GENITAL WARTS

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By

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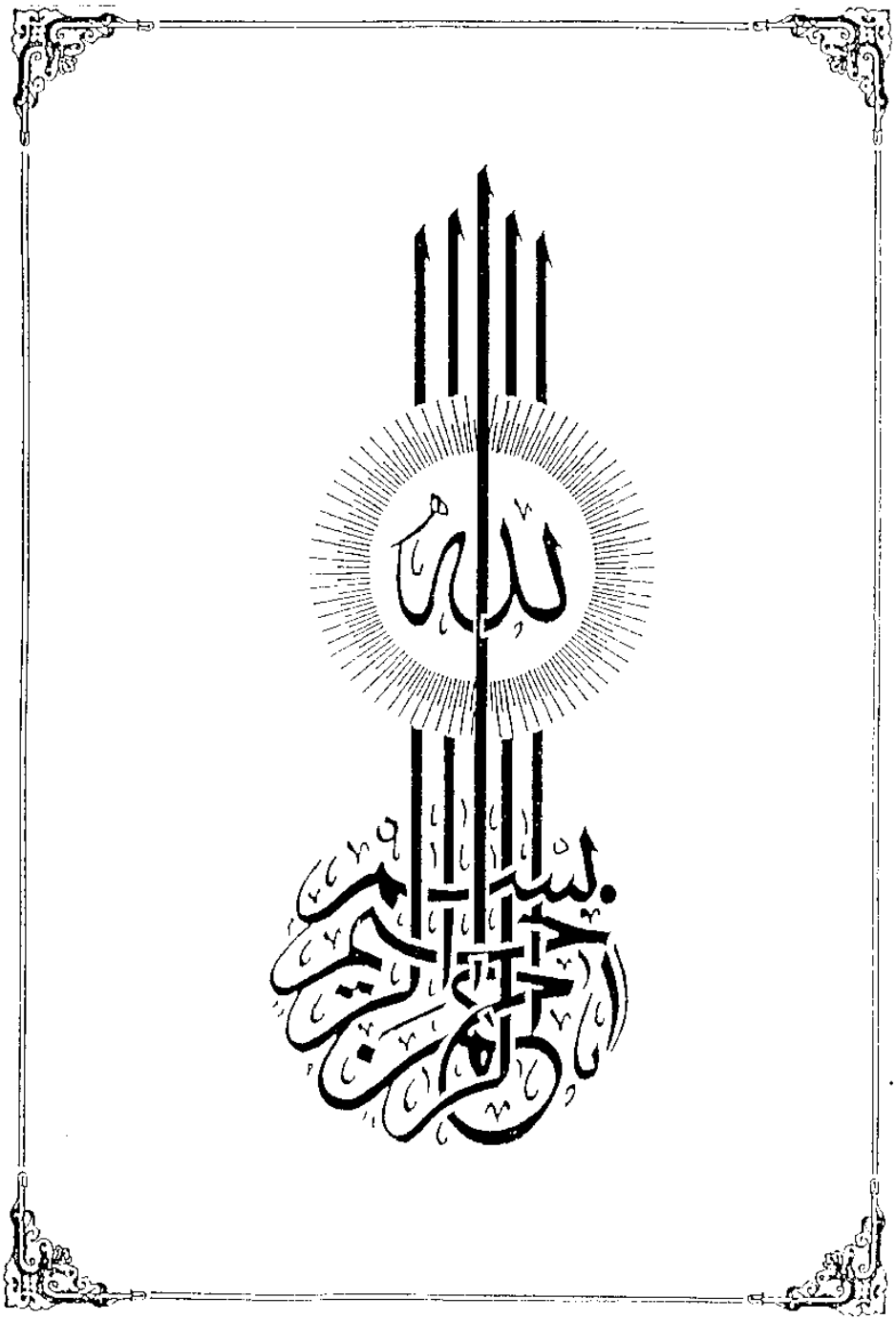

ABBREVIATIONS

AID	:	Artificial Insemination by Donor.
AIDS	:	Acquired Immunodeficiency Syndrome.
BP	:	Bowenoid Papulosis.
$CD8^+$	:	Cluster of Differentiation : An Antigenic Marker of Suppressor/Cytotoxic T cells.
CIN	:	Cervical Intraepithelial Neoplasia.
CMI	:	Cell-Mediated Immunity.
CO_2	:	Carbon Dioxide.
DNA	:	Deoxyribonucleic Acid.
DNCB	:	Dinitrochlorobenzene.
ELISA	:	Enzyme-Linked Immunosorbent Assay.
EM	:	Electron Microscope.
EMLA	:	Eutectic Mixture of Local Anaesthetics.
EV	:	Epidermodysplasia Verruciformis.
5-FU	:	5-Fluorouracil.
HIV	:	Human Immunodeficiency Virus.
HLA-DR	:	Human Leucocyte Antigen-Disease Related.
HLI	:	Human Leucocyte Interferon.
HPV	:	Human Papillomavirus.
HSV	:	Herpes Simplex Virus.
IF	:	Immunofluorescence.
IFN	:	Interferon.
Ig	:	Immunoglobulin.
MH	:	Molecular Hybridization.
mRNA	:	Messenger Ribonucleic Acid.
ND: YAG Laser	:	Neodymium-Yttrium Aluminium Garnet Laser.
PAP	:	Peroxidase-Antiperoxidase.
Pap Smear	:	Papanicolaou Smear.
PV	:	Papillomavirus.
REA	:	Restriction Enzyme Analysis.
RNA	:	Ribonucleic Acid.
SDS	:	Sodium Dodecyl Sulphate.
SLE	:	Systemic Lupus Erythematosus.
SPI	:	Subclinical Papillomavirus Infection.
STD	:	Sexually Transmitted Disease.
T Lymphocyte Cells	:	Thymus Lymphocyte Cells.
USP	:	United States Pharmacopia.
VAIN	:	Vaginal Intraepithelial Neoplasia.
VIN	:	Vulvar Intraepithelial Neoplasia.

CONTENTS

INTRODUCTION AND AIM OF WORK

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The incidence of condylomata acuminata infection has shown a steady increase for adults and children in recent years (Stumpf, 1980). Pregnancy may predispose women to active human papilloma virus (HPV) infections and clinically evident condylomas are often observed to grow more rapidly during pregnancy (Rando et al., 1989). Anal condylomata and sexually transmitted diseases (STDs) are common in patients who test positive for the human immunodeficiency virus (HIV) (Beck et al., 1990).

Few patients have progression to aggressive, regionally distributed lesions that can be life-threatening (Alex et al., 1990). With the discovery that the viral agents of this disease are potentially neoplastic (Lynch, 1985), a disorder that was once considered a nuisance is now taking on new-found importance and concern. It is also important that female patients have cervical cytology, because cervical intraepithelial neoplasias (CINs) are often associated with genital HPV infection (Reid et al., 1984a). HPV infection has been incriminated with dehiscence of episiotomies in the immediate postpartum period (Russell et al., 1990).

Although the natural history of HPV infection of the female genital tract is now well characterized (Reid et al., 1987), less is known about the productive lesion in men responsible for the transmission to women. Semen specimens from men with intrameatal penile warts, tested by Southern blot hybridization, were positive for HPV types 6/11 (Jonathan et al., 1989), this observation may

have implications for screening of semen used for artificial insemination by donor (AID). It has been recommended that all men attending AID clinics should be examined clinically and those who give a history of genital warts or have lesions be excluded (Barratt et al., 1989).

Treatment of anogenital warts is often difficult, and no one form of therapy is effective. None of the treatment methods eradicates the HPV, and genital wart recurrences are seen with each method. Furthermore, the knowledge that these lesions are often sexually transmitted, and the ever-increasing concern over child abuse have combined to make the recognition and treatment of this disease in the pediatric population of even greater significance.

The aim of this work, owing to the importance of the subject of genital warts, is to present a thorough review of this disease.

REVIEW OF LITERATURE

NOMENCLATURE AND DEFINITIONS

The term condyloma acuminatum (condylome = knuckle; acuminatum = pointed), pl. condylomata acuminata, was originally used to emphasize the difference between anogenital warts, which are usually protuberant, and the flatter syphilitic lesions, condylomata lata. Condylomata acuminata became an accepted term, mostly in the American literature, for viral anogenital warts.

With recent developments in the understanding of HPV disease, it is clear that the term is used variously to denote (1) the classical protuberant type of anogenital wart only, (2) all clinically identifiable HPV disease of the anogenital region including flat warts on the external genitalia and cervical 'flat condylomas', (3) all clinical lesions due to the HPV types usually associated with genital warts, including those in extragenital sites, e.g. the mouth.

The term condyloma acuminatum, which strictly referred to a particular clinical and histological lesion, has generally been dropped in favour of genital (or anogenital) wart. Warts are benign proliferative lesions of cutaneous epithelium (Rowston and Mahy, 1967), whereas lesions arising from metaplastic or nonkeratinizing squamous epithelium of the mucosa are referred to as condylomata or papillomas (De Villiers, 1989).

The so-called flat or non-condylomatous condylomata, now often termed sub-clinical HPV infection (SPI) refer to occult infection, the lesions being demonstrable only by colposcopy, cytology or biopsy. The recognition by Meisels et al., in 1982, of the similarity of changes in cervical dysplasia to those

seen in condylomata prompted them to reclassify 90% of mild dysplasias as condyloma planum.

The possibility of designating a subset of cervical papillomaviral lesions in which there is a particular risk of malignant transformation was discussed by Meisels et al., in 1981. The distinction between these 'atypical condylomas' and conventional flat condylomas can be made by analysis of their nuclear DNA content and histology. Lesions which are euploid or polyploid rarely progress, whereas lesions which are aneuploid often proceed to higher grades of CIN. The presence of abnormal mitoses is the most reliable histological criterion for aneuploidy (Fu et al., 1981). Meisels et al., in 1977, reserved the term inverted condyloma for similar clinical lesions that histologically show an endophytic growth pattern. Latent (i.e. immunologically controlled)infection, in which sequences of HPV are identified in clinically and histologically normal epithelia, is common on the cervix and undoubtedly occurs on the external genitalia as well (Toon et al., 1986).

In rare instances, appear giant condylomas with clinical features of invasively growing, non-metastasizing carcinomas, but with no histological signs of malignancy. These tumours are called Buschke-Loewenstein tumours and are regarded as a variant of true extensive condylomas or as an intermediate state in the development of cancer from condylomas (Schmauz and Owor, 1980a) and/or as a variant of well differentiated squamous-cell or verrucous carcinoma (Kraus and Perez 1966).

EPIDEMIOLOGY OF GENITAL WARTS

Prevalence And Incidence of Genital Warts:

While many studies have focused on infections of females, far fewer have examined the prevalence of genital HPV infection in males, probably owing to the comparatively lower frequency of genital malignancy in males and to difficulties in obtaining adequate specimens. Grussendorf et al., in 1987, demonstrated HPV DNA in 5.8% of penile swabs from the glans and sulcus corona glandis of men without clinical evidence of genital HPV infection.

A steady seven-to eightfoldincrease in the incidence of anogenital warts between 1950 and 1978 was recorded from unusually comprehensive morbidity statistics in Rochester, Minnesota (Chuang et al., 1984). The Rochester study found an adjusted male: female incidence ratio of 1:1.4 for anogenital warts, with median ages of 22 for women and 26 for men. Anogenital warts are also being reported with increasing frequency in children (Shelton et al., 1986), and the reported age of onset varies from one day to 13 years. Girls are more often affected than boys (De Jong et al., 1982). Published data from an STD clinic in Georgia also reflect that genital warts are more common among whites than blacks (Becker, 1984).

Condylomata acuminata involvement of the urinary tract is considered rare. Kleiman and Lancaster, in 1962, estimated that 5% of all cases of condylomata acuminata involving the external genitalia would result in involvement of the urinary tract, but estimates as high as 23% are found in the

literature (Fuselier et al, 1980). In their review, Kleiman and Lancaster found that the disease was most commonly limited to the external urethral meatus or distal urethra, rarely involved the entire urethra, and never involved only the posterior urethra.

Natural History of Genital Warts:

Although cervical condylomata acuminata are a benign proliferation usually with a polyploid or diploid DNA content (Winkler et al., 1984), the lesions represent a marker for possible exposure to high-risk HPV types. They also represent a marker of high risk of synchronous or metachronous development of CIN. At least 20% of women with clinically apparent cervical condylomata acuminata will have coexistent CIN. Condylomatous changes were identified in 85% of cervices that were affected by CIN and were in direct contact with 68% of CINs. This shows a direct topographic relationship between cervical condyloma and CIN (Kaoru et al, 1987). The implications of this should be clear to the practicing dermatologist. Patients with cervical condyloma need close gynecologic follow-up to look for malignant transformation. Cervical visualization for women with external genital warts would seem advisable. Female partners of men with penile warts should also be examined for CIN. Women with clinically detected cervical condylomata acuminata should have colposcopy and biopsy.

SPI apparently represents the earliest stage in the CIN continuum and should be seen as the earliest cervical lesion capable of progressing to invasive cancer (Reid et al., 1984a). Women with a history of koilocytotic atypia on a

cervical smear have an increased risk of CIN_3 and invasive cancer (Mitchell et al., 1986). Evans and Monaghan, in 1985, demonstrated that 16% of histologically proven cervical SPI progressed to CIN 2-3, including one micro-invasive carcinoma, within a 12-month period. This progressive potential of mild cervical atypia was also documented by Campion and colleagues in a recent prospective study (Campion et al., 1986). Of women with cytologic and colposcopic evidence of mild cervical atypia, 26% progressed to histologically proven CIN3 within a 2-year period. Moreover the spontaneous regression rate was very low (11%). Those women who did regress remained at high risk of future recurrence of their cervical disease. These results were very similar to the earlier prospective study of Richart and Barron (Richart and Barron, 1969), but the transit time to CIN_3 for the modern group of young women was shorter.

The natural history of vaginal condylomata acuminata tends to be one of spontaneous regression. However, the length of time over which this occurs is extremely variable. In particular, treatment of cervical and vulvar disease may be followed by spontaneous regression of vaginal lesions. The presence of vaginal condylomata acuminata also indicates an increased risk of exposure to high-risk HPV types. Thus colposcopic examination of the cervix should be performed in the presence of vaginal condylomata acuminata regardless of the cervical cytology report. Vaginal intraepithelial neoplasia (VAIN) including $VAIN_3$ (severe dysplasia/carcinoma in situ) has been reported in association with vaginal condylomata acuminata (Woodruff, 1981) and malignant conversion of vaginal condylomata has been reported (Schmauz and Owor, 1980b).