Accidental Early Diagnosis of Endometrial Adenocarcinoma by Pap Smear during a Cervical Cancer Prevention Study: A Case Report

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Abstract

Endometrial carcinoma is less common than cervical cancer but the disadvantage is that there is no mass screening method that can be used for early detection or prevention. The Papanicolaou (Pap) smear is useful for screening and preventing cervical cancer but occasionally also detects endometrial cancer, usually in advanced stages. Here we describe a case of endometrial cancer which was not detected in the initial Pap smear of a 40 year old woman. She had Low-Grade Intraepithelial Squamous Lesion (LSIL) with normal endocervical cells in the initial smear. Since she participated in a cervical cancer prevention study with antimicrobials and turmeric extract, her Pap smear was repeated within 5 weeks. Endometrial adenocarcinoma was clearly suspected in this follow-up Pap smear and the case was subsequently investigated and confirmed as Endometrial carcinoma. This case is presented for its rarity of clinical features: younger age, absence of common risk factors, and early detection because of cervical cancer prevention programs. A review of the literature reveals the potential of curcumin and turmeric extracts in controlling gynaecological cancers.

Keywords: Pap smears, Endometrial carcinoma, Cervical Cancer Prevention, Cancer screening, Risk factors for cancer, Early diagnosis of endometrial adenocarcinoma

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Introduction

Endometrial cancer is less common in Indian women[1] as compared to cervical cancer and Pap smear is not routinely used in screening for endometrial cancer. The diagnosis is usually made in women with irregular heavy bleeding or postmenopausal bleeding. Methods of diagnosis include i) Dilatation & curettage and histology ii) Endometrial biopsy with canula iii) Endometrial aspiration cytology or biopsy iv) Transvaginal ultrasonography can detect thickened or irregular endometrium beyond normal limits iv) Lastly Papanicolaou (Pap) smears used for Cervical cancer screening programs can occasionally detect endometrial carcinoma, but are not reliable[2-6]. MRI is usually used to gauge the extent of spread and staging.

None of the above diagnostic tests are advocated for routine mass screening for endometrial cancer because they have poor sensitivity and/ or specificity, or are invasive techniques so that they cannot be easily repeated regularly[2,4]. We have been involved in cervical cancer screening and cervical cancer prevention programs for several decades and have discussed the diagnosis of adenocarcinoma of endometrium in Pap smears[5]. It was possible to detect endometrial adenocarcinoma cells in Pap smears, however most of these cases were in an advanced stage and usually associated with postmenopausal bleeding or heavy menstrual bleeding in obese or Diabetic women.

This case report is of a young woman who had a negative Pap smear for cervical squamous, endocervical or endometrial cancer in the initial Pap smear collected in a screening program. The Pap smear revealed Low –Grade-Intraepithelial-Lesion (LSIL) with inflammatory changes. She agreed to participate in a study on cervical cancer prevention by integrated treatment with antimicrobials and a standardised turmeric extract[7]. The study was approved by an Independent Ethics Committee (IEC). However when she came for a check-up after 5 weeks, abnormal endometrial cells were observed in the Pap smear and later confirmed by endometrial curettage. The case report has been submitted to IEC as an unrelated Adverse Event requiring surgical treatment.

Case Report

Case No 7, aged 40 years, attended the routine Out Patient Department of a general hospital for chronic pain in neck and back following an accidental fall 3 years ago. She was referred for routine screening for cervical cancer with Pap smear on 8th March 2017, and the Pap smear was reported as LSIL with Inflammatory changes. She was invited to participate in cervical cancer prevention study for investigation of the effect of integrated treatment, with antimicrobials (single dose) and holistic extract of Turmeric (*Curcuma longa* Linn) given orally for 10 weeks after informed consent. The interim report for this study has been presented recently in an International conference[7].

Obstetric and Menstrual History:

The patient had menarche at the age of 15. She was Gravida 4, Para 2, had 2 induced abortions, and had 2 living children; last child was 17 years old. Her last pregnancy ended in severe postpartum haemorrhage with retained placenta in her village. She reported history of shock, and had required Manual Removal of Placenta under anaesthesia, but did not have a discharge card. She required blood transfusion. Subsequently she had failure of lactation and amenorrhoea and was treated with hormonal therapy for about 1 year, after which spontaneous regular menstruation returned with a cycle of 25-30 days till the age of forty. The periods were slightly delayed and irregular, but not profuse, only for last 2-3 months and her date of last menstrual period was 15-2-2017.

Contraception:

Husband used condoms. There was no conception in last 17 years.

Medical history:

The patient was treated by an endocrinologist for secondary postpartum amenorrhoea with hormonal therapy for 1 year. She had undergone investigations by a neurologist also and was informed that she had no residual pituitary lesion 14 years ago. She did not have her old reports but mentioned clearly that she had had X'rays of the skull and blood tests which were all within normal limits and did not require Thyroid hormone treatment. Thus she appeared to be a case of Partial Sheehan's Syndrome with full recovery[8].

She had history of a fall 3 years ago following which she had chronic pain in the neck. She had chikungunya and joint aches 6 months ago. For her aches and pains she required paracetamol tablets, 500 mg, occasionally (once or twice in a month). She was prescribed Ayurvedic pills twice daily for 1 week by Ayurvedic expert in the hospital.

Surgical history:

Not significant, except for 2 induced abortions and Manual Removal of Placenta after last delivery.

Initial examination:

Patient was apparently healthy, with a weight of 50 Kg and a blood pressure of 100/60 mm Hg. Neck movements were slightly painful with tenderness. There were no other positive symptoms on history or

signs on general examination.

Gynecological examination:

A small circum-oral erosion of the cervix was seen. There was no abnormal discharge from cervix or vagina. After collecting Pap smear, VIA and colposcopy could not be done because patient had a little bleeding from the cervix. Uterus was anteverted, normal in size and mobility was unaffected, not tender. Pap smear report was LSIL with inflammatory changes (Figure 1)[9].

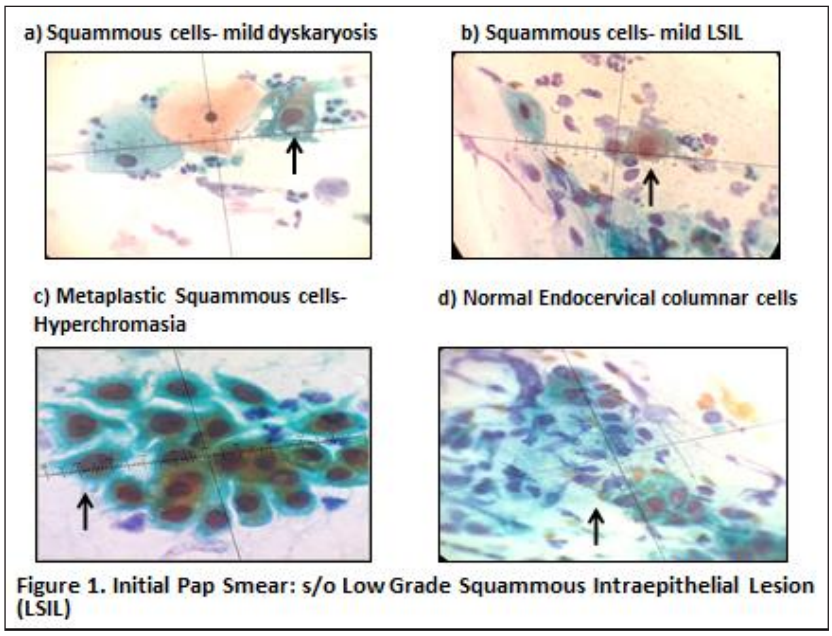

Figure 1. Initial Pap Smear: s/o Low Grade Squammous Intraepithelial Lesion (LSIL)

Initial biochemistry and routine urine test:

All biochemical reports were within normal limits- Complete blood count, Serum cholesterol, Liver enzymes, Serum creatinine, Serum Thyroid stimulating hormone, *Treponema pallidum* Hem-Agglutination test, HIV test, bleeding time, clotting time, and routine urine examination- Microscopic, sugar, and protein.

Integrated treatment:

This was started with syndromic treatment with antimicrobials (single dose, combination kit with forcanazole 150 mg + azithromycin 1 gm + secnidazole 2 gms) for associated asymptomatic infections as part of the preventive research study. There were no side effects. The standardised holistic turmeric extract (Haldone®, 600 mg, orally twice daily) was started after 1 week, after breakfast and dinner, and she tolerated it well as reported at 2 weeks and 5 weeks follow up[7].

Follow up at 5 weeks:

Patient took Haldone® regularly during this period. She had a normal monthly menstrual period 19 days ago. Her general and gynaecological examination remained within normal limits. She informed that she wanted to go to her native place and a follow up blood test and urine examination was also carried out. Haldone® was discontinued. No abnormality was detected on general examination and gynaecological examination.

Pap smear at 5 weeks showed regression of LSIL, normal endocervical cells and clusters of Abnormal columnar Cells (AGC) with multiple nucleoli suggestive of endometrial carcinoma (Fig 2).

All routine biochemical and urine tests which were repeated (except TSH, TPHA and HIV) were within normal limits after 5 weeks.

Differential Diagnosis:

The differential diagnosis of abnormal columnar cells in Pap smear is: a) Adenocarcinoma of cervix b) Adenocarcinoma of Endometrium c) Papillary adenocarcinoma of Ovary or Fallopian Tube d) Vaginal Adenocarcinoma e) Secondary Adenocarcinoma, in order of frequency[3,5,6]. The type of columnar cells and the clinical gynaecological examination, as observed, were not suggestive of the later 3 options. However cells from Adenocarcinoma of cervix and endometrium can look similar. In this case the

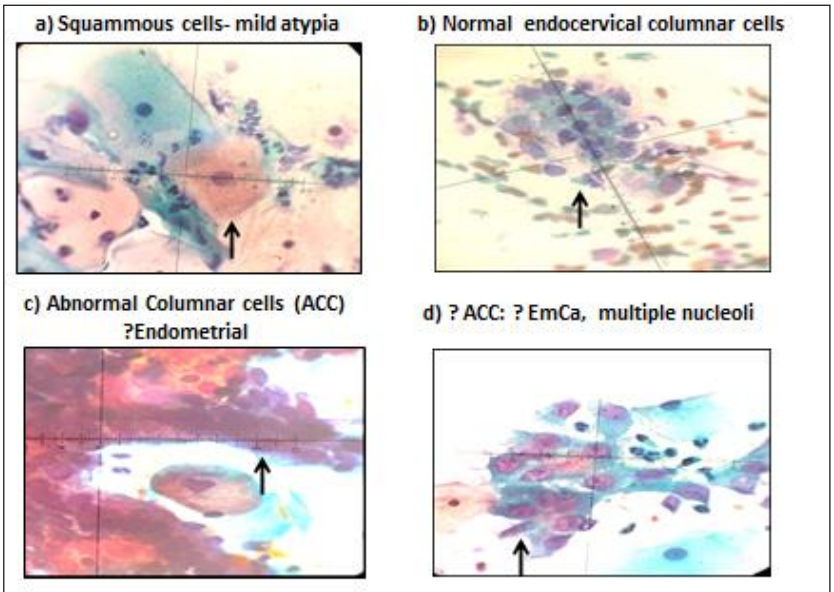

Figure 2. Pap smear – Post treatment Follow up after treatment for 5 weeks

presence of abundant normal endocervical mucus containing cells in both initial and follow up Pap smear, and a normal looking cervix favoured the source as endometrial. Besides the presence of clusters of degenerated tight clusters of abnormal nuclei in the second smear alongwith malignant looking columnar cells, in the absence of clinical cervicitis or vaginitis, was suggestive of a source higher up in the genital tract (such as uterine cavity) leading to shedding followed by degeneration down the passage. The patient was advised to undergo a Dilatation & Fractional Curettage with Multiple Cervical biopsies before she ventured going to her native place.

Histopathology report:

Histology was reported as a),b) Cervix- Koilocytotic atypia of Cervical squamous epithelium c),d) Endometrium: Moderately differentiated adenocarcinoma of the endometrium (Figure 3).

Following the curettage she was advised Trans-Vaginal Sonography. MRI could not be done.

TVS report:

Endometrial Thickness- 10 mm on 10th day after Fractional Curettage; Em-Normal, homogenous; No mymetrial abnormality, lymph nodes or other mass; Ovaries –Normal. Liver, kidneys and lymph nodes were within normal limits.

Thus her endometrial thickness was reported as 10 mm even after the fractional curettage. However myometrial invasion was not seen.

The case was diagnosed as early endometrial cancer and was advised a total hysterectomy. However patient did not stay on in Mumbai and went to native place. Subsequently patient could not be contacted for several months.

Post-hysterectomy Gynecological Follow up in Mumbai:

Patient returned after 6 months and reported that she had undergone a total hysterectomy in her home town. She had an uncomplicated post-operative recovery and stayed in native place for several months. Patient was well and had no complaints. She had a normal gynaecological speculum and bimanual examination with no residual mass, tenderness or granulation tissue. Uterus or ovaries were not palpable. She did not have symptoms of estrogen withdrawal.

She had brought her histology slides from hysterectomy and appendicectomy specimen for confirmation of diagnosis. These were then reviwed by the pathologist. Cervix showed Inflammatory reaction. There was no neoplasia or malignancy in the cervical columnar or squamous epithelium. Endometrial tissue was reported as early invasive, moderately differentiated, adenocarcinoma of endometrium (Figure 4). Appendix showed normal histology.

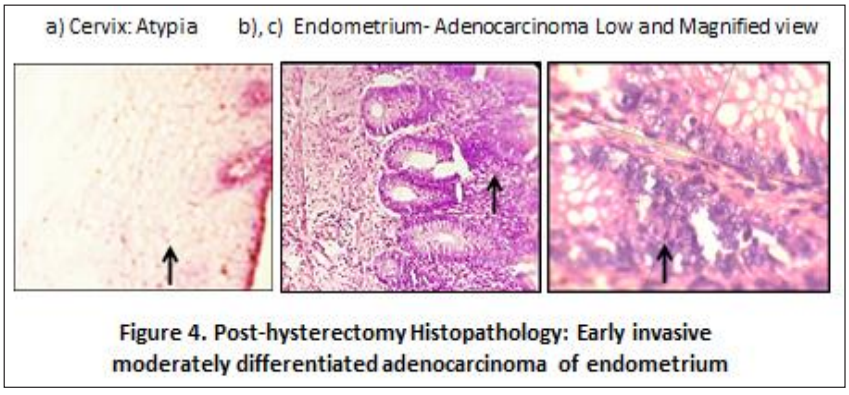

Figure 4. Post-hysterectomy Histopathology: Early invasive moderately differentiated adenocarcinoma of endometrium

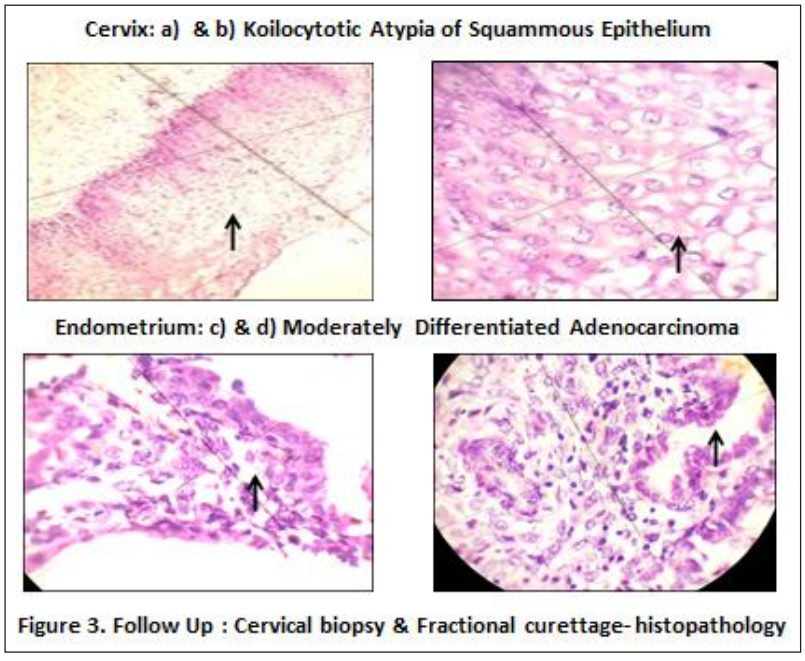

Figure 3. Follow Up : Cervical biopsy & Fractional curettage- histopathology

She was told about confirmation of the diagnosis and that treatment was adequate but that a regular follow up was necessary. She was advised an MRI or transvaginal ultrasonography but did not return to the centre and was again lost to follow up.

Discussion

In India, endometrial cancer is unusual in women in their early forties. This case is presented for its unique features: i) Relative rarity in a 40 year old woman. ii) Absence of risk factors like obesity, Irregular Heavy

Menstrual Bleeding, Diabetes, Nulliparity or Uniparity. iii) Uncommon history of hormonal therapy for 1 year, 16 years ago for a possible Partial Sheehan's Syndrome iv) Suspected initial diagnosis in a Pap smear, which is not routinely used for screening for endometrial carcinoma.

We have earlier reported on the role of Papanicolaou smear in endometrial cancer and have observed malignant endometrial cells, but usually in older women or in cases with postmenopausal bleeding[5]. The shedding of endometrial cells in a Pap smear must be reported and can occur in cases of heavy menstrual bleeding or in those with estrogen induced irregular heavy bleeding, due to cystic glandular hyperplasia. Menopausal Hormone Replacement Therapy is known to induce endometrial cancer in older women, but this case was not in that category[10].

In this case the first Pap smear had not revealed any endometrial cells but the second Pap smear within 5 weeks showed abnormal columnar cells and the case was confirmed later by histology as early endometrial carcinoma. Endocervical adenocarcinoma was excluded with careful initial and follow up Pap smears and this was confirmed by histopathology on 2 occasions-biopsy and hysterectomy specimens.

Effect of Turmeric extracts on gynaecological cancers:

This case also gave us the opportunity to review the effect of Turmeric extracts on gynaecological cancers. The potential of curcumin and turmeric extracts and anticancer mechanisms in cervical carcinogenesis are well known[7,11-14]. However recently there are reports of anticancer activity against endometrial cancer also, and may be ovarian cancer[15-19].

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