# Cervical Tuberculosis Mimicking Tumor Persistence: A Case Report

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## ABSTRACT

Tuberculosis can coexist with malignancy in the same organ, but cancer with TB in the cervix is rare. This is a case of cervical tuberculosis diagnosed in a cervical cancer patient after concurrent chemoradiotherapy and brachytherapy.

This is the case of a 38-year-old G2P2 (2002) diagnosed with squamous cell carcinoma, large cell non-keratinizing cervix, Stage IIIB. The patient underwent concurrent chemoradiotherapy and brachytherapy.

One month after the last brachytherapy dose, the attending physician noted a nodularity on the anterior lip of the cervix. A cervical punch biopsy was done to rule out tumor persistence. The histopathology revealed chronic granulomatous inflammation with Langhan's type multinucleated giant cells consistent with tuberculous infection.

She was diagnosed with cervical tuberculosis, postulated to be from latent TB reactivation, and was given Anti-Koch's medication for six months. After receiving Anti-Koch's treatment, the cervical nodularity was no longer appreciated, and the rest of the cervix was smooth on palpation. Her Pap Test was negative for any intraepithelial lesion and was declared with no evidence of carcinoma.

A possible latent TB infection should always be screened in cancer patients from high-burden areas or those with close contact treated for tuberculosis because immunosuppression during cancer treatment can cause the reactivation of tuberculous disease.

Cervical tuberculosis complicating cervical malignancy is treatable with Anti-Koch's therapy and has not been shown to affect the course of the carcinoma.



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## INTRODUCTION

Tuberculosis can coexist with malignancy, but tuberculosis and cancer in the cervix is rare. This is a case of cervical tuberculosis, initially thought to be tumor persistence, in a cervical cancer patient who has completed concurrent chemoradiotherapy and brachytherapy.

## CASE PRESENTATION

This is the case of a 38-year-old G2P2 (2002) who came in with a one year history of vaginal spotting and foul-smelling vaginal discharge associated with hypogastric pain.

On IUD removal, the physician noted a nodular cervical mass. A biopsy was done, which revealed invasive carcinoma, probably adeno-squamous type. Patient was subsequently referred to a tertiary institution for further management.

During her initial consult at the Out Patient Department, she had stable vital signs with normal systemic PE findings. On speculum examination, there was note of a nodular cervix with ulcerations that bled on manipulation. On bimanual examination, she had normal external genitalia, parous vagina, the cervix is converted to an 8 x 8 cm hard, nodular mass with circumferential involvement of the upper 3rd of the vagina, corpus small, and there were no adnexal masses or tenderness. On rectovaginal examination, she had good sphincter tone, intact rectal vault, and no intraluminal masses noted; bilateral parametria were fixed.

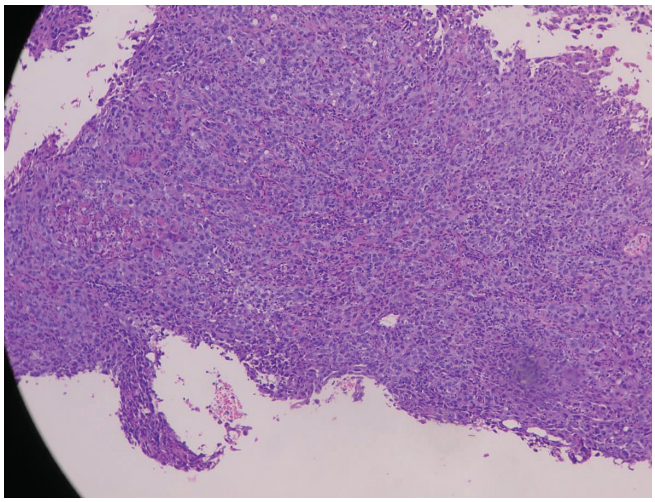

**Figure 1.** Proliferation of cells forming nests, trabeculae, and sheets. Note the remnant of eosinophilic stroma invaded by tumor (H&E, x4).

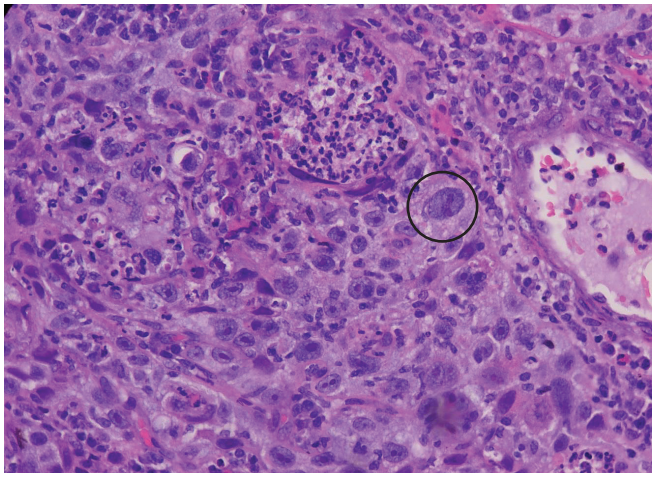

**Figure 2.** Note the increased pleiomorphism of the malignant cells *(encircled)*. No note of Langhan's type giant cells or epithelioid histocytes (H&E, x40).

The initial impression was a cervical carcinoma Stage IIIB. A repeat punch biopsy was done, which revealed squamous cell, large cell non-keratinizing carcinoma (Figures 1 and 2).

A transvaginal ultrasound was done, which revealed the cervix to be converted to an irregular mass involving the upper 3rd of the vagina, uterine isthmus, and bilateral parametria.

Metastatic workup was done. On chest radiography, infiltrates were read as minimal PTB, with activity undetermined. Holo-abdominal ultrasound revealed nephrolithiasis on the right.The patient was not referred to Pulmonology or Urology, as the priority was to start chemoradiotherapy.

The patient underwent pelvic extended beam radiotherapy (EBRT) with six cycles of Cisplatin from February 3 to March 19, 2015. Brachytherapy with 4000 centi Grays was given from March 27 to 29, 2015. Patient had no adverse reactions to both chemotherapy and pelvic EBRT.

One month after the last brachytherapy dose, the patient reported no episodes of spotting and discharge. On internal examination, she had normal external genitalia, the cervix was 2 x 2 cm, with nodularity on the anterior lip of the cervix, the corpus was small, no adnexal masses and tenderness, and bilateral parametria thickened but smooth. The primary consideration for the nodularity was tumor persistence. The patient was referred for colposcopy.

On colposcopic examination, diffuse partial Lugol uptake and leukoplakia were noted at the 11-1 o'clock position, the same site as the nodularity. A cervical punch biopsy revealed chronic granulomatous inflammation with Langhan's type multinucleated giant cells consistent with tuberculous infection. Negative for atypical/malignant cells (Figure 3).

The patient was diagnosed with cervical tuberculosis and was prescribed Anti-Koch's medication. She was enrolled in the TB-Directly Observed Treatment Schedule (DOTS) and completed treatment with no adverse events noted. She

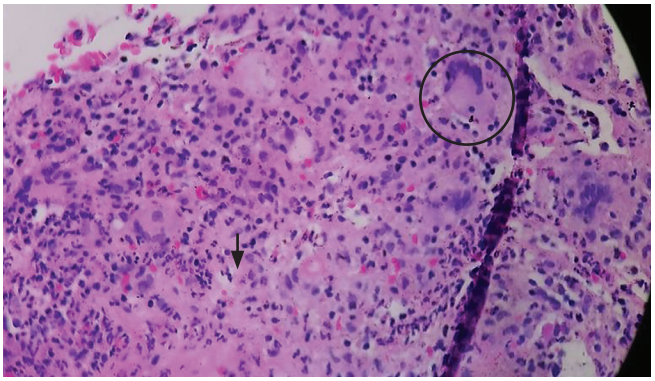

**Figure 3.** TB granuloma, note the presence of epithelioid histiocytes *(arrow)* in the background of caseous necrosis. There is superimposed acute inflammation (as evidenced by the presence of neutrophils), and at the periphery of the granuloma, multinucleated Langhan's giant cells were seen *(encircled)* (H&E, x10).

was seen on the 4th month of treatment at the Out Patient Clinic, and there was a decrease in the size of the nodularity. A repeat Pap Smear done in the 6th month of treatment was negative for intraepithelial lesions. The patient was declared treated for cervical tuberculosis and "no evidence of disease" for carcinoma.

## DISCUSSION

Tuberculosis remains one of the world's deadliest communicable diseases. According to the WHO, the Philippines has the 4th highest incidence of tuberculosis globally, accounting for 6% of all TB cases globally.[1] Although the lungs remain the most common site of tuberculous infection, they can affect almost any body organ.

Genital tuberculosis was first reported by Morgagni in 1744 after a postmortem examination of a patient with pulmonary tuberculosis revealed caseous material filling the uterus and fallopian tubes. There are three theories for the involvement of the pelvic organs: 1) hematogenous or lymphatic spread, 2) direct contiguity with an intraabdominal or peritoneal focus, and 3) genital tuberculosis as a latent disease where the lesion lies dormant only to reactivate at a later time during immunosuppression.[2]

Cervical TB is rare, comprising only 0.1-0.65% of cases of TB[3] and 5-15% of genital tuberculosis[2]. Cervical TB may also represent a primary infection introduced by a partner with tuberculous epididymitis or other genitourinary diseases. It has been suggested that sputum, used as a lubricant, is also a possible route of transmission.[4]

Tuberculosis has been said to be the "great mimic." Cervical tuberculosis has been shown to mimic carcinoma of the cervix.[5–7] The symptoms are similar; they present with abnormal discharge, vaginal bleeding, and vague abdominal pain. On speculum examination, tuberculous cervices can be ulcerative, friable, nodular, or polypoid—the index case presented with a nodularity in the anterior lip with noted leukoplakia and partial Lugol uptake.

Isolation of mycobacterium is considered the gold standard for diagnosis, but a third of cases are culture negative. A cervical punch biopsy with findings of chronic inflammation with granulomas is regarded as sufficient evidence of tuberculous disease.[8] In the index case, anti-Koch's medication was initiated based on histopathologic evidence of tuberculous granulomas.

If cervical tuberculosis is rare, then cervical tuberculosis in patients with cervical cancer is even more uncommon. There are only 12 reported cases of cervical TB co-existing with cervical cancer.[8,9]

In two recent case reports, patients presented with vaginal bleeding and friable cervical masses that, on biopsy, revealed carcinomatous nests along with epithelioid granuloma, Langhan's type of giant cells, and acid-fast bacilli. The two cases involved the coexistence of tuberculosis and cervical carcinoma.[8,9] The index case is unique because it is a case of cervical tuberculosis diagnosed after treatment for cervical carcinoma.

Malignancies and anti-cancer therapies simulate the appropriate conditions for either the reactivation of a latent mycobacterial infection or, more rarely, for acquiring a primary tuberculous infection. Immunosuppression, especially depression of the T-cell defense mechanisms during chemotherapy, is associated with mycobacterial infections.[10] Solid organ tumors have been shown to increase the vulnerability to reactivation of tuberculosis through immune suppression by the malignancy and anti-cancer chemotherapy.[11]

The index patient received concurrent chemo-radiotherapy and brachytherapy. Platinum-based chemotherapy inhibits DNA synthesis and interrupts the crosslinking of the DNA helix, which causes generalized immunosuppression and has been shown to have a radiosensitizing effect that confers better tumoricidal effect when used together with radiotherapy.[12] Radiotherapy affects the immune system via three modes of action: 1) local tissue damage, which causes the breakdown of local infection barriers; 2) reduction in circulating lymphocytes, which causes ineffective systemic immune response; and 3) a shift in the immune cellular balance of the innate (natural killer cells) and adaptive immune system (B cells and T cells). This synergistic effect of immune-suppressing chemotherapy and radiation therapy could explain the development of cervical tuberculosis in the index case. It could represent primary infection or reactivation of latent disease.

On further probing, the index patient had a history of exposure to tuberculosis in household contacts - two of her brothers were treated for pulmonary tuberculosis in 2008 and 2010. It is possible that this patient had a latent TB infection and her immunocompromised state, secondary to malignancy and chemo-radiotherapy, predisposed to the reactivation of her lesions. According to WHO, around one-third of the population has a latent TB infection, and this can undergo reactivation in those with an incompetent immune system.[13] Her baseline chest radiograph revealed minimal infiltrates which were suspicious for tuberculosis, but because the priority was to start her on chemotherapy, work-up and treatment for latent tuberculosis were not pursued.

Latent tuberculous infection (LTBI) is "a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifested active TB".[1] The Centers for Disease Control has identified patients with malignancy at increased risk of progression from latent infection to disease.[14] LTBI can be treated to prevent the progression to active disease, and it was shown to reduce progression by as high as 60%.

Testing for LTBI includes either a tuberculin test or an interferon gamma release assay (IGRA). In patients who test positive for LTBI, the WHO recommends several regimens: 6-month or 9-month isoniazid daily, 3-month rifapentine plus isoniazid weekly, 3- or 4-month isoniazid plus rifampicin daily, and 3– or 4-month rifampicin alone daily.[15] These

regimens could have been offered to the index case if there was a high index of suspicion of latent tuberculous infection.

The latest Philippine Clinical Practice Guidelines for Tuberculosis recommends a 6-month regimen consisting of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) for two months (initial phase), followed by isoniazid and rifampicin for four months for extra-pulmonary tuberculosis with a fully susceptible organism.[16]

Patients must be followed up closely to assess treatment response. Treatment surveillance includes regular speculum examination and the cervical lesion is a marker to assess the response to therapy.[3,7] Lesions have been shown to resolve as early as four weeks from the initiation of anti-Koch's medication.[5,6] Serial biopsy can also be done to assess for adequacy of treatment if the lesion persists even after initiation of anti-Koch's therapy.

In the index patient, there was note of a decrease in the nodularity at the 4th month of therapy. A colposcopic exam revealed normal findings on the 6th month of Anti-Koch's treatment. The Pap Test was also negative for intraepithelial lesions. This illustrates that cervical tuberculosis is highly curable and does not adversely affect the course of malignancy.

## CONCLUSION

This case provides several learning points: 1) tuberculosis complicating malignant disease may occur in regions with a high prevalence of TB, 2) cervical tuberculosis should always be a differential in malignant-appearing lesions of the cervix initially be thought to be tumor persistence or recurrence, 3) latent tuberculous infection should always be considered in a cancer patient who has exposure to a TB case and LTBI therapy should be initiated to prevent progression to active disease, and 4) genital tuberculosis complicating genital malignancy is curable with Anti-Koch's therapy.

### Informed Consent

Written informed consent was obtained from the daughter of the patient for publication of this case report and accompanying images. The patient succumbed to complications of cervical cancer in 2021, before the submission of this case report.

### Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

### Author Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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