



Original Research Article (Clinical)

Cytologic follow up of Low-grade Squamous Intraepithelial Lesions in Pap smears after integrated treatment with antimicrobials followed by oral turmeric oil extract



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ABSTRACT

Cervical cancer is preventable because the carcinogenesis is slow and there are opportunities to detect precancerous lesions by Papanicolaou (Pap) smears, colposcopy, or HPV DNA tests and to treat them by antimicrobials, surgery or cold CO₂ vapourization. We have earlier reported on the chemopreventive potential of integrated treatment with antimicrobials therapy followed by a standardized oral Turmeric Oil (TO) extract upto 12 weeks in women who had persistent Low-grade Squamous Intra-epithelial Lesion (LSIL) in their Pap smears. In this communication we report their post-therapy follow up for 36 months (N = 18) with Pap smears. We were also able to follow up for 36 months control cases (N = 10) who had only standard therapy with antimicrobials.

During 36 months of follow up none of the cases with integrated treatment, progressed to HSIL or cancer. Out of 15/18 cases which had a regression of Pap smear, all 15 remained free of LSIL from 6 to 36 months post-therapy showing persistent therapeutic effect of integrated therapy. In one case there was recurrence of LSIL in Pap smear, ten months post-therapy, which regressed to mild atypia after a second course of oral TO for 8 weeks.

In the control group, persistence of LSIL after antimicrobials was observed in Pap smears in 5/10 cases when followed up by Pap smears up to 36 months. This preliminary report indicates some post-therapeutic benefit with integrative treatment as compared to the use of antimicrobials alone. A large scale controlled study is warranted.

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1. Introduction

Cervical cancer is a global health hazard and is more common in developing countries. There are an estimated 123,000 new cases of cervical cancer in India every year with 67,000 deaths in women in India alone [1,2]. This cancer has a long precancerous phase, of about a decade, in most women and screening methods like the Papanicolaou (Pap) smear, colposcopy and HPV DNA test are available for population screening yet, the disease continues to claim the lives of women in their forties and fifties, particularly

from low socioeconomic groups [3]. Human Papilloma Virus (HPV) is the principal causative factor in most cervical cancers though chemical carcinogenesis is also known. HPV vaccine has been developed against major High Risk HPV (HRHPV) types, yet it is not available universally and chemical carcinogenesis has been reported in murine models [4]. A large number of cases of cancers are still detected in women in an advanced stage. What is worse is that a large number of precancerous lesions, Low-grade Squamous Intra-epithelial Neoplasia (LSIL) and High-grade Squamous Intra-epithelial Neoplasia (HSIL) which are also detected by Pap smear remain untreated due to lack of treatment facilities or recurrences. These may regress spontaneously, after medical or surgical treatment, or progress to invasive cancer over some years [5–7].

Ayurveda has described cancer like lesions (arbuda, granthi, dushtavrana, sannipatikvyadhi) in various texts and described different therapies for the same. Based on the concepts of Rasayana

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therapy and Arbudachikitsa in Ayurveda, Kuttan et al. and Hastak et al., demonstrated the preclinical and clinical potential of oral Turmeric oil (TO) for Oral cancer [8–11]. Reverse Pharmacology principles were applied and safety studies have been conducted with Turmeric oil in animals and in healthy volunteers [12,13]. Baseline data on cancer screening, standard antimicrobial therapy and persistent LSIL was reported from women who came for follow up [14]. Subsequently a pilot study on integrative therapy of LSIL persistent after antimicrobial treatment and treated with oral administration of a standardized extract of TO [NBFR-03] was carried out and gave encouraging results. Out of 19 women with persistent LSIL who were treated for 12 weeks, none progressed and 16 regressed to Atypical or Negative smears [15].

This communication describes the follow up data of women in the above study who could be followed up till 36 months (N = 18), and compares them with other LSIL cases treated with antimicrobials alone but who did not take Turmeric oil treatment and came for follow up. The interim data with documentation of colposcopy and cytology was presented at the National Colposcopy and Cytology conference at Tata Memorial Hospital in 2012 [16]. It is important to note that it is after screening a very large number of women (> 1500) the precancer cases were identified and out of these, few came for follow up as the hospital caters to a population from far and near and also to cases outside Mumbai.

2. Patients & methods

All women with a diagnosis of LSIL in Pap smears were advised treatment with antimicrobials including their husbands (when applicable) and all were advised to come for a six monthly follow up for repeat Pap smears, whether they participated in the Turmeric oil study or not [14,15]. Those with persistent or recurrent LSIL or HSIL were referred to other hospitals for colposcopy, HR HPV DNA test and cervical biopsy when indicated. A total of 14 cases who had undergone integrative treatment with antimicrobials (Azithromycin, Forcanazole, Secnidazole, and if endocervicitis persisted, Cephadroxy) followed by standardized oral extract of TO as described earlier came for follow up in our clinic (Group 1) [15]. Another four cases who had completed the study, but could not come to our clinic regularly for follow up, had their Pap smears collected in their nearby clinics or hospitals and communicated their report telephonically. Some study cases (Group 1) have come for a longer follow up upto seven years. Ten cases who did not participate in the TO study but only took the antimicrobials also came for follow up smears up to 36 months (Group 2).

3. Results

The mean age of Group 1 (Antimicrobials followed by Turmeric oil treatment group) and Group 2 (only Antimicrobial therapy) was 41 ± 2.6 and 46 ± 3.5 years respectively; the range was 27–67 vs 36–65 years. The mean parity of Group 1 was 1.7 ± 0.2 vs 4 ± 3.5 in Group 2; the range was from 0 to 3 vs 2 to 8. The findings in repeat Pap smears at 36 months are reported in Table 1.

The microphotographs of representative Pap smears classified as per the Bethesda Classification from 1 case each of study group 1 and 2 are given in Fig. 1.

Other diagnostic tests were employed as required: HR HPV DNA in 2/18 in Group 1, 4/10 in Group 2; Colposcopy at follow up 5/18 cases in Group 1 and 7/10 cases in Group 2; and Cervical Biopsy in 3/18 in Group 1, and 3/10 in Group 2. None of the cases has developed HSIL or invasive cancer as confirmed by these investigations. Duration of follow up was upto 36 months in both groups.

Two cases had some unusual features on follow up and hence are described briefly.

Case No. 17 had an uneventful treatment period with integrative therapy but reported transient hematuria for 2 h under conditions of domestic shock (suicide in the family and unplanned stay in hospital for several hours in hospital). She was investigated thoroughly for renal and bladder disease but had negative reports. She was treated with Ayurvedic therapy for the single episode of hematuria for three months. Her smear had regressed from LSIL to Negative during study period but there was mild abnormality and slight increase in Nucleocytoplasmic ratio after one year and ten months. She consented to have TO therapy again for eight weeks. There was no hematuria or other urinary abnormality during or after treatment and smear regressed to negative status second time again [16]. Subsequently for four years she had negative smears. At six years follow up there was recurrence of LSIL. She was referred for colposcopy and biopsy [17].

Case No 12, had an extensive erosion covering 80% of cervix and history of recurrent post-coital bleeding prior to the study. She had undergone cauterization of cervix earlier and her previous cervical biopsy report was chronic cervicitis, negative for cervical cancer or neoplasia. However following a report of LSIL in our screening program she underwent standard antimicrobial therapy followed by oral Turmeric oil extract therapy for 12 weeks and had regression in the Pap smear to Mild Atypia at 12 weeks. Her erosion had healed and postcoital bleeding stopped. She came for six monthly follow ups and had recurrence of cervical erosion, LSIL in Pap

Table 1

Status of cases and controls, initially and after follow up – upto 36 months.

	Group 1 antimicrobials followed by TO	Group 2 only antimicrobials
No of cases	18	10
Pap smears initially LSIL	18	10
Antimicrobials taken	18	10
TO taken	18	0
Follow-up#		
LSIL	3	5
HSIL	0	0
Cacx	0	0
ASCUS	2	4
Atypia- or negative	13	1

#Pap smears after follow up at 36 mths 14 cases followed up in our clinic, 4 cases followed up outside, informed telephonically.

a. LSIL: Low grade intra-epithelial neoplasia.

b. HSIL: High grade intra-epithelial neoplasia.

c. Cacx: Cancer cervix.

d. ASCUS: Atypical squamous cells of unknown significance.

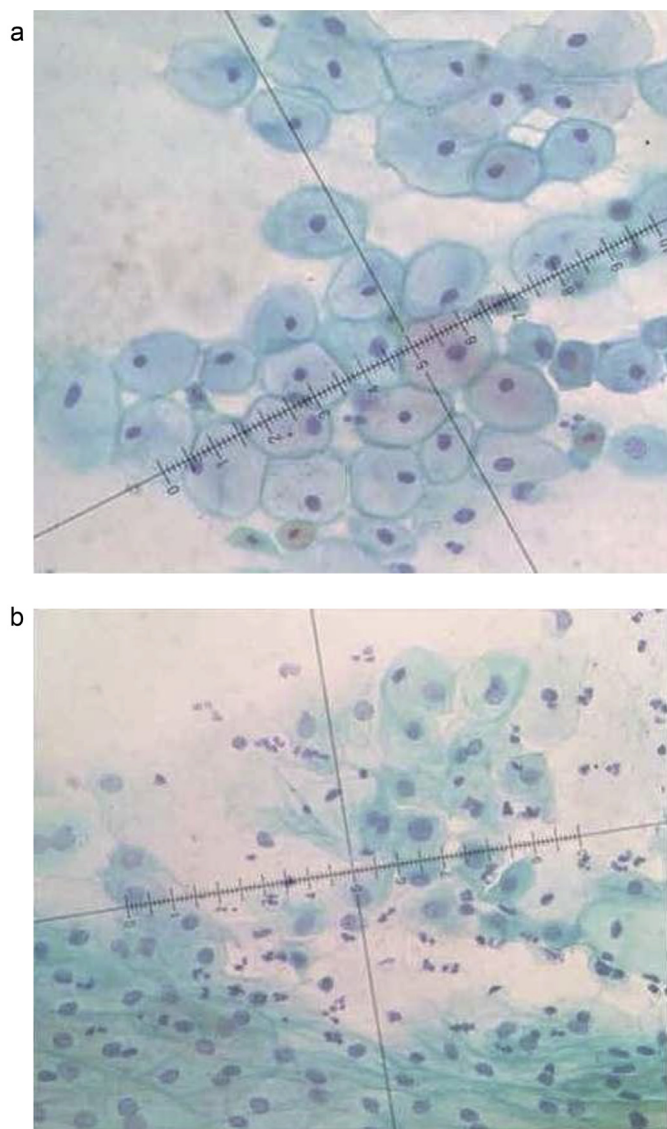


Fig. 1. Pap smears (X400) of cases in Group 1 and control group. a) Case no 1 in Group 1. b) Case no 10 in Group 2. a) Case in Group 1, one who showed negative smear after 3 years, and b) Control case who remained positive for LSIL after 3 years during the follow up*. *Patient was referred for immediate colposcopy and biopsy.

smears after two years but not on colposcopy. She had recurrence of postcoital bleeding. She underwent HPV DNA study, colposcopy and biopsy and which were all negative. She underwent douching with Panchavalkal Kwath in another Ayurvedic hospital and took oral Ayurvedic formulations and responded to treatment as her erosion healed and postcoital bleeding stopped. Her repeat smear in our laboratory after three years was Inflammation (Negative) and she has decided to undergo six monthly Pap smears and colposcopy.

4. Discussion

Cervical cancer is preventable because the carcinogenesis is usually slow and there are opportunities to detect and treat precancerous lesions by Pap smears, colposcopy, or by HPV DNA tests. Secondary chemoprevention has been attempted with compounds like folic acid, retinoic acid analogues, grape extract, fluorouracil, and other plant extracts which showed variable success and side

effects [5,18]. We have reported on the chemopreventive potential of integrated treatment of antimicrobials followed by oral Turmeric Oil (TO) extract, 0.2 ml twice daily, for 12 weeks in a group of women who had persistent Low-grade Squamous Intra-epithelial Lesion (LSIL) in their Pap smears after antimicrobial therapy. In this study we report their post-therapy long-term follow up with Pap smears and colposcopy when needed. Although the numbers are small, integrated treatment appears to have not only arrested or reversed Pap smear abnormalities but also appears to have persistent post-therapeutic benefit. Similarly one case who had mild deterioration in Pap smear improved again when she was administered TO for two months. This indicates the possibility of repeating the TO therapy without side effects, if needed.

Lindeque et al. and Söderlund-Strand et al. have reported a recurrence rate from 5 to 15% in cervical neoplasias after surgical treatment in long term follow up [19,20]. In conclusion integrative therapy with antimicrobials and oral TO extract appears to be a viable non-invasive option to surgical or cold knife therapy for reversal or arrest of Low Grade Squamous abnormality detected by Pap smear and confirmed by colposcopy. The limitation of this report is the small sample size and hence we recommend a larger long term study.

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