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Review Article

Carcinoma-In-Situ of the Cervix - Where the Story Must End

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Carcinoma in situ of the cervix, by definition and classification is a malignant transformation of the Cervical epithelium in which the basement membrane is intact. It is further understood that when endocervical glands are involved and the basement membrane of the glands is intact, it is still classified as carcinoma in situ. FIGO staging refers to it as stage O.

Carcinoma in-Situ is but a phase in the continuum of a disease process of carcinogenesis. It begins as mild dysplasia, which progresses to moderate and severe dysplasia. The next stage is carcinoma in situ. Laboratory data has conclusively proved that C.I.S. is a stage when the tumour has reached an autonomous growth potential, is no longer dependent upon the action of carcinogens. Further, in the lifetime of the individual this will progress to invasive cancer, which is potentially a fatal condition.

In 1969, WHO announced that Cervical cancer is a preventable disease. Many questions were then asked. How is it prevented? Has any society been able to prevent it? Clarifications involved explaining that INVASIVE Cervical Cancer can be prevented, if diagnosis is made at a PRECANCEROUS stage. Further correct treatment has to be given to the woman to eradicate to precancerous stage and a strict follow-up ensured. This squarely rests the responsibility on the Medical personnel involved, health care authorities and the women individually to participate in what is called "Screening programme for the detection of asymptomatic precancerous stage namely carcinoma-in-situ".

Tremendous research has been done in the last 30 years to make this dream a reality. In certain developed countries like Holland it has become a reality as incidence of invasive cervical cancer has gone down to less than one per 1,00,000 women. In most developed countries success has been substantial with a low incidence of invasive cervical cancer and a high detection rate of carcinoma in situ. In USA, the mortality from invasive Cervical Cancer has come down to 4 per 1,00,000 in the year 2000.

So the message is clear, the story of cervical cancer must end with carcinoma in situ and that invasive cervical cancer must be prevented.

Classification of preneoplastic lesions is undergoing constant change. Several new classifications have come into use. Richart (1968) described the cervical intra epithelial neoplasia (CIN classification). In this CIN I and CIN II are considered reversible lesions. CIN III includes severe dysplasia and carcinoma in situ, which are irreversible lesions.

Further in 1991, Bethesda classification was

introduced. By this time the role of Human Papilloma Virus infection was well understood and it had to be incorporated. Bethesda divides the lesions into 2 categories, Low Grade Squamous Intra Epithelial Lesion (LGSIL) which includes HPV lesions and mild dysplasia. The other is High Grade Squamous Intra Epithelial Lesions (HGSIL) which includes moderate and severe dysplasia and carcinoma in situ.

It does not matter which classification is being used as long as there is a good understanding between the Clinician and the Cytopathologist.

Historical Survey.: Novak (1962) has reviewed in detail the historical background of carcinoma in situ. In the 19th Century, references were made to conditions like early cervical cancer, which were perhaps in situ lesions. However, as quoted by Novak, the first accepted credit goes to Schottlaender and Kermauner of Germany who in 1912 described what is now known to be carcinoma-in-situ. Most of the early literature is in German language. German students Reuben and Schiller who came to USA further called attention to the presence of neoplastic epithelium which occurred on the surface adjacent to invasive cancer. At that time it was thought that cancer spread by in situ lesion. It was Walter Schiller who called it "Beginning" cancer indicating that it precedes invasion. Telinde and Galvin (1944) reported on minimum histological changes in biopsies to justify diagnosis of Cervical Cancer.

Pemberton and Smith (1929) were the first pathologists to accept the new entity as an early carcinoma and the tide turned after that.

It was Hamperl (1959) from Germany who first described in 1935 Micro-invasion and first described the important role that the basement membrane plays in controlling the lesion.

Friedel et al in 1960 published a Monogram on Carcinoma in situ and reviewed the pathology and clinical features.

The privilege and pleasure of diagnosing a case of carcinoma-in-situ goes to those who painstakingly and diligently screen women with Pap Smears. For this a dedicated group of Cytotechnicians and Cytopathologists are required and a large number of women screened. Further evaluation with Colposcopy and Biopsy and a close follow up are essential.

In the Cytology Clinic (AMWH of Cama & Albless Hospital 1,00,747 women were screened over a 30 year period from 1970 to 1999. Out of these 96.87% smears were normal or inflammatory.

The abnormal smears are given in Table No. I

Mild and Moderate Dysplasia accounted for 551 and 261 respectively. They were given conservative treatment and followed up.

There were 94 cases of severe dysplasia and 193 of Carcinoma-in-situ which together form CIN III group. As many as 108 were diagnosed as early occult invasive Cancers. During the same period of time 953 cases of advanced cancers were seen. Despite the continuous screening and awareness campaign the number of advanced cancers has not been decreasing.

It is interesting to note the age groups in which these lesions are seen. The mean age of mild dysplasia is 30.5 years while for early occult lesions it is 45.3 years. This emphasises two important facts.

1) Screening must begin by age 35 years.
2) Women between the ages of 30 and 45 are attending hospitals for various Gynaecological and Family Planning Problems. Every attempt must be made to screen these women. It will be very rewarding. In a hospital setting it is possible to further investigate the case and keep under followup. For this the starting of Cytology Clinics and Dysplasia Clinics in all major Gynaecological Institutions is a pre requisite.

Table I

Year 1970 1999
Total number of patients : 1,00,747
Normal and Inflammatory : 96,871

	Mild Dysplasia	Moderate Dysplasia	Severe Dysplasia	CIS	Early Occult	Total
Number of Cases	551	261	94	193	108	1207
Per Thousand	5.52	2.70	0.90	1.93	1.08	12.13
Mean Age	30.5	34.00	37.50	38.9	45.3	30 to 45

Suspicious Cases : 263
Advanced Cancers : 953

Our experience of managing 287 cases of CIN III indicates that Colposcopic evaluation with acetic acid and Schiller Iodine tests is a necessary step. The case is reviewed with all other reports and interviewed with family members. A fractional curettage with a cone biopsy is planned under anaesthesia. For very large lesions, cone biopsies are not advisable and may be replaced with multiple punch biopsies.

In young women who have not completed their families a cone biopsy may be diagnostic and therapeutic. Serial sections of the cone must indicate that the lesion has been totally excised. Post-cone Cytology is done after 6 months. If negative patient may plan a pregnancy. In our series we had 4 cases who have conceived and delivered after cone biopsy. Currently LLETZ procedure is used instead of cold knife conisation. It was first described by Prendeville & Cullimore in 1989. Later Luesley and Cullimore (1990) reported a large series of loop diathermy excision of transformation zone.

For all women who are over 40 years of age and who have completed their families a simple Hysterectomy is treatment of choice. An abdominal or vaginal Hysterectomy may be performed. Ovaries may be preserved in younger patient. The morbidity and mortality of these procedures is negligible. Moreover it can be done in any setting, by any Gynaecologist. A patient may not have to go far to get the treatment. There is no need for radiation or Chemotherapy. Hence the treatment becomes simple, affordable and acceptable to a large majority of women.

In a developing country like India which has a large number of practicing Gynecologists and a small number of cancer institutes this offers a solution to the control of Cervical Cancer.

The other modalities of treatment used by the author (Saraiya 1998) include CO_2 Laser, either ablation or conisation and Cryotherapy. Andersen & Nielson (1990) have reported very satisfactory results when CO_2 Laser is used for conisation.

These different modalities enable one to select the correct treatment for each patient and thus individualise the therapy.

Basement Membrane

It is the basement membrane, which controls the spread of Carcinoma in situ. However, it is not just an anatomical barrier, which contains the malignant cells for a very long time. Nair et al (1997) from Trivandrum have studied the basement membrane in health and disease. They did immuno histochemical studies of Laminin, Collagen IV and fibronectin. Their studies indicate:

1) A strong and continuous basement membrane is seen in normal cervices.
2) Breaks in Basement membrane are seen in high grade SIL.
3) There is a correlation between the grade of SIL and the number of breaks.

Further Richards and Turness (1990) have reported that virus especially HPV, causes breaks in basement membrane.

The basement membrane is the location where tumour-host interaction takes place. The host response is assessed by the stromal response. There is an active inflammatory exudates. Cells are recruited from the mononuclear phagocyte system. These are transformed into Langherhan's cells. They produce alpha interferon which destroys cancer cells that escape into the stroma from the breaks in the basement membrane. It is only when the host response is inadequate that invasive lesion starts. Hence on the cone biopsy specimen, a study of the host response and histochemical studies would be of prognostic value.

Extent of the Lesion

The size of the lesion is not taken into consideration in the classification. The size of the lesion is however all important to the Clinician faced with treatment. It also perhaps has a relationship to the prognosis. How long the lesion has persisted prior to diagnosis may also be determined by the size. It seems reasonable to believe that a small lesion is perhaps recent. As time passes the lesion becomes larger and therefore a large lesion may have been there for a number of years. We have come across 4 cases of extensive carcinoma in situ.

Case No. I : The entire endometrial cavity was lined by squamous cell carcinoma in situ.

Case No. II : There was extensive CIS of the entire endocervical epithelium. In addition there were several foci of microinvasion.

Case No. III : There was carcinoma in situ of the vagina upto middle 1/3 of the vagina.

Case No. IV : There was extension to lower 1/3 of the vagina almost reaching the introitus. This was a case of multicentric HPV disease.

Angiogenesis

Why carcinoma in situ remains static for upto

5-10 years is a much-studied subject. One of the reasons is because of an inadequate blood supply. The tumour outgrows it's own blood supply and then it cannot grow further.

Stafl (1998) has studied the terminal vascular architecture in cervical biopsies. He has proved that as epithelium starts growing the existing vessels become tortuous and try to supply additional blood. The intercapillary distance increases in carcinoma in situ as growing cells compress the vessels. However at some stage the tumour secretes a factor know as "Angiogenesis Factor' which helps to sprout new immature capillaries on the surface. There is a spurt of growth and soon invasion occurs. This corresponds to the clinical finding of Cervix bleeding on touch.

Today Research indicates that blood supply is really a tumours "Achille's Heel". If blood supply can be blocked, the growth of cells cannot occur, neither will the growth spread. Several agents are discovered which block the angiogenesis factor. Many are under trial. One drug, which is already available, is Angiostatin. It inhibits endothelial proliferation and induces dormancy in a tumour. Proliferation equals apoptosis of tumour cells and there is regression over a period of time, which is without toxicity. Hence in the near future DORMANCY will be an additional modality of Cancer therapy.

Folkman (2000) has reviewed the current status of tumour angiogenesis.

Conclusion

The principle of management of CIN III and Carcinoma in situ remain the prevention of invasive cancer. Although many modalities are currently available, it is difficult to say which one is better. Treatment has to be individualised. The wishes of the patient and her family have to be taken into account. The fear of developing cancer can cause phobia and such patients usually request a hysterectomy.

As we enter the new Millenium in India, awareness regarding pre-cancerous lesions is just being developed. When screening becomes more universal, many more patients will be detected who will need special management. It will then be the duty of every Doctor, whether a General practitioner, a Physician or a Gynaecologist to advice the women on what is the most suitable treatment.

"Preventable but not yet prevented" remains the reality of invasive cervical cancer today. However it is hoped that the dawn of the new century will succeed in bringing down the curtain on invasive cancer. It is hoped that invasive Cervical Cancer will become a truly prevented condition and all cases will be diagnosed and treated in intraepithelial or in-situ stage.

To end, I would like to quote Amarty a Sen, India's Nobel Prize winner.

"Among the most important freedoms that we can have, is the freedom from avoidable ill health and from escapable mortality".

This is ever so true of cervical cancer. We must all remember that for Cervical Cancer there is still an "Unfinished Agenda". Everyone needs to address it.

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