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Postmenopausal bleeding: squamous cell carcinoma of cervix with coexisting endometrial tuberculosis

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Abstract *Case report:* A case of squamous cell carcinoma of cervix co-existent with endometrial tuberculosis presenting as postmenopausal bleeding is being reported for its rarity. The atrophic postmenopausal endometrium is thought to be poorly supportive of tubercle bacilli. Following a radical Wertheim's hysterectomy patient had a hectic postoperative period, which responded to antitubercular treatment. Diagnosis of tuberculosis in this case was made on histopathology postoperatively and confirmed by polymerase chain reaction (PCR) on scrapes from the granulomas obtained by microdissection. *Conclusion:* Tuberculosis complicating malignant disease may occur in regions with a high prevalence of disease; with a resurgence of tuberculosis worldwide this association may not be uncommon. The diagnosis and treatment of tuberculosis in a patient with cancer assumes importance as a high mortality has been seen in patients with co-existent disease.

Keywords Squamous cell carcinoma cervix · Endometrial tuberculosis · Postmenopausal bleeding · Polymerase chain reaction for Mycobacterium tuberculosis

Introduction

Postmenopausal endometrial tuberculosis is a rare entity [12, 16] and associated squamous cell carcinoma of the cervix rarer still [2]. Literature is scarce on the co-

existence of the two entities although sporadic case reports of carcinoma and tuberculosis of the uterine cervix are available [7, 13]. The low incidence of tuberculosis in the postmenopausal women may be attributed to atrophic endometrium, which is poorly supportive of tubercle bacilli [20]. In a western study of 475 cases of postmenopausal bleeding no case of tuberculosis was reported, while Indian studies report that in women with genital tuberculosis, 1–1.6% present with postmenopausal bleeding [1, 6, 18]. In a recent report of primary endometrioid adenocarcinoma co-existing with endometrial tuberculosis the authors concluded that although the two entities are extremely rare, occurrence in regions with a high prevalence of tuberculosis may not be uncommon [19]. A more logical reason would be a diminished immunity due to local or systemic effects of the tumor and/or its therapy that would lead to reactivation of a dormant disease [9]. Several reports suggest that human immunodeficiency virus increases incidence of new tuberculosis, exacerbates severity and reactivates latent tuberculosis. The two diseases co-exist in developing countries contributing to prevalence and mortality of each other [5]. A quadrupling of the prevalence of HIV in patients with invasive cervical cancer has been noted over a 10-year period in South Africa [15].

Case Report

A 55-year-old postmenopausal woman, menopausal for 8 years presented with irregular bleeding for the past one month associated with passage of clots. There was no pain abdomen, foul smelling discharge, fever, loss of weight, loss of appetite or prior postcoital bleeding.

Patient was P₀L₅, the last childbirth being 21 years back. She was married at the age of 15 and cohabited with her husband ever since. She denied a history of sexually transmitted disease or promiscuity in self or husband. Her socio-economic status was middle-class, diet vegetarian and was not addicted to tobacco, alcohol or substance abuse. Patient was a known hypertensive for the past 15 years on irregular treatment. There was no history of diabetes mellitus or tuberculosis in the past or in the family. She never underwent a screening test for cervical cancer.

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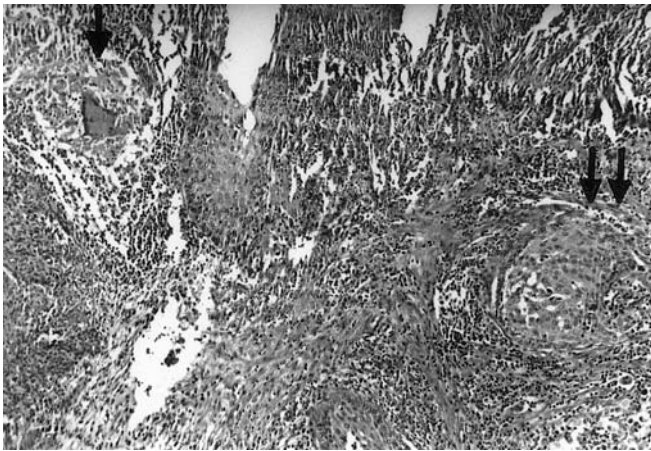


Fig. 1 Microphotograph showing co-existent epithelioid cell granuloma with Langhan's cells (*arrow*) and focus of squamous cell carcinoma in the endometrium (*arrows*). H&E, $\times 200$

General physical examination was essentially normal. Supra-clavicular, axillary and inguinal lymph nodes were not palpable. Abdominal examination revealed no mass, no ascites and no hepatosplenomegaly. On per speculum examination vagina was healthy and cervix flushed with vault. Anterior lip showed a small ulcer, which did not bleed on touch. Uterus was anteverted, 6–8 weeks in size and bilateral fornices free.

Ultrasound examination showed the uterus to be enlarged 9.2 \times 6.2 \times 4.5 cm and 50 cc of fluid collection was seen in the cavity. Bilateral ovaries were normal. Suspect invasive cancer was diagnosed on colposcopy; the cervix biopsied and endocervical curettings taken. Under anesthesia hematometra was drained and endometrium curetted. Cervical biopsy, endometrial and endocervical curettings showed a large cell non-keratinizing squamous cell carcinoma of cervix.

Patient was clinically staged as squamous cell carcinoma stage I B₁ and a radical Wertheim's hysterectomy performed. Uterus was bulky with multiple filmy adhesions between tubes and ovaries on both sides. Two large lymph nodes 2 \times 2 cm were dissected from the right external iliac and obturator group. Rest of the dissected pelvic nodes were normal in size and feel. Cut section of uterus and cervix showed an endocervical growth 2 \times 2 cm extending onto the isthmus and lower part of uterus.

Continuous low-grade fever with vomiting and abdominal distension occurred post-operatively which did not respond to conservative management. Histopathologic examination confirmed the diagnosis of large cell non-keratinizing squamous cell carcinoma of the cervix infiltrating the endometrium. However, the endometrium also showed epithelioid cell granulomas with Langhan's giant cells (Fig. 1). Right obturator and external iliac lymph nodes showed extensive tubercular lymphadenitis with caseation.

PCR was performed on the formalin fixed paraffin embedded tissue for diagnosis of tuberculosis. Microdissection was used to scrape the granulomas and DNA was extracted by 'salting out method' and precipitated by isopropanol. DNA obtained was amplified by PCR and detected by southern blot hybridization. Oligonucleotide primers INS 1 and 2 were used to amplify DNA sequence of 245 bp. This nucleotide sequence corresponds to mycobacterial insertion sequence IS 6110 and is specific for 'mycobacterium tuberculosis complex'. Purified H37 Rv strain of mycobacterium tuberculosis DNA was included as a positive amplification control. Negative control included all reaction components without addition of template DNA. PCR was positive for mycobacterium tuberculosis in the endometrium and pelvic lymph nodes (Fig. 2).

Other tests for tuberculosis namely Mantoux, was positive at 20 mm and ESR was 72 mm. A repeat X-ray chest showed mild cardiomegaly but no evidence of pulmonary tuberculosis. A barium

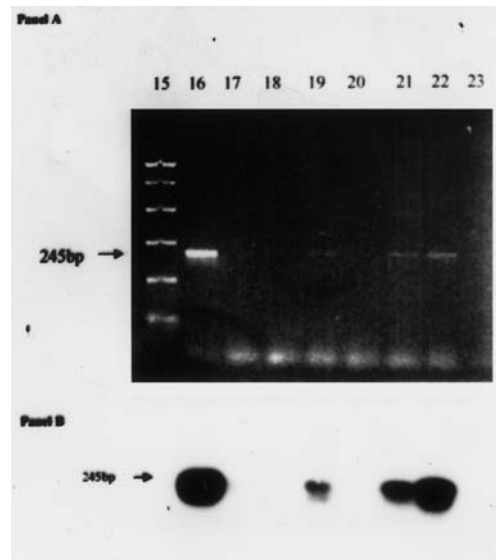


Fig. 2 *Panel A* Gel photograph of polymerase chain reaction (PCR) product and *Panel B* corresponding Southern blot of patient sample using INS primers. Lane 15 is the PCR marker. Lane 16 is the positive control while lane 23 the blank control. Lane 22 is the patient's sample showing a positive PCR product in *Panel A* and reconfirmed by Southern blot in *Panel B*

meal follow through was normal. HIV 1 and 2 by ELISA was negative. Patient was started on antitubercular treatment (4 drugs: INH, rifampicin, ethambutol and pyrazinamide) and discharged. At subsequent follow –up visits patient is doing well and has been disease free for 2 years.

Discussion

This case is presented for its rarity and to the best of our knowledge is the only other reported case of endometrial tuberculosis and squamous cell carcinoma of cervix co-existing in a postmenopausal woman [2]. Despite extensive tuberculosis existing in the endometrium, fallopian tubes and pelvic lymph nodes; fever, weight loss and other constitutional symptoms were absent preoperatively. Reactivation of a silent infection may have been responsible for a difficult postoperative period in this patient, which responded to antitubercular therapy. The diagnosis of tuberculosis in this case was made by use of PCR on archival tissue following detection by histopathology of extensive granulomatous reaction in the endometrium, tubes and lymph nodes.

The finding of epithelioid granulomas in association with malignancy is well documented in surgical literature and may occur within the neoplasm, in regional lymph nodes either involved or uninvolved, in sites of distant metastases or even in uninvolved organs [9]. Sometimes the granulomatous reaction may be so overwhelming that the underlying malignancy is obscured [10]. Host response has been suggested as the basic mechanism of granulomatous reaction in malignant neoplasms but the specific host and tumor factors that enable such a

response are unknown [17]. It is important to distinguish between this granulomatous reaction and tuberculosis by more specific methods [3]. Culture and acid fast staining was not possible as the granulomas were noted at histopathology after specimen fixation. Here, PCR helped clinch the diagnosis. The diagnosis and treatment of tuberculosis in a patient with cancer assumes importance as a high mortality has been seen in patients with co-existent disease [4, 8].

In a recent report from an oncology center in India, over a 15-year period, tuberculosis in association with malignancy was studied. Highest incidence occurred in head and neck cancer (42%) followed by gastrointestinal cancer (14.1%), lung cancer (13.8%), hematological cancer (10.7%), reproductive cancer (10.3%) and miscellaneous group (9%) [11].

With resurgence of tuberculosis worldwide, associated malignancy will not be uncommon and more cases of genital tuberculosis may be seen in women with postmenopausal bleeding. A meticulous curettage of the endometrium to include the cornual regions is suggested as the diagnosis was missed in this patient pre-operatively. In the event that this patient was treated with primary radiation/chemo-radiation a fatal disseminated tuberculosis may have occurred given the silent but extensive genital tuberculosis in this patient [9]. The HIV pandemic occurring worldwide especially in developing countries may well contribute to progression of both tuberculosis and cervical cancer [14, 15].

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