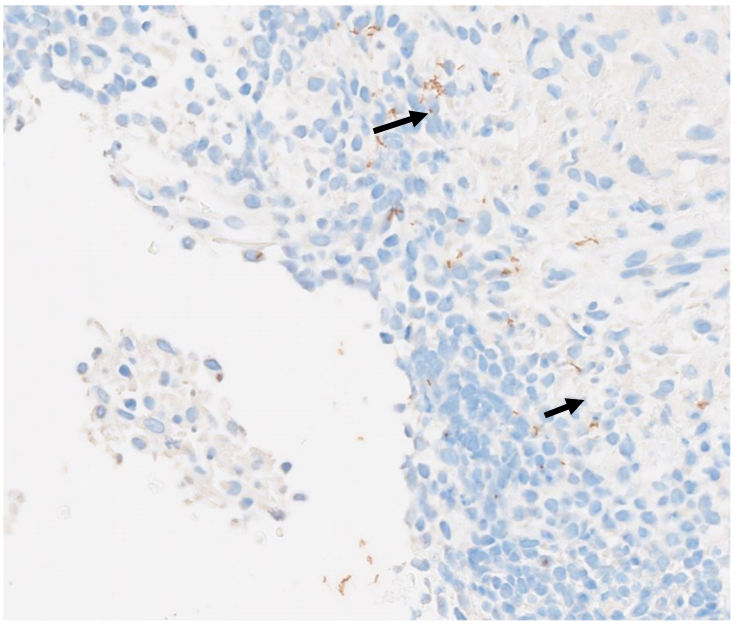

Figure 4. Immunohistochemistry (IHC) for *Treponema pallidum* revealed the presence of scarce, spiral-shaped bacillary forms in foci of the lesion (arrows). *Treponema pallidum*—polyclonal, Vitro master diagnostica®, Optiview–DAB, Benchmark Ultra.

Real-time PCR for *Mycobacterium tuberculosis* performed on FFPE tissue was positive, while PCR for *Treponema pallidum* was negative, corroborating the diagnosis of cervical tuberculosis. The patient started the therapeutic regimen for TB. The result of the microbiological culture for *Mycobacterium tuberculosis* was positive, confirming the etiological agent and its sensitivity to drugs of the standard therapeutic regimen. During the follow-up, the patient showed good adherence to the tuberculosis treatment, without any clinical complications. There was an improvement in her general condition, including resolution of the pelvic lesion.

3. Discussion

We describe the case of an elderly woman presenting with asthenia, anorexia, weight loss, and elevated plasma levels of CA-125, raising suspicion of gynecologic neoplasia. Pelvic MRI showed a single infiltrative lesion in the cervix, sparing the parametria. The set of clinical and imaging findings favored a clinical diagnosis of cervical cancer. However, histological study revealed a chronic granulomatous inflammatory process in the cervix, ruling out malignancy. The final diagnosis of cervical tuberculosis was confirmed by PCR testing and microbiological culture.

Cervical cancer (CC) continues to rank among the top gynecologic cancers worldwide, corresponding to the fourth most common malignancy in the female population [13]. More than 75% of CC cases are due to high-risk HPV types 16 and 18. However, other HPV types can also cause malignancy, such as HPV 33, 31, 45, 52, and 58. Primary prevention and screening are the best methods for decreasing the burden and mortality of CC. Screening by cytology and/or HPV testing is essential in the workup and diagnosis of patients with CC and its precursor lesions and is generally recommended until age 65 [14]. Patients with CC are usually asymptomatic during the early stages of the disease, with no positive findings on physical examination [13]. Due to this and the screening age cut-off, the incidence of CC may be underestimated in older women. Individuals in this age group (≥65 years)

are more often diagnosed with late-stage disease and show worse outcomes compared to younger patients [15].

Imaging plays an important role in CC diagnosis, tumor staging, and the monitoring of response to therapies over time. Currently, MRI is the preferred imaging modality due to its higher sensitivity and specificity, as well as its capability to provide comprehensive insights into the anatomical morphology of a patient's pelvis, highlighting specific findings of CC, namely tumor size, stromal invasion, and parametrial involvement of the tumor [16]. In our case, the MRI images showed a heterogeneous mass in the cervix, with the largest diameter of 37 mm, highly suggestive of malignancy, with no evidence of parametrium involvement.

The differential diagnosis of ulcers, papillary or vegetative, or infiltrative growths of the cervix is vast and includes several malignancies, reactions to foreign bodies, autoimmune disorders, vasculitides, and a range of infectious diseases, including syphilis, granuloma inguinale, lymphogranuloma venereum, actinomycosis, schistosomiasis, and amebiasis, among other entities [9,11,17,18]. In this case, a histological study revealed a chronic granulomatous inflammatory process in the cervix, ruling out malignancy. Granulomas usually indicate the use of histochemical and IHC stains for infectious agents, often accompanied by a clinical attempt to isolate the pathogen through culture, which remains the gold standard for diagnosis [19].

Detecting and identifying micro-organisms in histology frequently proves quite challenging, requiring meticulous observation to confirm positivity and avoid morphological mimics and technical artifacts. In fact, the sensitivity of histochemical stains can be low, and false negatives are frequent [18]. IHC can be a useful technique in this context, enhancing the detection of pathogens [20–22]. That is, IHC directed against *Treponema pallidum* has been shown to be more sensitive than classical silver staining methods, such as WS, for the detection of spirochetes in skin biopsy samples [23,24].

Immunostaining is not without pitfalls and caveats, however. For instance, changes in tissue antigenicity, inherent to the fixation process, or cross-reactions between different pathogens can lead to either false negative or false positive results [21,25,26].

In the present case, the histochemical stains (ZN and WS) were negative. IHC for *Treponema pallidum* was performed with a sensitive antibody and adequate controls and showed positive staining in bacillary forms, favoring a diagnosis of syphilis. However, this was discordant with serologies, and further studies were indicated.

We proceeded with molecular methods, performed on the paraffinized material, and it was decided to collect fresh material for the microbiological culture of *Mycobacterium tuberculosis* in parallel. The final diagnosis of cervical TB was confirmed by PCR testing and microbiological culture.

Cervical TB accounts for only 0.1 to 0.65% of all instances of TB [27–29] and is known to occur in women of varying ages, including the elderly (28). In most cases reported in the literature, patients presented with vaginal discharge or bleeding, and the presence of ulcerated or vegetative lesions of the cervix was noted. Systemic symptoms were generally absent, as were pulmonary lesions [28,29]. Our patient lacked these typical gynecologic symptoms, making the diagnosis more challenging.

This single case report is illustrative of a rare disease with an atypical presentation and has strengths and limitations. Its major strength is the comprehensive diagnostic approach described, integrating clinical evaluation, imaging, histopathology, IHC, serological studies, molecular methods, and microbiological culture. This multidisciplinary approach is essential in reaching the correct diagnosis. The most relevant limitation is the impossibility of correctly identifying the contaminant microorganism that led to the false-positive IHC result due to cross-reactivity.

Here, we underscore the need for a heightened awareness of rare presentations of TB among clinicians and pathologists. Future research on this topic may focus on improving histopathological diagnostic accuracy in infectious diseases through the development of more specific IHC antibodies and the development of integrated workflows incorporating molecular diagnostics early in the evaluation of granulomatous lesions when initial studies are inconclusive. Enhanced reporting and compilation of such rare cases may aid in better understanding the spectrum of cervical TB presentations, leading to earlier diagnosis and appropriate treatment.

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