Journal of Korean Medical Science
Vol. 8, No. 2, 160-161 April 1993

Urethral Caruncle Occurring in a Young Girl

— A Case Report —

Ki Kyung Kim, M.D., Dae Yeol Sin, M.D., Heung Won Park, M.D.

Department of Urology, Kangnam Sungshim Hospital, College of Medicine, Hallym University, Seoul, Korea

Urethral caruncles are the most common benign tumors in the female urethra, and are usually found in the posterior lip of the urethral meatus of post-menopausal women. It is very rare in young girls. Its etiology is unknown. We add a case of urethral caruncle occurring in a 2 year and 5 month-old girl's mid-urethra. We believe that further accumulation of unusual cases may be helpful in discovering the pathogenesis.

Key Words: *Urethral caruncle, mid-urethra, young girl.*

INTRODUCTION

Urethral caruncles are the most common benign tumors in the female urethra. These are usually found in the postmenopausal period and in the posterior lip of the urethral meatus (Marshall et al., 1980). The etiology is still unknown.

Only a few cases of urethral caruncles in young girls have been reported in the literature and one of them was found at birth (Thukeri and Akdas, 1989; Jarvi et al., 1984; Campbell, 1970).

We present a case of urethral caruncle occurring in the mid-urethra of a young girl.

CASE REPORT

A 2 year and 5 month-old girl was transferred from the pediatric department. She had been in management of URI for the previous 7 days. In the meanwhile, she was suddenly affected by burning pain on urination and urethral bleeding two days before admission to the pediatric department. CBC, ESR and blood chemistry were within normal limits. CRP and ASO were all negative. In urine, RBC was 1-2/HPF, WBC was 0-1/HPF and no bacteria was cultivated.

We couldn't initially find any abnormal lesion in the external urogenital system in spite of suprapubic compression. We fortunately found a fleshy, reddish and pedunculated small mass headed out of the urethral opening by abdominal strain just before trying cystoscopy under light sedation. So, we thought that it might be a caruncle even though it was very rare at this age and that it might be the cause of urethral bleeding.

There was no improvement after one week in spite of conservative management and we excised it under general anesthesia.

The tumor had its stalk in the posterior lip of the mid-urethra and it was about 0.6cm in whole length.

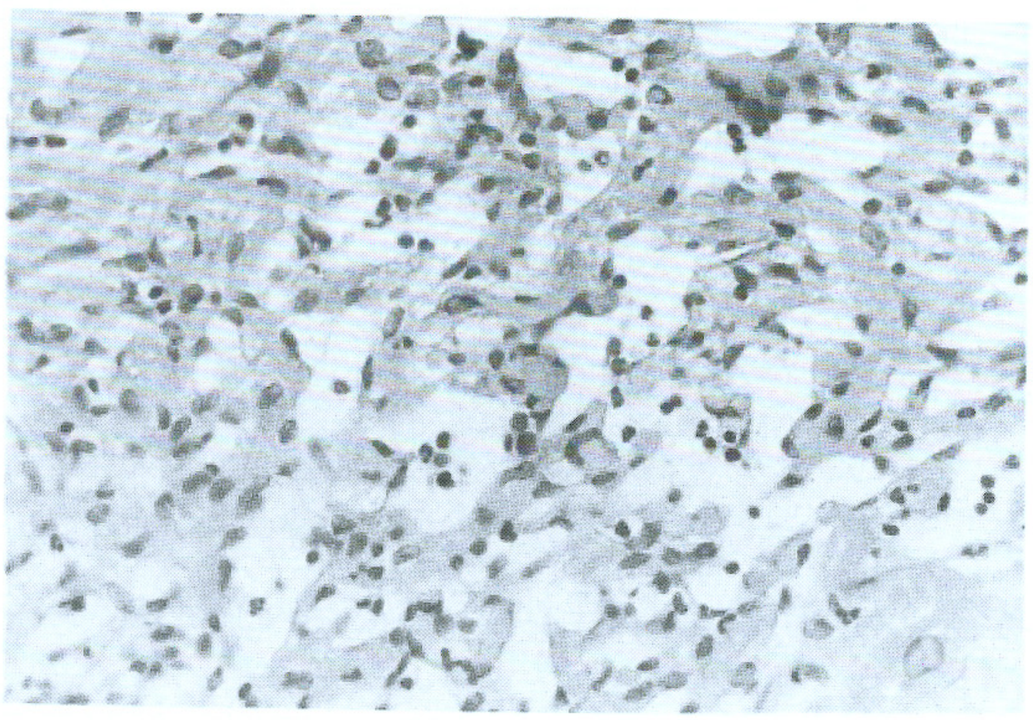

Fig. 1. Microscopic finding of the specimen shows vascular proliferation (H&E, ×400).

Address for correspondence: *Ki Kyung Kim, Department of Urology, Kangnam Sungshim Hospital, 948-1, Daelim 1 Dong, Youngdeungpo-Ku, Seoul, 150-071, Korea (02) 833-3781 (ext. 269)*

Microscopic findings of the specimens revealed proliferation of vessels and mild infiltration of inflammatory cells (figure 1). It was covered with transitional epithelium (figure 2).

She was discharged on the postoperative second day and has been well without any problems for two years thereafter.

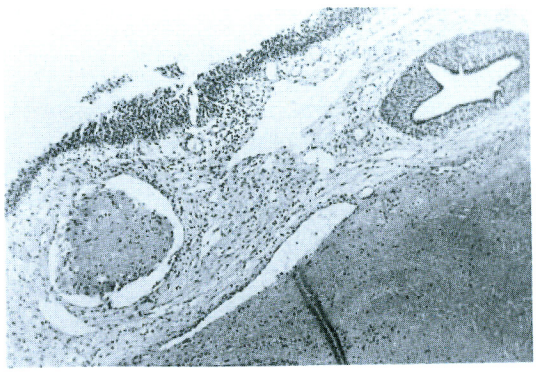

Fig. 2. Dilated vessels and covering transitional epithelium (H&E, ×100).

DISCUSSION

Urethral caruncles may be pedunculated or sessile and may bleed easily. Overlying epithelium is either transitional or squamous cell in type. They are arbitrarily classified as papillomatous, angiomatous and granulomatous type according to the degree of inflammation, vascularity and fibrosis present (Marshall et al., 1960; Hill, 1989). But Nasah presented that urethral caruncles were divided into two types of true caruncle (vascular papilloma) and pseudo-caruncle (granuloma) according to the clinical features and not on histologic study (Nasah, 1968), The former is nearly always permanently cured by efficient surgical treatment, in which the infection is secondary, while the latter is almost always associated with the presence of chronic trichomonas infection and tends to recur and in which the infection is primary and causal of hypertrophy.

Furthermore, if they were not visible, it would not be easy to diagnose them because it is very rare at a young age. Turkeri and Akdas presented that only two cases had been reported in the literature since 1964 excluding their case of a 9 year-old girl (Turkeri and Akdas, 1989). One of them revealed the lesion at birth and this suggested the possibility of it being congenital in etiology (Jarvi et al., 1984). Campbell described 11 cases of urethral caruncles occurring in female children (Campbell, 1970.)

We believe that additional accumulation of unusual cases may be helpful in making the etiology clear.

REFERENCES

Campbell MF: *Tumors of Urogenital Tract. In: Campbell MF, Harrison JH, 3rd, eds. Campbell's urology. WB Saunders Co. Philadelphia. p1926, 1970.*

Hill GS: *Urethral Caruncle. In: Uropathology. Churchill Livingstone, New York. pp 463-465, 1989.*

Jarvi OH, Marin S, de Boer WGRM: *Further studies of intestinal heterotopia in urethral caruncle. Acta Path Microbiol Immunol Scand Sect (A) 92:469-474, 1984.*

Marshall FC, Uson AC, Melicow MM: *Neoplasms and caruncles of the female urethra. Surg Gyncol Obstet 4:723-733, 1960.*

Nasah BT: *Urethral caruncle. J Obstet Gynecol Brit Cwlth 75:781-783, 1968.*

Turkeri L, Akdas SA: *Urethral Caruncle in an Unusual Location Occurring in Prepubertal Girl. Eur Urol 16:153-154, 1989.*

Journal of Korean Medical Science
Vol. 8, No. 2, 162-165 April 1993

Cervical Intraepithelial Neoplasia 3, Coinfected with HPV-16 and -18

— Case Report —

Jong Sup Park, M.D., Sung Eun Namkoong, M.D., Joon Mo Lee, M.D.,
Eun Jung Kim, M.D., Yong Hun Chee, M.D., Gu Taek Han, M.D., Seung Jo Kim, M.D.

Department of Obstetrics and Gynecology, Catholic University Medical College, Seoul, Korea

Recently, detection of human papillomavirus(HPV)mRNA expression was made possible by in situ hybridization. We described a patient with cervical intraepithelial neoplasia (CIN) 3, showing a distinctive and rare form of co-infection with HPV type 16 and 18. HPV-16 was detected in high grade squamous intraepithelial neoplastic lesion (CIN 3) and HPV-18 was in low grade lesion just adjacent to the HPV-16 infected area.

This case suggests that HPV infection may be one of the most responsible causative agents producing malignant transformation and two distinctive HPV types can also simultaneously infect the squamous epithelium of the uterine cervix.

Key Words: *Human papillomavirus (HPV), in situ hybridization, cervical intraepithelial neoplasia (CIN)*

INTRODUCTION

Invasive cervical cancer is preceded by a progressive spectrum of abnormalities of the cervical epithelium which are considered precancerous lesions, such as CIN 1, 2, and 3 (Richardt, 1973; Hertig, 1979). The evidence linking HPVs with CIN has been derived from clinicopathological investigations and from molecular studies examining the presence and expression of HPV genes in preinvasive cervical tissues (Gissmann et al., 1986; Gupta et al., 1989; Park et al., 1991b). HPV-16 and 18 are usually associated with high grade (2 and 3) CIN lesions (up to 80%) and invasive cancer (up to 90%). HPV-16 is the predominant virus in cervical neoplasia (Lorincz et al., 1987; Fuchs et al., 1988), and HPV-18 is regarded as a more rapidly progressive or aggressive form of cervical cancer than HPV-16 (Barnes et al., 1988; Kurman et al., 1988).

Address for correspondence: *Sung Eun Namkoong, Department of Obstetrics and Gynecology, Kangnam St. Mary's Hospital, Catholic University Medical College, 505 Banpo-dong, Seocho-ku, Seoul, 137-040, Korea, Tel: (02)590-1743.*

This study was supported in part by a research grant from the Sam Mi Scientific Research Foundation (1991).

A case of CIN 3 showing double infection with different HPV types in the serial histologic sections of the same patient is presented.

CASE REPORT

A 34 year old, para 2, gravida 4, woman was admitted to the Dysplasia Clinic of the Department of Obstetrics and Gynecology, Catholic University Medical College Hospital, Seoul, Korea, when an abnormal cytopathologic result was reported by an outpatient clinic. Until her admission, she has been relatively healthy, except for profuse leukorrhea. There was no history of intermittent vaginal bleeding or contact spotting. On speculum examination a red erosive lesion was seen in the portio of the cervix. Cytologic smear was suggestive of severe dysplasia showing atypical koilocytotic cells and nuclear atypical cells with numerous inflammatory cells. After acetic acid was applied, a colposcopic complex appeared, formed by white epithelium (W-II), punctation (P-II) and several glandular orifices in atypical transformation zone. Therefore, cervical conization was performed and histologic section revealed that dysplastic immature parabasal cells were fully replaced in the whole epithelial layer at the squamo-columnar junction (CIN 3), (Fig. 1 & 2). She was well with no evidence of recurrence after 24 months by cytologic and colposcopic follow-up.

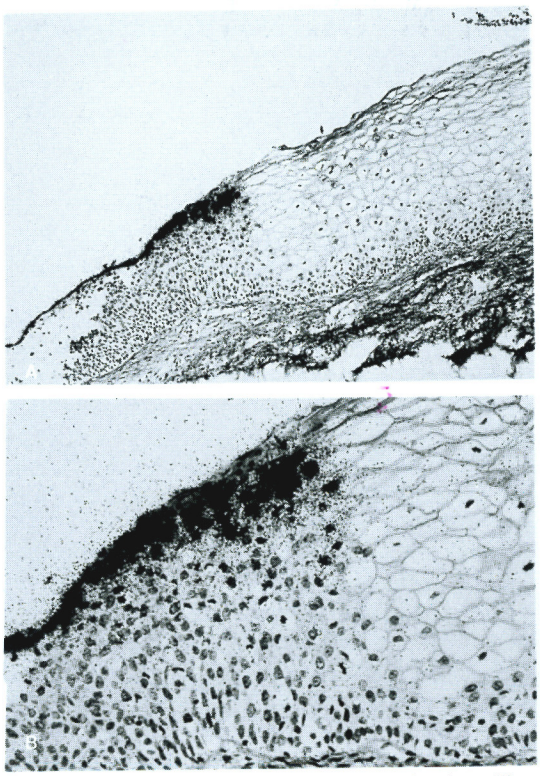

Fig. 1. Section of a cervical cone biopsy showing different grades of cervical intraepithelial neoplasia (CIN) hybridized with a ^{35}S-labelled HPV-16 RNA probe. (Hematoxylin-eosin counterstain)
A) A low-power view (× 100) showing the superficial location of the positive cells.
B) A high-power view (× 250) demonstrates HPV-16 positive cells only in the high grade cervical intraepithelial lesion (CIN 3).

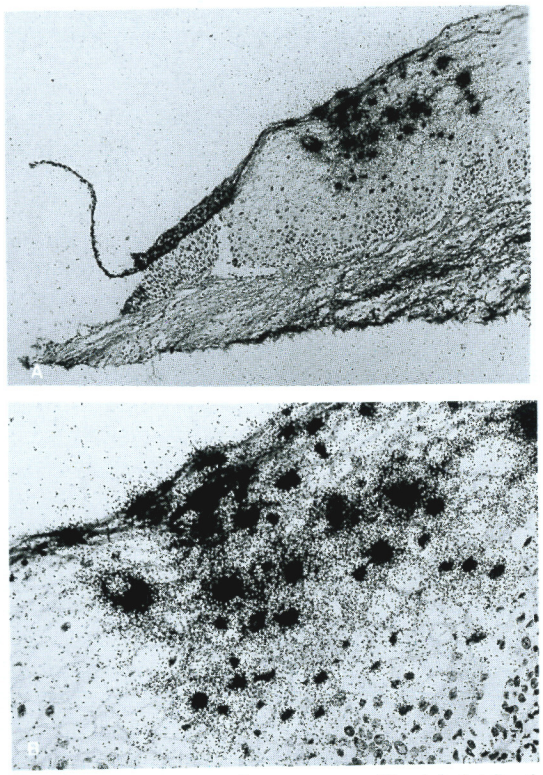

Fig. 2. A serial section of same area as Fig. 1. hybridized with a HPV-18 probe. (Hematoxylin-eosin counterstain)
A) Low magnification showing heavily positive cells in an area of CIN 1 with viral induced changes (× 100).
B) High magnification demonstrates focal high-intensity signals on the koilocytotic cells (× 250).

IN SITU HYBRIDIZATION FINDINGS

To detect the presence of HPV in cervical intraepithelial neoplastic tissue, we employed in situ hybridization with ^{35}S-labeled, single-stranded antisense RNA probes against HPV-6/11, -16 and -18 mRNAs in specific cells in tissue sections. Details of tissue processing and in situ hybridization procedure had been described previously elsewhere (Park et al., 1991a). Viral transcripts of HPV-6 and -11 were not identified in that specimen. The HPV-16 transcripts were definitely identified in high grade dysplastic lesion (CIN 3) just adjacent to low grade CIN lesion (Fig. 1A & B). The HPV-16 signal was not seen in the morphologically normal epithelium or in the stroma. Incontrast, the HPV-18 transcripts were detected only in mild dysplastic lesion (CIN 1) just next to the HPV-16 infected CIN 3 lesion (Fig. 2A & B). The hybridization was strongest toward the surface and became progressively weaker toward the basal layer. The HPV-positive areas displayed focal pattern of hybridization. The hybridization signal was especially intense in well-differentiated, koilocytotic cells of the cervical epithelium (Fig. 2B).

DISCUSSION

The sensitivity of the morphological features of HPV infection of the cervix (koilocytosis and dyskaryosis), as identified by hybridization, has been examined in several recent studies (Sato et al., 1987; Schneider et al., 1987; Park et al., 1989). Histopathologic features of HPV infection were found in 15-68% of HPV-positive lesions and 3% of HPV-negative lesions. These results suggest that the pathognomonic morphological fea-

tures of HPV infection may be detectable in cervical tissues and cells, but the proportion may be lower than we expected.

Among the oncogenic HPV types, HPV-16 is the most common and HPV-16 containing dysplastic lesion is more frequently associated with marked nuclear atypia and an aneuploid karyotype (Crum et al., 1984). In one recent study (Lorincz et al., 1987) comparing the distribution of HPV in CIN versus invasive carcinoma, it was found that HPV-16 accounted for 41% and HPV-18 for 22% of all invasive carcinoma. In contrast, HPV-16 was found in 37% of all grades of CIN whereas HPV-18 was found in only 3%. The detection of high risk HPV infection from the cervical lavages of Korean patients of cervical cancer was identified by Southern blot hybridization and the infection rate of HPV-16 or -18 were 51% (25/49) in the extracted DNAs of cervical neoplasia (Ryu and Song, 1990). In one microinvasive cancer, HPV was identified that hybridized to both HPV-16 and -18. The result of Reid et al. (1987) showed that only six of 416 specimens contained multiple HPV types within the same sample. But the published reports have not described the simultaneous infection of oncogenic HPVs in the same tissue section of CIN with the histologic feature of *in situ* hybridization. In our sample HPV-16 was identified in high grade cervical intraepithelial lesion with HPV-18 mixed infection in just adjacent low grade lesion. It reveals a remarkable specificity of HPV-16 infection in transformed cells. This case also showed the presence of HPV-18 in non-tumorous epithelium. In general, there was no significant difference in the distribution of HPV-16 in CIN as compared with invasive carcinoma. But, of particular interest was the striking deficit of type 18 in intraepithelial neoplasia as compared with invasive carcinoma (Kurman et al., 1988). The deficit in type 18-related CIN compared to invasive carcinoma was thought to be possibly due to the rapid transit time of type 18 associated lesions through the CIN stage. The possibility is considered that is our finding represents the latent status or the helper activity of HPV-18 for the oncogenic ability of HPV-16. HPV genome has also been detected in cervices that are colposcopically, cytologically, and/or histologically normal (Wickenden et al., 1985). The potential biological behavior of HPV infection that occurs in the absence of morphologic lesions is unknown and may not be analogous to the latent state characteristic of the herpes viruses. Although the oncogenic HPV types are capable of immortalizing human keratinocytes in experimental systems (Durst et al., 1987b), the presence of the virus is not a sufficient condition per se to induce invasive neoplastic lesions. Recent studies of invasive cervical cancers have shown that these viral types may be integrated with host DNA (Choo et al., 1987; Cullen et al., 1991) or interact with cellular proto-oncogenes (*myc, ras, raf, erb-A,...*) (Durst et al., 1987a; Riou et al., 1987) and tumor suppressor genes specifically Rb (Dyson et al., 1989) and p53 (Werness et al., 1990). These different lines of evidence have demonstrated that carcinogenesis is a complex, multistep process with several options at different stages of development.

In situ hybridization the detection of DNA or RNA sequences in fixed cells adhered to microscopic slides, permits for histologic assessment of viral nucleic acid localization within tissue. Furthermore, *in situ* hybridization with single-stranded, antisense RNA probes allows detection of viral m RNA expression, i.e., of active viral genome rather than of latent infection (Stoler et al., 1986; Barnes et al., 1988). The distribution of HPV transcripts in our CIN tissue resembles that observed in benign condylomata showing strong hybridization signals specifically in well-differentiated superficial cells of the dysplastic layer. This observation suggests that expression of HPV transcripts is dependent on the stage of maturation of the cell rather than on the stage of the disease.

With the strong relationship that has been established between HPV infection and cervical neoplasia, routine testing for viral typing from every high-risk cervical intraepithelial patient may be advisable. When nonradiolabeled and more sensitive probes become advailable, it should be possible to perform this test in any diagnostic pathology laboratory. The finding of HPV coinfection in apparantly low grade intraepithelial lesion with CIN 3 has implications for the pathogenesis, treatment, and follow-up of CIN. Further, molecular analysis of HPV-associated pathologic tissues may be expected to contribute significantly to the understanding of the natural history of cervical neoplasia.

REFERENCES

Barnes W, Delgado G, Kurman RJ, Petrilli ES, Smith DM, Ahmed S, Lorincz AT, Temple GF, Jensen AB, Lancaster WD: *Possible prognostic significance of human papillomavirus type in cervical cancer. Gynecol Oncol 29:267-273, 1988.*

Choo KB, Pan CC, Han SH: *Integration of human papillomavirus type 16 into cellular DNA of cervical carcinoma: preferential deletion of the E2 gene and invariable retention of the long control region and the E6/E7 open reading frames. Virol 161:259-261, 1987.*

Crum CP, Ikenberg H, Richardt RM, Gissmann L: *Human*

papillomavirus type 16 and early cervical neoplasia. N Engl J Med 310:880-883, 1984.

Cullen AP, Reid R, Campion M, Lorincz AT: *Analysis of the physical state of different human papillomavirus DNAs in intraepithelial and invasive cervical neoplasm. J Virol 65:606-612, 1991.*

Durst M, Croce CM, Gissmann L, Schwarz E, Huebner K: *Papillomavirus sequences integrated near cellular oncogenes in some cervical carcinomas. Proc Natl Acad Sci USA 84:1070-1074, 1987a.*

Durst M, Dzarlieva-Pertrusevzka P, Boukamp P, Fusenig NE, Gissmann L: *Molecular and cytogenetic analysis of immortalized human primary keratinocytes obtained after transfection with human papillomavirus type 16 DNA. Oncogene 1:251-256, 1987b.*

Dyson N, Howley PM, Munger K, Harlow E: *The human papillomavirus 16 E7 oncoprotein is able to bind to the retinoblastoma gene product. Science 243:934-937, 1989.*

Fuchs PG, Giarrdi F, Pfister H: *Human papillomavirus DNA in normal, metaplastic, preneoplastic and neoplastic epithelia of the cervix uteri. Int J Cancer 41:41-45, 1988.*

Gissmann L, Schneider A: *Human papillomavirus DNA in preneoplastic and neoplastic genital lesions. In: Peto R, zur Hausen H, eds. Viral etiology of cervical cancer. Banbury Report 21. Cold Spring Harbor Laboratory Press, New York, 217-224, 1986.*

Gupta JW, Saito K, Saito A, Fu YS, Shah KV: *Human papillomaviruses and the pathogenesis of genital neoplasia. A study of in situ hybridization. Cancer 64:2104-2110, 1989.*

Hertig AT: *Early concepts of dysplasia and carcinoma in situ (a backward glance at a forward process): a brief historical review. Obstet Gynecol Surv 34:795-803, 1979*

Kurman RJ, Schiffman MH, Lancaster WD, Reid R, Jensen AB, Temple GF, Lorincz AT: *Analysis of individual human papillomavirus types in cervical neoplasia. A possible role for type 18 in rapid progression. Am J Obstet Gynecol 159:293-296, 1988.*

Lorincz AT, Temple GF, Kurman RJ, Jensen AB, Lancaster WD: *Oncogenic association of specific human papillomavirus types with cervical neoplasia. J Natl Cancer Inst 79:671-676, 1987.*

Park JS, Namkoong SE, Lee HY, Kim SJ, Lee KY, Kim WI, Shim SI, Kim SM: *Detection of human papillomavirus type in paraffin sections of uterine cervix by in situ hybridization with ^{35}S-labeled viral DNA probes. Korean J Obstet Gynecol 32:1115-1122, 1989.*

Park JS, Jones RW, McLean MR, Currie JL, Woodruff JD, Shah KV, Kurman RJ: *Possible etiologic heterogeneity of vulvar intraepithelial neoplasia. A correlation of pathologic characteristics with human papillomavirus detection by in situ hybridization and polymerase chain reaction. Cancer 67:1599-1607, 1991a.*

Park JS, Namkoong SE, Lee HY, Kim SJ, Daniel RW, Shah KV: *Detection of human papillomavirus genotypes in cervical neoplasia from Korean women using polymerase chain reaction. Gynecol Oncol 41:129-134, 1991b.*

Reid R, Greenberg M, Jensen AB, Husein M, Willet J, Daoud Y, Temple G, Stanhope CR, Sherman AI, Phibbs GD, Lorincz AT: *Sexually transmitted papillomaviral infections. I. The anatomic distribution and pathologic grade of neoplastic lesions associated with different viral types. Am J Obstet Gynecol 156:212-222, 1987.*

Richardt RM: *Cervical intraepithelial neoplasia, In: Sommers SC ed. Pathology annual. Appleton-Century-Crofts, New York, 1973.*

Riou G, Le MG, Le Doussal V, Barris M, George M, Haie C: *C-myc proto-oncogene expression and prognosis in early carcinoma of the uterine cervix. Lancet 1:761-763, 1987.*

Ryu KS, Song SK: *Identification of human papillomavirus in patients with cervical cancer by DNA hybridization. Korean J Gynecol Oncol Colpo 1:72-79, 1990.*

Sato S, Okagaki T, Clark BA, Twiggs LB, Fukushima M, Ostrow R, Faras AJ: *Sensitivity of koilocytosis, immunocytochemistry, and electron microscopy as compared to DNA hybridization in detecting human papillomavirus in cervical and vaginal condyloma and intraepithelial neoplasia. Int J Gynecol Pathol 5:297-307, 1987.*

Schneider A, Meinhardt G, de Villiers EM, Gissmann L: *Sensitivity of the cytologic diagnosis of cervical condyloma in comparison with RNA-DNA hybridization studies. Diagn Cytopathol 3:250-255, 1987.*

Stoler MH, Broker TR: *In situ hybridization detection of human papillomavirus DNAs and messenger RNAs in genital condylomas and a cervical carcinoma. Human Pathol 17:1250-1258, 1986*

Werness BA, Levin A, Howley PM: *Association of human papillomavirus type 16 and 18 E6 protein with p53. Science 248:76079, 1990.*

Wickenden C, Steel A, Malcolum ADB, et al.: *Screening for wart virus infection in normal and abnormal cervices by DNA hybridization of cervical scrapes. Lancet 1:65-67, 1985.*