Original Article

Clinico-morphological Spectrum of Neoplasms of Uterine Cervix in a Tertiary Care Center in North Karnataka, South India

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Abstract

Introduction: Carcinoma of cervix is third most common malignancy encountered among women globally. About 80% of cases occur in developing countries. It has been estimated that approximately 2,30,000 women die annually from cervical cancer, and over 1,90,000 are from developing countries.

Materials and Methods: It is a 5 years study done in SDMCMSH, Dharwad. Cervical biopsy and hysterectomy specimen received in the department of pathology were involved in the study. Specimen were fixed in formalin, processed in automated tissue processor, paraffin embedded, sectioned and stained by hematoxylin and eosin. Special stains were done wherever necessary. Clinical details were collected from records.

Results: A total number of 324 cervical neoplasms were studied. Patient's age ranged from 24 to 80 years and mean age was 48.47 years. The most common age group involved was 41-50 years. Bleeding per vagina was the most common presenting complaint followed by vaginal discharge. Epithelial tumors constituted major bulk comprising 284 cases (88%). Among 324 cases, 223 (68.8%) cases were malignant, 32 (9.9%) cases were benign, and 69 (21.3%) cases were precursor lesions (i.e., cervical intraepithelial neoplasm (CIN) I, CIN II, and CIN III). Squamous cell carcinoma (SCC) (174 cases) was the most common malignant neoplasm. There were 8 cases of adenosquamous cell carcinoma, 5 neuroendocrine tumors, and 3 adenoid basal cell carcinoma. The least common malignant neoplasms were undifferentiated carcinoma, carcinosarcoma, and leiomyosarcoma with one case each. Leiomyoma was the most common benign tumor with 22 cases followed by adenomyoma and adenofibroma.

Conclusion: Neoplasms of uterine cervix include a wide range of lesions arising from both epithelial and stromal components. Malignant tumors were most common, and SCC was predominant. Women in the 5th decade are most commonly involved, however, with a wide range of age group (24-80 years). Patients may be asymptomatic or present with various complaints such as severe bleeding per vagina and urinary disturbances.

Key words: Carcinoma, Cervical intraepithelial neoplasia, Clinical presentation, Histopathology, Leiomyoma, Uterine cervix

INTRODUCTION

Carcinoma of the uterine cervix is the third most common cancer in females globally only next to breast and lung cancer. With the effectiveness of cytological screening programs, the incidence and mortality of cervix cancer have decreased drastically in developed countries. However, it is still the most common cancer of females in developing countries. Studies have shown that more than 80% of patients dying of cervical carcinoma are from developing countries.[1,2]

According to Indian council of medical research reports in India, the incidence is 14.42/1,00,000 population with a mortality rate of 2.83/1,00,000 population.[1] Particularly in South India, carcinoma cervix is the most common form of cancer in females. The disease is more prevalent in people living in poor living conditions and low-income groups, probably because of lack of hygiene and lack of regular health check-up due to financial constraints. India

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stands out not only for their high incidence but also for the unfavorable mortality ratio.[2]

It has been estimated that in an average women in the 4th decade has 2% chance of developing cervical cancer. Almost 50% of death from cervical carcinoma occurs in the middle aged women. Since this age group constitutes major working population, not only on the mortality, cervical cancer has major impact on the socioeconomic status of the families.[3] However, women from wide age groups, i.e., in their 20's to 90's are seen affected, and the patient may present with a wide array of signs and symptoms from being asymptomatic to fatal emergency.

Persistent human papillomavirus infection is found to be the predominant risk factor of carcinoma cervix. Lack of awareness, early age at marriage, low socioeconomic status, parity, race, tobacco smoking, etc., is also proven to be risk factors. Prognosis depends mainly on the stage of the disease at the time of detection. Histological type is also one of the important prognostic factors. Histological subtypes such as adenocarcinoma, small cell carcinoma, clear cell carcinoma, and sarcoma have poor prognosis.[4]

This study was undertaken to observe clinical features, associated risk factors, demographic features, and incidence of cervical neoplasms in our tertiary care center and to analyze the gross features and histomorphological distribution of the same.

MATERIALS AND METHODS

This study was conducted for 5 years in SDM College of Medical Sciences and Hospital, Dharwad. Before the study, ethical clearance was obtained from the institutional ethical board.

All the cervical biopsies and hysterectomy specimen submitted in the institution were evaluated and cases histopathologically diagnosed to show cervical neoplasm and precursors of cervical neoplasm were included in the study excluding those with non-neoplastic features, i.e., normal, inflammatory changes and infection from specific organisms.

Patients' data comprising of age, religion, presenting complaints, menstrual history, obstetric history, and examination findings were collected from medical records.

The data were analyzed by descriptive analysis, and results are expressed in percentages.

Cervical biopsy specimen and hysterectomy specimen received were examined grossly, fixed in 10% buffered formalin overnight. Cervical biopsies were processed completely, and multiple sections were given from the cervix in hysterectomy specimens, processed in automated tissue processor (Leica), paraffin embedded and sections of 3-4 micron thickness are cut using rotary microtome (Leica). Stained with hematoxylin and eosin stain, and detailed histomorphological analysis was performed as per the World Health Organization (WHO) classification of cervical tumors.

Special stains such as Periodic Acid-Schiff (PAS), reticulin, mucicarmine, and grimelius were done wherever required.

RESULTS

In this 5 year period of study, a total number of 3,152 hysterectomy and cervical biopsy specimen were received among them 324 (10.28%) cases showed features of uterine cervix dysplasia and neoplasm which were included in the study. The demographic features and clinico-morphological changes were thoroughly analyzed in these 324 cases.

Among 324 cases studied, 223 (68.8%) cases were malignant, 32 (9.9%) cases were benign, and 69 (21.3%) cases were precursor lesions (i.e., cervical intraepithelial neoplasm (CIN) I, CIN II, and CIN III). Patient's age ranged from 24 years to 80 years and mean age of distribution of cases was 48.47 years. Maximum number of cases, i.e., 100 (31%) were in the age group of 41-50 years, followed by 79 (24%) cases in 51-60 years, 77 (24%) cases in 31-40 years, 37 (12%) cases in 61-70 years, and 20 (6%) cases in 21-30 years and least number of cases, i.e., 11 (3%) were in age group 71-80 years (as seen in Table 1).

The majority of the patients presented with h/o bleeding irregularities (177 cases) such as post-menopausal bleeding, intermenstrual spotting, post-coital bleeding, and menorrhagia. This was followed by complaints of discharge per vagina (144 cases) comprising of white discharge per vagina, foul smelling discharge, and blood stained discharge. Urinary symptoms such as anuria and hematuria in 3 (0.95%) cases each were observed in Stage IV cases. Majority presented with more than one complaint. Mass per vagina in 24 (7.4%), mass per abdomen 16 (5%), loss of appetite 12 (3.7%), amenorrhea in 4 (1.2%) cases, and dyspareunia in 12 cases were other symptoms. Duration of symptoms ranged from 3 days to 10 years (Table 2).

About 50% of patients were post-menopausal. Menstrual cycles were irregular in 110 (34%) cases and regular in 52 (16%) cases. Among 324 cases, 322 were parous and

Table 1: Distribution of cervical neoplasms with reference to age

Age (years)	SCC	MIV	CIN	ADE	AB	AS	NE	UD	BEN	LMS	CAS	SEC	Total
21-30	3	6	7	-	-	1	-	-	3	-	-	-	20 (6.2)
31-40	29	3	23	5	1	-	2	1	10	-	-	3	77 (23.8)
41-50	41	4	23	10	-	4	1	-	17	-	-	-	100 (30.9)
51-60	54	1	10	6	-	1	1	-	2	1	-	3	79 (24.4)
61-70	25	-	5	2	2	1	1	-	-	-	1	-	37 (11.4)
71-80	8	-	1	1	-	1	-	-	-	-	-	-	11 (3.3)
Total (%)	160 (49.4)	14 (4.3)	69 (21.3)	24 (7.4)	3 (0.9)	8 (2.4)	5 (1.5)	1 (0.3)	32 (10.1)	1 (0.3)	1 (0.3)	6 (1.8)	324 (100)
Mean years	53.37	36.9	44.7	49.25	56	51.4	48.8	39	40.3	58	65	56.1	48.47

SCC: Squamous cell carcinoma, MIV: Microinvasive carcinoma, CIN: Cervical intraepithelial neoplasm, ADE: Adenocarcinoma, AB: Adenoid basal carcinoma, NE: Neuroendocrine carcinoma, UD: Undifferentiated carcinoma, BEN: Benign lesions, LMS: Leiomyosarcoma, CAS: Carcinosarcoma, SEC: Secondary tumors

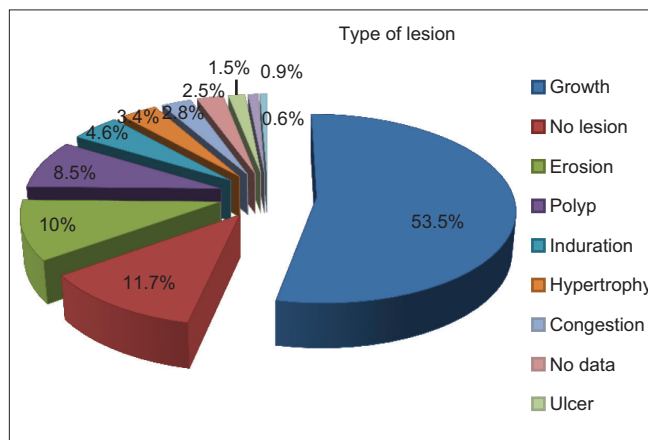## Table 2: Various clinical presentations in this study

Symptom	Number
Bleeding manifestations	177
Post-menopausal bleeding	78
Menorrhagia	67
Intermenstrual spotting	20
Post-coital bleeding	12
Vaginal discharge	144
White discharge per vagina	112
Foul smelling discharge per vagina	20
Blood stained vaginal discharge	12
Pain abdomen	69
Constitutional symptoms	41
Urinary disturbances	28
Mass per vagina	24
Mass per abdomen	16
Asymptomatic	13
Dyspareunia	12
Vulvar edema	6

Graph 1: Distribution of type of lesion

Graph 2: Classification of neoplasms of epithelial origin

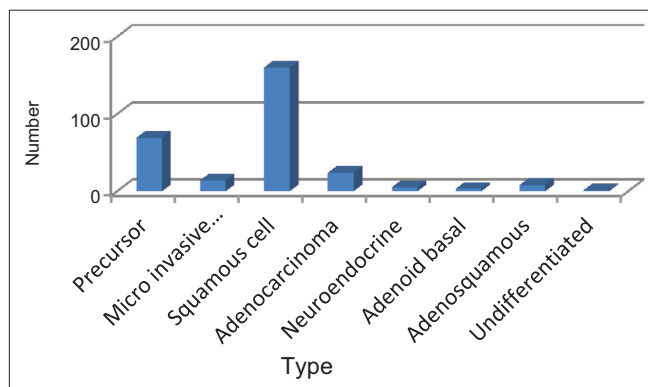only 2 were nulliparous parity in different neoplasms is shown in Table 3.

Friable growth was the most common lesion seen in 173 cases followed by erosion in 33 cases, polyp in 27 cases (multiple polyps in 2 cases) induration in 15 cases. Hypertrophy of both lips observed in 11 cases and congestion in 9 cases. Barrel shaped cervix was seen in 3 cases and multiple polyps in 2 cases. However, there was no observable lesion in 38 cases (Graph 1).

In 324 cases studied, epithelial tumors constituted the major bulk comprising 284 cases (88%). There were 32 benign cases (23 (7%) cases of mesenchymal tumors, 11 (3.2%) cases of mixed epithelial and mesenchymal tumors) and 6 (1.8%) secondary tumors. In our study, squamous cell carcinoma (SCC) (56.5%) is the most common tumor of epithelial origin, and undifferentiated carcinoma (UC) was the least common (0.4%) (Graph 2).

Squamous cells carcinoma was the most common neoplasm (160 cases). Variants of SCC seen were large cell non-keratinizing SCC 88 (55%) cases, large cell keratinizing SCC 65 cases (40.6%) with mean age of presentation being 51.9 years and 52.78 years. There were 6 papillary SCC and one warty variant. All patients were parous with only two nulliparous cases. The majority of them showed friable growth (129 cases) post-menopausal bleeding was the most common complaint followed by foul smelling discharge.

There were 16 cases of microinvasive SCC, with the mean age being 36.9 years (28-58 years). Erosion was the most common finding on examination (6 cases).

There were 69 cases of precursor lesions comprising of 22 cases of CIN I, 16 cases of CIN II, and 31 cases

Table 3: Parity in different cervical neoplasms

| Histopathological subtype	Parity (%)				Total (%)
	1-3	4-6	7-9	10-12	
Squamous cell carcinoma	61 (38.6)	88 (55.6)	9 (5.8)		158 (100)
Adenocarcinoma	7 (29.1)	15 (62.5)	2 (8.4)	-	24 (100)
Precursor lesion	39 (56.5)	27 (39.1)	3 (4.4)		69 (100)
Microinvasive carcinoma	10 (71.4)	4 (28.6)	-	-	14 (100)
Adenosquamous carcinoma	3 (37.5)	3 (37.5)	2 (25)	-	8 (100)
Adenoid basal carcinoma	1 (33.3)	1 (33.3)	-	1 (33.3)	3 (100)
Neuroendocrine carcinoma	1 (20)	4 (80)	-	-	5 (100)
Undifferentiated carcinoma	1 (100)	-	-	-	1 (100)
Benign tumors	25 (78.1)	7 (21.9)	-	-	32 (100)
Leiomyosarcoma	-	-	1 (100)	-	1 (100)
Carcinosarcoma	-	-	-	1 (100)	1 (100)
Secondary tumors	3 (50)	-	3 (50)	-	6 (100)
Total	151 (46.9)	149 (46.3)	20 (6.2)	02 (0.6)	322 (100)

of CIN III. The majority of the cases were seen in the 4th decade; however, a good number of cases were seen in the 3rd decade. Discharge per vagina and intermenstrual spotting were the most common presenting complaints. Per speculum examination showed erosion in many cases (Graph 3).

In 24 cases of adenocarcinoma, the mucinous variant was more common 9 cases, with mean age of presentation being 49.25 years, and endometrioid type was seen in 5 cases. All patients were multiparous and bleeding per vagina was the most common complaint (14 cases). All cases showed PAS and mucicarmine stain positivity.

There were 3 cases of adenoid basal carcinoma, 8 cases of adenosquamous, and 5 cases of neuroendocrine carcinomas (4 large cell type and 1 small cell type) with mean age of presentation being 56, 51.4, and 48.8 years, respectively, and one undifferentiated tumor (39 years). Discharge per vagina was the most common complaint. One case of adenosquamous carcinoma showed clear cell change which was PAS positive. All 5 neuroendocrine tumors showed positivity for grimelius stain.

In 32 benign tumors, 22 were leiomyomas, 6 adenomyoma, and 4 adenofibroma. The mean age of leiomyoma was 40.3 years, majority of the cases presented with h/o intermenstrual spotting, and others with post-menopausal bleeding. On examination, polypoidal growth was noted. One case of leiomyosarcoma (LMS) (58 years) and one case of carcinosarcoma (CAS) (65 years) were noted.

There were 6 cases of secondary tumors with mean age 56.1 years (34-56 years). Primary of 3 cases were endometrium, 2 cases were ovary, and 1 case from the fallopian tube. On examination, 3 cases showed growth over both lips of the cervix, erosion in others.
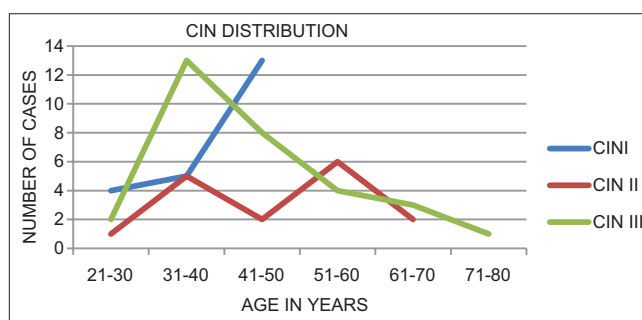
Graph 3: Cervical intraepithelial neoplasm distribution

DISCUSSION

Cervical Neoplasms are one of the important causes of morbidity and mortality in females worldwide, more so in developing countries. Approximately 2,30,000 women die annually from cervical cancer, and over 1,90,000 of those are from developing countries.[3] Carcinoma cervix is considered as one of the preventable diseases since it can be detected in the preinvasive stage by simple screening procedure like pap smear and treated accordingly. With the effective implementation of screening procedure and awareness of the public toward it, the incidence of carcinoma cervix has been dramatically decreased in western countries; however, it is still one of leading cancers in developing countries. In India, incidence of cervical cancer is more in rural area compared to the urban population; low socioeconomic status, lack of awareness, early age at marriage, multiparity may be the contributory factors for this disparity.[2,5]

In this study age of the cases ranged from 24 years to 80 years with mean age of presentation being 48.47 years. The most common age group affected was 41-50 years (31%) (Table 1) which is similar to the studies done by Pradhan *et al.,*[3] Shruthi *et al.,*[5] Fotra *et al.,*[6] Sinha *et al.,*[7] and

Jashamy KA *et al.*[8] Mean age of presentation of benign tumors was 42.36 years which is close to the studies done by Usha *et al.*[9] and Solapurkar *et al.*[10]

Bleeding irregularities (EB, PCB, IMS, and PMB) was the most common complaint followed by discharge per vagina (WDPV, FSD, BSD) which is similar to the studies done by Shruthi PS *et al.*,[5] Das *et al.*,[11] Sinha *et al.*,[12] and Peel *et al.*[13] Urinary symptoms such as increased frequency of micturition, burning micturition was observed in 8.1% cases in this study which is comparable to the study done by Das *et al.*,[11] were in 12.02% cases presented with these symptoms. Patients presented with back ache in 5% cases and pain abdomen in 21.3% cases which are similar to the study done by Usha *et al.*,[9] in which back ache and pain abdomen were observed in 5.68% and 31.03% cases, respectively.

Only 2 cases were nulliparous in this study accounting to 0.6% of all the cases which is similar to the study done by Das *et al.*[11] (0.4% cases). It was observed that in all studies including ours parity was >98%, i.e., 99.4% cases in our study comparable to the other studies such as by Das *et al.* 99.6%,[11] Shalini *et al.*[14] 100%, Peel *et al.*[13] 100%, and Usha *et al.*[9] 98.26% indicating its role as a risk factor in developing carcinoma cervix. Multiparity (>3) accounted to majority number of cases which is similar to the study done by Shruthi *et al.*[5] and Fotra *et al.*[6]

In this study, women in premenstrual age group and post-menopausal age group is 50% each which is comparable to the study done by Jeong *et al.*[15]

Hysterectomy specimens accounted for 19.2% cases and other small biopsies to 80.8% which in this study which can be compared to the study done by Solapurkar *et al.*[10] Less number of hysterectomy specimens in our study can be attributed to the reference of carcinoma cases after detection to higher cancer centers for radiotherapy.

Incidence of CIN III was more compared to CIN I and CIN II in this study, which is comparable to the studies done by Sinha *et al.*,[7] Jashamy *et al.*,[8] and Choudhury M *et al.*[16] In our study, it was observed that more number of precursor lesions were concentrated in the 3rd and early 4th decades, compared to the overt malignancy which is more common in 5th decade suggesting that more emphasis should be given for early screening of the disease and educate people about the same.

Among invasive neoplasms SCC, adenocarcinoma and adenosquamous cell carcinoma constituted the major bulk in this study. Among these, 3 SCC was most common accounting to 84.5%, followed by adenocarcinoma (11.7%)

and adenosquamous carcinoma (3.8%). Distribution of these 3 tumors in this study is similar to the study done by Shingleton *et al.*[17] and closely comparable to the studies done by Jeong *et al.*,[15] Alfsen *et al.*,[18] and Galic *et al.*[19] It was observed that in all studies compared SCC was the most common tumor and adenosquamous cell carcinoma the least common one.

Large cell non keratinizing (SCC) squamous cell carcinoma was the most common variant of SCC accounting for 55% followed by Large cell keratinizing squamous cell carcinoma SCC in this study. There were 3.75% cases of papillary variant of SCC and 0.65% cases of warty carcinoma. This distribution is similar to the study done by Sinha *et al.*[7] However, in the study done by Sinha *et al.*,[7] they followed classification of SCC of 3 tiered system, i.e. .LCK SCC, LCN SCC, and small cell type SCC, whereas in this study, we followed classification of 2 tiered system proposed by the WHO. It was observed that in all the studies compared LCN SCC was more common except for the study done by Bisht *et al.*[20] where in LCK SCC was most common accounting to 45.45%.

Adenocarcinoma was the second most common epithelial neoplasm with 24 cases. Endocervical variant accounted for 23.76% and intestinal variant accounted for 2.4% which is comparable to the study done by Alfsen *et al.*[18] Bleeding irregularities was the most common complaint. Only one case of UC accounting to 2.4% of all tumors was observed which is similar to the study done by Alfsen *et al.*,[18] in which it accounted for 3.1% cases.

There were 8 cases of adenosquamous cell carcinoma with age range being 30-70 years. Mean age is 51.4 years. This can be compared to the study done by Alfsen *et al.*,[18] in which the mean age was 53 years. 5 cases of adenosquamous cell carcinoma in this study showed clear cell change which was similar to the study done by Fujiwara *et al.*,[21] in which 11 cases of adenosquamous carcinoma showed clear cell change. In our study, 3 cases of adenoid basal carcinoma was seen with mean age of presentation being was 56 years which can be compared to the study done by Parwani *et al.*[22] There were 5 cases of neuroendocrine tumors, small cell variant being more common accounting to 80% with mean age of presentation being 48.8 years which is comparable to the study done by Alfsen *et al.*[18]

There was only one case of CAS in this study accounting for 0.31% of total tumors which is similar to the study done by Solapurkar *et al.*,[10] in which it constituted 0.4% (2 cases) and a single case of LMS accounting to 0.31% of total cases where a 58-year-old female patient presented with h/o bleeding per vagina, on examination showed diffuse

growth involving entire cervix which is similar to the study done by Wright *et al.*[23]

In this study, there were 14 cases of microinvasive SCC accounting to 4.3% of total tumors which can be compared to the study done by Solapurkar *et al.*[10]

There were 32 cases of benign tumors in our study, leiomyomas constituted the most common benign tumor of cervix with 22 cases accounting for 6.8% of total cases which is similar to the study done by Usha *et al.*[9] Age range in this study was 20-46 years with mean age of presentation being 40.3 years which is similar to the study done by Tiltman,[24] in which the mean age was 41 years. Adenomyomas were the second most common benign tumors in our study with 6 cases accounting to 1.85%. Mean age of cases with adenomyomas was 40.8 years which is similar to the study done by Gilks *et al.*[25] on adenomyomas in which mean age was 40 years. In our study, endocervical variant of adenomyoma was more common which is comparable to the study done by Gilks *et al.*[25]

Adenofibromas are rare benign mixed epithelial and mesenchymal tumor of the cervix. In our study, there were 4 cases of adenofibroma with age range 42-49 years with mean age being 46 years. Haberal *et al.*[26] studied one case of adenofibroma, in which 55-year-old lady presented with bleeding per vagina on examination there were multiple polypoidal lesions. In our study in 3 out of 4 cases showed multiple polyps.

CONCLUSION

Cervical carcinoma is the third most common malignancy encountered among women globally with a wide variation of incidence. It is more common in developing countries like India cause maybe attributable to the lack of awareness, low socioeconomic status of the people. Patients may be asymptomatic but most commonly present with various complaints such as bleeding per vagina, discharge per vagina, and even features of renal failure. In our study the mean age of presentation was 48.74 years and 99.4% cases were multiparous both these findings reiterate the time honored teaching that cancer cervix is more common in multiparous women in their 5th decade of life. Precursor lesions were seen a decade earlier to the neoplasms, and few cases of SCC was also noted in the 3rd decade. These findings urge that screening procedures should be started in an earlier age group in women who are sexually active, and a thorough check-up is indicated in women with simple complaints like white discharge per vagina.

Neoplasms of uterine cervix include a wide range of lesions arising from both epithelial and stromal components.

Among them, epithelial neoplasm is most common and SCC being predominant. However, other histologic types such as adenocarcinoma, adenosquamous carcinoma, and neuroendocrine tumors occur in relative frequency.

This study highlights a wide spectrum of histological subtypes in a small study population and the importance of subtyping in view of prognosis and further treatment since management depends largely on the histological type of carcinoma.

To conclude carcinoma of cervix presents with varied clinical presentations affecting women from 2nd to 8th decade and shows various histopathological features.

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