Synopsis of GYNECOLOGIC ONCOLOGY

Third Edition

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Preface

This book is intended to be a complete guide to the practice of gynecologic oncology for the physician in training, the general gynecologist, and the cancer specialist. The contents integrate the essential clinical characteristics of the various gynecologic tumors (symptoms, physical findings, epidemiology) with detailed, explicit information concerning their diagnosis, treatment, and outcome. The scope has been expanded in this, the third edition, by incorporating unusual malignant tumors, benign tumors, and related conditions such as genital warts and the vulvar dystrophies. In addition, chapters have been added on breast diseases (Dr. Marchant) and medical statistics (Dr. Blessing). The section on chemotherapy has been completely rewritten by J. Tate Thigpen, M.D., and Malcolm S. Mitchell, M.D., has contributed a new chapter on immunology.

There has been a reordering of the chapters for organizational purposes. Every section has been revised on the basis of a detailed review of the literature and changes in clinical practice since the last edition. Thus, the third edition has undergone major revisions in order to broaden its scope and update its information. The breadth of coverage, we believe, makes this volume uniquely qualified to serve as a basic textbook as well as a reference work for clinical practice.

The volume and quality of new information in the discipline of gynecologic oncology continue to increase at a formidable pace. It is clearly beyond the capacity of a single individual to master. All of us, then, must rely upon the work, advice, and experience of others. We have solicited contributions from experts in several important areas: John A. Blessing, Ph.D., in medical statistics; John E. Byfield, M.D., Ph.D., and Conley G. Lacey, M.D., in radiation therapy; Douglas J. Marchant, M.D., in diseases of the breast; Malcolm S. Mitchell, M.D., in the field of immunology; and J. Tate Thigpen, M.D., in chemotherapy. For assistance in reviewing portions of the manuscript, we wish to thank our clinical fellows, Joseé Dubuc-Lissoir and Fredrick J. Montz. Rogerio A. Lobo, M.D., provided invaluable assistance with the endocrinologic aspects of this book. We are especially indebted to John B. Schlaerth, M.D., friend and associate of many years, who is an unfailing source of information, advice, and support. We wish to acknowledge the secretarial assistance of Sylvia P. Rivera and Joann Little. Finally, we give our enduring thanks to Dianna Livingstone who singlehandedly organized and put onto computer disks, according to the publisher's specifications, the entire manuscript for this book.

C. Paul Morrow, M.D.
Duane E. Townsend, M.D.

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Premalignant and Related Disorders of the Lower Genital Tract

HUMAN PAPILLOMA VIRUS INFECTIONS

General Considerations

Also known as anogenital or venereal warts, condylomata acuminata are caused by several highly infectious, sexually transmitted serotypes of the human papilloma virus (HPV). At least four distinct benign epithelial lesions of the female genital tract attributable to HPV infection have been described: (1) the typical verrucous or papillary acuminate wart, (2) the flat or intraepithelial condyloma, (3) the inverted condyloma, and (4) the giant condyloma. Multiple sites of involvement are common. The presence of extensive warts suggests an immune suppressed state such as pregnancy, organ transplantation, or an immune deficiency disease.

During the past two decades the prevalence of anogenital warts has reached near-epidemic proportions. The accumulating evidence that certain HPV serotypes can be oncogenic in humans has intensified the general concern regarding the prevalence of HPV infections. HPV strains 16 and 18 are commonly associated with invasive cervical carcinoma, as well as the more severe aneuploid dysplasias, while strains 6 and 11 occur almost exclusively in the lesser dysplasias and condylomas that have a polyploid DNA distribution. Since aneuploidy confers a substantial risk of progression, and since polyploidy is associated with spontaneous regression, it appears that the oncogenic risk of HPV infections is, among other things, dependent upon the infecting viral strain or serotype (Fu et al, 1981; Crum et al, 1982a, 1984b; Rastkar et al, 1982; Stanbridge and Butler, 1983; Reid et al, 1984b; Winkler et al, 1984). The evidence that HPV is related to malignant and premalignant squamous neoplasia of the lower genital tract is further described in Chapter 5.

Vulvar Condylomas

The spiculated or filiform perineal warts are managed initially with weekly 25% podophyllin or trichloracetic acid (TCA) applications two to three times per week. If the warts fail to regress, biopsy 4–6 weeks after the last treatment is indicated. With an incubation period of 4–12 weeks or longer, new lesions may develop, however, and these should not be taken as evidence of treatment failure. Management of the typical case also requires treatment for associated infections, especially trichomonas. Extensive or refractory lesions are best treated by laser therapy. The giant condylomas (Fig. 1.1) do not respond to podophyllin or TCA therapy. Excision with a knife, laser, or wire loop cautery is recommended after adequate biopsy has excluded the presence of carcinoma. Intramuscular and intralesional

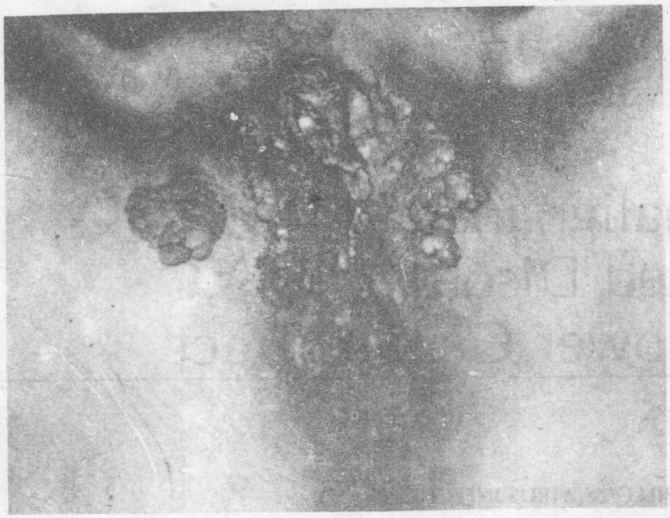

Figure 1.1. Giant condyloma. These cauliflower-like growths had been present for over 30 years. When removed from a patient 65 years of age, foci of severe squamous dysplasia were present. This form of condyloma does not respond to medical therapy. (From Morrow, 1987. Reproduced with permission of Churchill Livingstone, London.)

interferon therapy appears to be effective in clearing 30–50% of resistant genital warts (Eron et al, 1986; Gall et al, 1986). Induration at the base is very suggestive of malignancy.

Flat condylomas of the vulva closely resemble the dysplastic lesions of bowenoid papulosis. Except for focal involvement, the treatment of choice is laser vaporization. This can often be accomplished in the office setting under local anesthesia. The lesions themselves are treated to the level of the dermal papillae. A 5-mm zone of surface epithelium surrounding each lesion, or all intervening epithelium in cases of extensive disease (Ferenczy et al, 1985), is treated by the low power density (350–450 W/cm^2) brush technique to minimize scarring (Reid, 1985). This is especially important when treating the anal canal or urethra. Laser therapy also provides a safe and effective means of treating selected anogenital condylomas complicating pregnancy (Ferenczy, 1984b). For the first month after therapy intercourse is interdicted. Thereafter, condoms should be used until both partners are clear of lesions for at least 6 weeks.

Vaginal Condylomas

Condylomata acuminata of the vagina may be isolated, but most are associated with cervical and/or vulvar condylomas, with which they share many common features. Their occurrence in conjunction with dysplasia is frequent. Vaginal condylomas of the spiculated variety generally present with vaginal discharge and pruritus, while flat (intraepithelial) condylomas are often detected only by routine cytology.

Evaluation begins with a careful gross examination of the lower genital tract and perineum followed by colposcopy, Lugol's staining, and directed biopsy of the vagina and cervix. TCA treatment of the fresh, spiculated condylomas can be successful if the lesions are not extensive, but this treatment is ineffective against the flat wart. For this type of condyloma, as well as the resistant or extensive papillary variety, intravaginal 5-fluorouracil (5-FU) or laser vaporization is recommended. The former is more cost effective but is not applicable to pregnant women (Ferenczy, 1984a). Laser treatment of multiple vaginal condylomas requires the use of the brush technique to eradicate the virus-

containing, normal-appearing epithelium between the warty lesions. Precautions against reinfection, as described for cervical condylomas, are necessary.

Cervical Condylomas

It is common knowledge that the cervix is an unusual site for the typical spiculated venereal wart. Consequently, the high frequency of cervical HPV infection was not appreciated until the late 1970s when Meisels and associates described the flat (intraepithelial) condyloma (Meisels and Fortin, 1976; Meisels et al, 1977; Meisels and Morin, 1981). The inconspicuous epithelial hyperplasia closely resembles squamous dysplasia clinically, colposcopically, cytologically, and histologically. Thus, it is not surprising that its true nature remained unknown until the technology to identify the HPV virus became available. These condylomatous lesions were previously classified as dysplasias when cytologic atypia was prominent and as inflammatory when atypia was absent or inconspicuous.

The widespread prevalence of cervical HPV infections has now been abundantly documented. In retrospective studies, about 75% of cervical intraepithelial neoplasia (CIN) I and 50% of CIN II lesions are reclassified as flat condylomas. Pap smear screening of the general population indicates a 1.5% prevalence rate of genital HPV infection, approximately three times that of squamous dysplasia. More than half of the cases of anogenital condylomas in women are now accounted for by cervical lesions (Meisels et al, 1982).

Diagnosis

The flat condylomas develop within the transformation zone. They are not usually visible until acetic acid is applied, after which they turn white. Typical colposcopic features include a micropapillary contour, inconspicuous vascular pattern, feathered margins, satellite lesions, and a shiny snow white color (Reid and Scalzi, 1985). Biopsy is required, however, to document the nature of the lesion. An intimate admixture of flat condyloma and bona fide dysplasia is common.

Histologically, the distinctive feature of the intraepithelial condyloma is koilocytosis (Fig. 1.2; Crum et al, 1982b). Crum and Levine (1984) have reported that HPV infection of immature squamous metaplasia does not produce koilocytic changes. In this situation, the pathologic diagnosis is likely to be atypical immature metaplasia.

Management

Although many cervical condylomas regress spontaneously, it is generally recommended that even the milder forms be treated because there is no practical way to determine which are potentially malignant, that is, those that are aneuploid or caused by HPV-16 and HPV-18. Furthermore, the lesions are considered highly infectious. Concurrent involvement of the vagina and/or vulva is common.

The preferred treatment for cervical condylomas whether flat, inverted, or papillary, is laser vaporization. The entire transformation zone is treated to a depth of 5–7 mm, with a lateral margin of 5 mm (Baggish, 1985). The sexual partner should also be examined, since reinfection is a frequent cause of treatment failure. Condylomas are reportedly found in 50–75% of male partners if colposcopic magnification is used (Levine et al, 1984; Sedlacek et al, 1986). Posttreatment precautions against reinfection are recommended. Cure rates with a single treatment have been somewhat poorer than those of dysplasia.

PREMALIGNANT LESIONS OF THE VULVA

Vulvar Dystrophies

The chronic vulvar dermatoses have now been sorted out on a histopathologic basis providing the clinician with a far simpler, more useful working classification than that based on

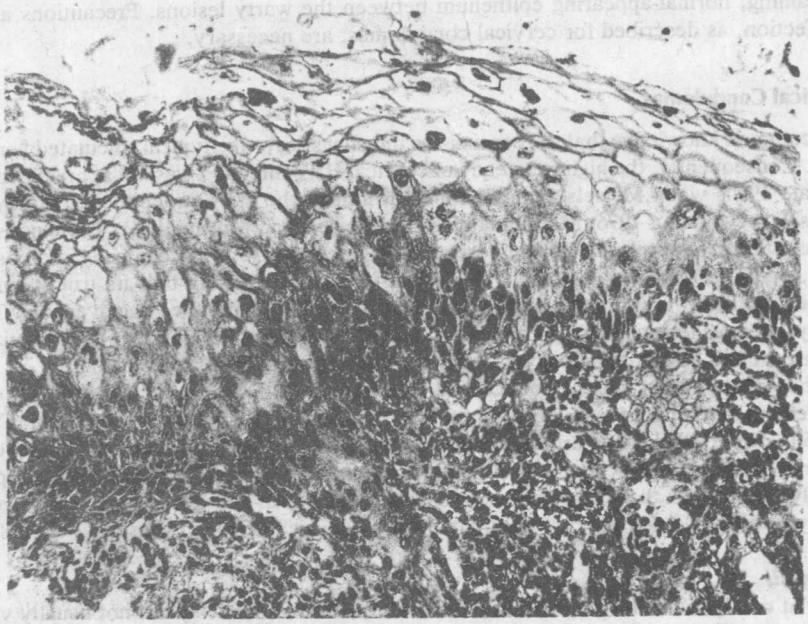

Figure 1.2. Cervical intraepithelial condyloma. Characteristic vacuolization and ballooning of the upper cell layer is termed *koilocytosis*. In the parabasal cells there is nuclear enlargement without abnormal mitoses. (Courtesy of Gerrit d'Ablaing, M.D.)

the gross morphology of these lesions. Instead of the red/white, keratinized/nonkeratinized grouping, the more specific diagnostic categories of lichen sclerosus (et atrophicus, LSA), hyperplastic dystrophy, and mixed forms, all with or without atypia [vulvar intraepithelial neoplasia (VIN) or dysplasia] are determined by tissue biopsy. The treatment is based on the specific histologic diagnosis and the presence or absence of dysplasia. In general when VIN is present, ablative therapy is indicated, while medical therapy predominates in the absence of dysplasia. The goals of treatment are to relieve symptoms, to prevent the development of carcinoma, and to restore tissue normalcy. In most instances, these goals can be achieved only in part.

Lichen Sclerosus (LSA)

Etiology Lavery and Pinkerton (1983) have proposed that the hyperplastic, atrophic (LSA) and mixed dystrophies are phases of a single disease process most likely of autoimmune origin. The association of LSA with autoimmune phenomena is well documented. Various authors have reported an increased incidence of achlorhydria, vitiligo, diabetes, thyroiditis, pernicious anemia, antibodies to gastric parietal cells, and intrinsic factor in patients with LSA (Harrington and Dunsmore, 1981). Meyrick-Thomas et al (1982) found that 75% of their LSA study group had at least one autoantibody and 20% had evidence of an autoimmune disease. Fifteen instances of familial LSA have been documented with recent evidence suggesting an HLA linkage (Friedrich and MacLaren, 1984).

Lavery and Pinkerton have proposed that the association of LSA with achlorhydria suggests that LSA may result from abnormal levels of gastrointestinal hormones, especially urogastrone. This peptide in excess inhibits the production of hydrochloric acid (HCL) while stimulating the production of epidermal growth factor. The latter, it is postulated, causes hypertrophy of the vulvar skin accompanied by increased levels of somatostatin, a