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REVIEW ARTICLE

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Significance of human papilloma virus (HPV) infection in cervical carcinogenesis

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Introduction

The control of cervical cancer has been on the agenda of health care workers all over the world for several years. It is more of a problem in the developing world as 80% of all cases are seen in low resource setting. India contributes 18% of total cases. Approximately 1.2 lakh cases occur in India each year out of these 80,000 present with advanced disease and succumb within a year. However, the scenario changed dramatically in the 20th century. With the introduction of radiotherapy, the concept of precancer, and routine use of Pap smear in the developed world the disease is finally getting under control.

Although it has been known since centuries that cervical cancer was in some way related to sexual activity no definite carcinogen was implicated. It was in the 1970s that Zur Hausen [1] in Germany implicated that the human papilloma virus was the causative organism which led to the development of cervical cancer.

Further developments were rapid. Over a 100 different types of HPV specific to human beings were discovered. At least 30 of these affect the genital mucosa. They are further divided into high oncogenic potential and low oncogenic potential HPV. Cervical cancer is the first solid tumor associated with virus infection. It is a spherical DNA virus, spherical with 72 capsomeres and double stranded circular viral genome, (Figure 1).

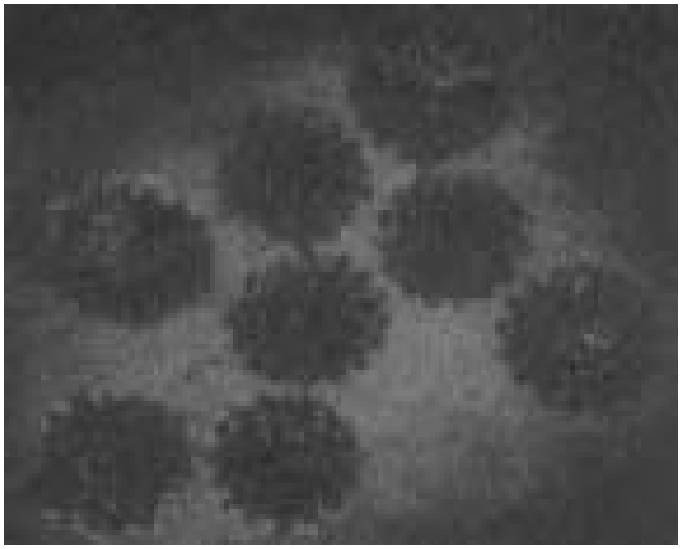

Figure 1. HPV virus.

Zur Hausen's [2] research resulted in a monumental work which explained molecular pathogenesis of cancer cervix and its causation by a virus, which radically changed our thinking. However, it is only in the last 30 years that there have been substantial changes in the understanding of the disease and major changes in the concepts of control.

Etiopathology

The virus enters the genital tract by sexual contact and may affect any part of the lower female genital tract. The incubation period is usually 1-6 months. After that the first lesions may appear and there is a rapid and active growth of

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the virus. At the same time, the immune responses occur and the host tries to contain the virus. After about 9 months of this activity, one of the two outcomes is expected. If the immune response is good there is a sustained clinical remission, which occurs in the majority. However, if the immune response is poor then there is a persistent and recurrent disease. Here the lesions go through the low grade squamous intraepithetial lesion (SIL) to high grade SIL (Figure 2) and eventually to invasive cervical cancer (Figure 3).

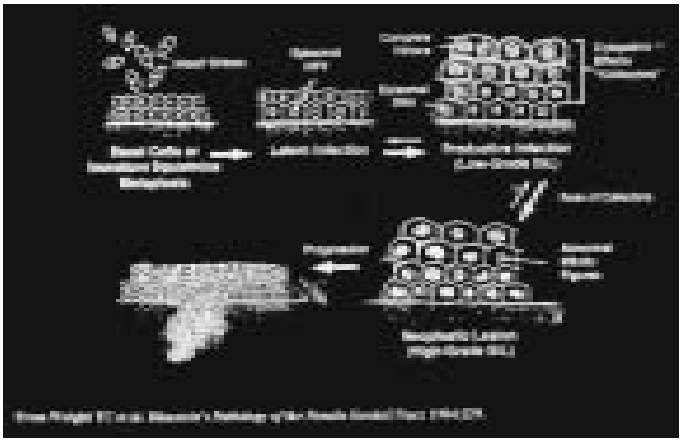

Figure 2. High grade squamous intraepithelial lesion.

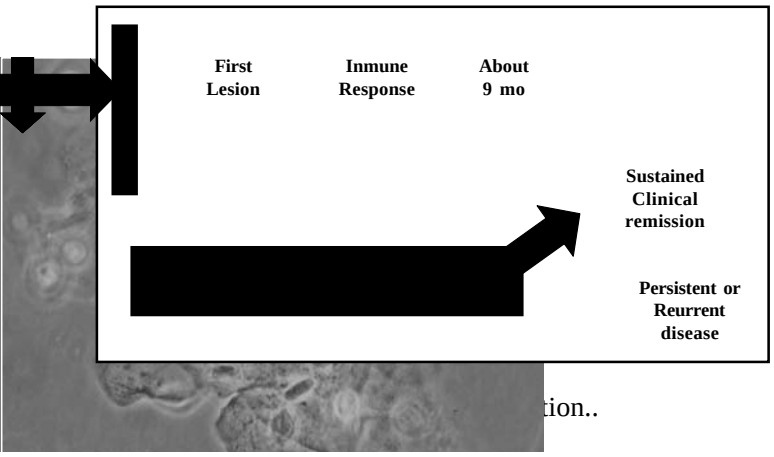

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Figure 3. Natural history of HPV infection.

Clinical presentation

This infection may not cause any symptoms hence diagnosis is difficult. HPV diagnosis is possible by [3] –

1. Clinical study
2. Cytology
3. Colposcopy
4. Histopathology
5. Molecular biology

1. Clinical diagnosis is based on the appearance of warts on the external genitalia, which are usually due to low oncogenic potential virus. Warty lesions on cervix and upper vagina usually indicate infection with highly oncogenic virus. Figure 4 shows giant condyloma.

Figure 4. Giant condyloma.

2. Cytology smears show koilocytes, multinucleated cells and cells with orangeophilic cytoplasm, which are called dyskeratocytes (Figure 5 to 9). Koilocyte is a cell pathognomic of HPV infection. It was Meisels [4] in 1983 who described in detail the cytology of HPV infection. A dedicated well trained cytologist can make the diagnosis of HPV infection on Pap smear. Miniello [5] recommends the use of phase contrast microscopy of a wet vaginal smear to diagnose HPV infection.

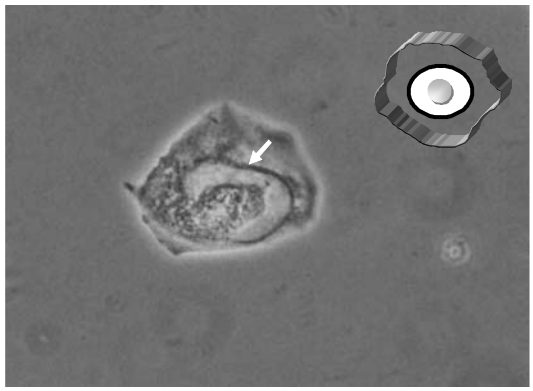

Figure 5. Koilocyte

Figure 6. Dark nuclei.

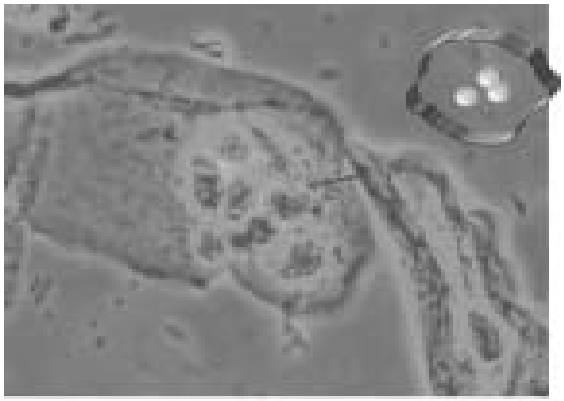

Figure 7. Multinucleation

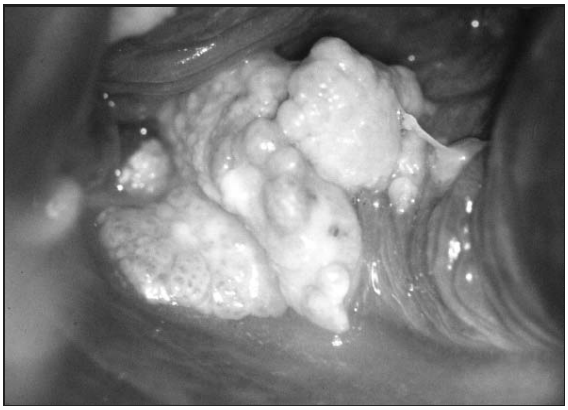

Figure 10. Vaginal florid condyloma

Figure 8. Associated findings.

Figure 11. Cervical florid condyloma

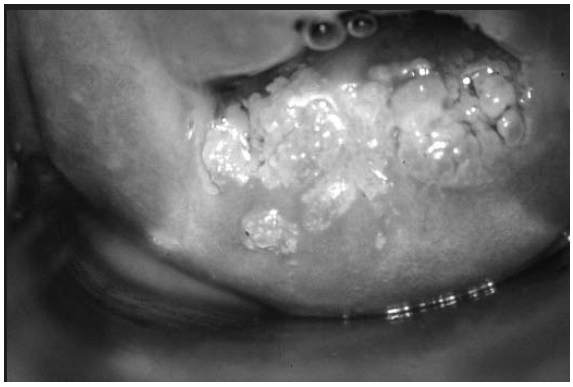

Figure 12. Micropapillary lesions

Figure 9. Cytologic features of HPV.

3. Colposcopy is the most important tool to make a clinical diagnosis. The lesions may be exophytic i.e. rising above the surface epithelium. These are either florid (Figures 10 and 11) or micropapillary lesions (Figure 12). They may also be flat which are then detected on the application of acetic acid. These may appear also as white punctations. Colposcopy enables the study of the entire vaginal walls. Lesions are very often in the posterior vaginal fornix. Acetowhite areas with thickening of the epithelium suggest the presence of HPV infection.

4. Histopathology

Characteristic change is koilocytosis with or without atypia and various grades of dysplasia may also be observed. The basement membrane is all important and contains the lesion for a long time. It is more than just an anatomical barrier. It is also an immunological barrier

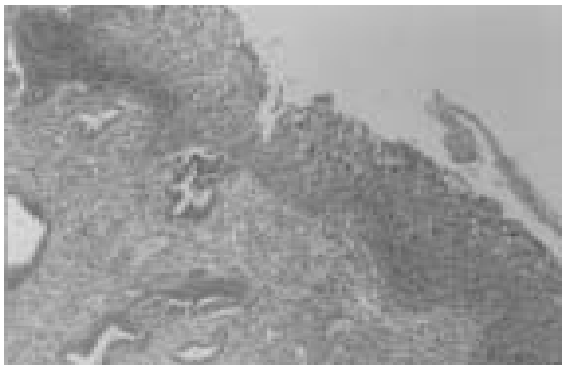

Figure 13. Breaks in the basement membrane caused by HPV

and the zone of host tumor interaction. Virus can cause breaks in the basement membrane leading to early invasion (Figure 13).

5. Molecular biology

These methods are expensive but are very reliable to detect HPV. HPV-DNA test by hybrid capture 2 is a simple test, which can also do viral typing. It can be used for primary screening. Currently it is expensive but much research is being done to make it available and affordable for women in the developing world. HPV-DNA detection can also be done by PCR. Genital swabs and cervical biopsies can be tested.

Immune response to HPV

It is the most important factor to clear infection. The response consists of innate and adaptive immunity. The Langerhans cell count and CD_4 cell counts are decreased and interferon signaling is inhibited if the immune response is poor [6]. Molecular and cell biological evidence is convincing that HPV E_6 and E_7 oncogenes down regulate the cell cycle. The E_6 oncogene inactivates the p^{53} tumor suppressor gene and E_7 oncogene suppresses the p^{RB} or the retino blastoma gene.Viral persistence implies ineffective host defence.

Clinically HPV 16-18 may be cleared in 8-16 months whereas HPV 6-11 may be cleared in 4-8 months if the immune response is adequate and the CD_4 count is high.

Management of HPV

There are many modalities of treatment available. Essentially the management is long term. The ultimate aim is to prevent the development of cervical cancer. The management may be considered as follows –

Counselling

This is very important. At times patients are devastated by the news that they have a sexually transmitted disease and that too something which may lead to cancer. It is important to allay their fears. Marital relationships can also be greatly disturbed [7].

It is necessary to give very positive messages. Some of these are –

- HPV infection has relevance to cervical cancer screening and regular check up is a must.
- HPV infection is common, about 10% of all women have it sometime in their lives.
- Cervical cancer is comparatively rare only 10 to 20 in 1,00,000 women get it.
- HPV infection is not a disease. Body immunity can overcome it.
- It is usually sexually transmitted. Not much is proved yet about other modes of transmission.
- Having HPV is not a sign of infidelity.
- Both partners need advice, check up and perhaps treatment.

Appropriate Management of cervical intraepithelial neoplasia

HPV may be associated with various grades of SIL. If so the appropriate treatment for SIL has to be carried out. In general low grade SIL can be kept under observation and treated conservatively. Almost 70% regress and become normal over a period of 6 months to 1 year. However, if the lesion persists, progresses or recurs it needs further treatment.

In high grade SIL, the treatment is excisional. A cold knife cone or laser conisation is advocated with multiple biopsies of the specimen to exclude invasion.

In developing countries where facilities are limited and follow up difficult, a simple hysterectomy may be advised to those women who have completed their family and are above the age of 40 years. Many women are reluctant for long term follow up and request hysterectomy

Medical Methods

The use of podophyllin resin for treatment of genital warts is age old. The application of 10% podophyllin in tincture benzoin should be followed by a soap and water wash after 6 to 8 hours. Podophyllin induces mitosis in the epithelium. The warts get shrivelled and fall off. It is acceptable to patients. However it is not suitable for large

and multiple lesions and is also contraindicated in pregnancy.

Trichloroacetic acid, and 5% fluorouracil cream are other drugs used for local application.

Surgical methods

Excision of vulval and perianal warts is possible by electrocautery. Depending on the size and the number of lesions it can be done under general or local anesthesia. Tissue should be sent for biopsy and if possible for viral typing. For cervical and vaginal lesions the best options are CO_2 laser and cryotherapy. Carbon dioxide laser is an extremely valuable tool especially in the management of multicentric disease. A large surface area of lower genital tract can be treated at a sitting. The lesions are evaporated and there is minimal blood loss and cell debris. Healing occurs well without scarring.

CO_2 laser treatment of the cervix is particularly suitable for young girls desirous of child bearing. It does not interfere with subsequent fertility status and obstetric performance of the cervix [8].

Cryo therapy is used effectively and is an inexpensive treatment. It can give upto 87% cure rates and may be used over 2-3 sittings [9].

Follow up

It is necessary on short and long term basis. In the short term follow up 3-6 monthly check up is advised till the lesions have healed and disappeared. During this time several tests may be needed.

In the regular long term follow up annual gynecological check up and Pap smears are advised for a lifetime.

The follow up is more intense for those with 16-18 infection as it is an oncogenic virus. HPV is a multicentric disease. The entire lower genital tract is exposed to the virus and is susceptible to the development of neoplasia. Hence follow up has to include a careful inspection of vulva, perineum, vagina, cervix and endocervix [10].

With good immunity a woman should clear her HPV infection in 6 months. The lesions become smaller and then disappear. During this period she may be given nutritional supplements of vitamins C,A and E and folic acid. These improve the immune status and are also effective in cell regeneration. Gloria et al [11] studied tocopherol and ascorbic acid assays in plasma. Their study indicated that vitamins C and E may play an independent protective role. They postulated that antioxidants may play a protective role in cervical dysplasia. Hence nutrition analysis and guidance are necessary in cases diagnosed with HPV infection.

Genital tract infections also need to be treated. Use of antifungals, antiprotozoals and antibiotics are effective and so also local use of vaginal pessaries and ointments. Boyle and Smith [12] have stated that bacteria produce nitrosamines which act in conjuction with HPV to increase the rates of cervical neoplasia. Genital tract infections reduce cellular immunity so that epithelium which is in a reparative and metaplastic phase is highly susceptible to carcinogens.

Contraceptive usage has to be discussed; barrier contraceptives are preferred. Oral contraceptive and IUCD should be discouraged. Steroid hormones increase the expression of E_6, E_7, HPV 16 oncogenes which leads to apoptotic failure and carcinogenesis as reported by Moodley et al [13].

Patients have to be cautioned against smoking and tobacco usage which are implicated in cervical carcinogenesis. It was Winkelstein [14] who first postulated that cigarette smoking is a co-factor in squamous cell carcinoma of the cervix. Later in 1990 he published a monumental study on smoking and cervical cancer [15]. McCann et al[16] measured nicotine and cotinine levels in cervical mucous of smokers, passive smokers and nonsmokers. They showed that concentration increases with consumption. Ylitalo et al [17] studied sexual habits, smoking, and oral contraceptive use in women with carcinoma-in-situ of the cervix. They report that although HPV is probably necessary but definitely not a sufficient cause of cervical carcinoma. Other factors are necessary. In their study there was a two fold higher risk in current smokers compared to that in never smokers. This was confined to women less than 45 years of age. There was a 4 fold higher risk in current OC users and an increase with duration of use of OC.Number of sexual partners was significant in HPV 16-18 negative women but was not significant in HPV 16-18 positive women. Since there is a high prevalence of sexually transmitted diseases, check up with HIV, HSV II, and chlamydia may be suggested for both partners [18]. The male partner can also be asked to undergo a check up. Penile warts and penile hygiene are significant factors.

Vaccines against HPV

There is no drug therapy available as yet against HPV virus. However, prophylactic vaccines are currently marketed in over 16 countries. The development of HPV

vaccines is a major medical achievement of 21st century. At last there is some hope that cervical cancer may be controlled globally.

The prophylactic vaccine is given as intramuscular injections in 3 doses at 0, 1, and 6 months. It can be given to all boys and girls of 10-12 years. Currently, it is recommended only for girls upto the age of 26 years preferably before starting sexual activity. The published results give an experience of 4-6 years during which it has been found to be very efficient [19]. However, long term trials are yet to be done. There are two types of vaccines available at present. The bivalent vaccine is against 16-18 virus but also gives cross protection against others. It is called Cervarix. The quadrivalent vaccine is against 6, 11, 16 and 18 and gives protection against genital warts which is a vexing problem. It is called Gardasil or Silgard and is currently marketed in 16 countries. It has become a part of routine national health care and cancer screening program in many countries including Poland. The cost of the vaccine in approx US $ 400 which is going to be a major deterrent for its use in the developing countries [20].

Global view of cervical cancer

The global incidence of cervical cancer is rising. In 2002 it was 4,98,000 cases, and out of these only 83,400 cases occurred in the developed countries and as many as 4,09,400 cases were seen in the developing countries. Projected cases in 2020 would be approximately 7,31,500. Out of these only 92,500 would be in developed countries and the remaining in developing countries. This also has to take into consideration that the total population in the developing world is seven times that of the developed world.

The HPV-DNA prevalence in normal women has been studied in various parts of the world [21]. It is found to vary for 7.63% in Asia, which is amongst the lowest to 23.41% in Africa which is the highest. The reason why the incidence of cervical cancer is high even though the global incidence of HPV is low is because of the presence of co-factors which decrease the immune status. The significant co-factors are high parity, prolonged use of oral contraceptive pills, smoking or use of tobacco, and concurrent HIV infection. Other significant factors are low socioeconomic status, poor diet, and concurrent HSV II and Chlamydia trachomatis infection.

The association of HPV and cervical cancer is causal and necessary [22]. HPV based preventive strategies, screening and vaccination should target all cases. Vaccines may provide a solution for the developing countries.

Conclusion

Public health issues regarding implementing the new strategies are challenging. There have been ethical objections to introducing vaccines in young girls. One point is clear and that is screening by Pap smear must continue and must be strengthened. It must reach those women from underpriviledged societies who need it the most. An integration of HPV vaccination, HPV detection and Pap smear screening on a mass scale is needed. For this to be undertaken funds have to be allocated. But more importantly, a thorough understanding of the disease process, factors involved, and therapies available must be known to all concerned. Finally, obstetricians and gynecologists and their professional associations must play a critical role in the introduction of these strategies and must become effective advocates for its use.

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