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Solid Tumour Section

Review

Vulva and Vagina tumors: an overview

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Classification

Note: Neoplasms of the vulva and vagina together account for less than 5% of all female genital tract cancers. Staging and grading of the lesions follows the TNM (Tumor, regional lymphoNode, Metastasis) and FIGO (International Federation of Gynecology and Obstetrics) recommendations.
According to WHO recommendations, the main Vulva and Vagina categories are:

VULVA NEOPLASIA:

- I. Epithelial neoplasms
  - A. Squamous and related Tumors and precursors
    1. Squamous cell carcinoma not otherwise specified
    2. Basal cell carcinoma
    3. Squamous intraepithelial neoplasia
    4. Benign squamous lesions
  - B. Glandular Tumors
    1. Paget disease
    2. Bartholin gland Tumors: carcinomas, adenoma and adenomyoma
    3. Tumor arising from specialized ano-genital mammary-like glands
    4. Adenocarcinoma of Shene gland origin
    5. Adenocarcinoma of other types
    6. Adenoma of minor vestibular glands
    7. Mixed Tumors of the vulva
    8. Tumors of skin appendage origin
- II. Soft tissue Tumors
    1. Embryonal rhabdomyosarcoma (sarcoma botryoides)
    2. Leiomyosarcoma
    3. fibrous histiocytoma
    4. Proximal epithelioid sarcoma
    5. Alveolar soft part sarcoma
    6. Liposarcoma
    7. Dermatofibrosarcoma protuberans
    8. Deep angiomyxoma
    9. Superficial angiomyxoma
    10. Angiomyofibroblastoma
    11. Cellular angiofibroma
    12. Leiomyoma
    13. Granular cell Tumor
    14. Other
- III. Melanocytic Tumors
    1. Malignant melanoma
    2. Congenital melanocytic naevus
    3. Acquired melanocytic naevus
    4. Blue naevus
    5. Atypical melanocytic naevus of genital type
    6. Dysplastic melanocytic naevus
- IV. Miscellaneous Tumors
    1. Yolk sac Tumor
    2. Merkel cell Tumor
    3. Peripheral primitive neuroectodermal Tumor/Ewing sarcoma
- V. Haematopoietic and lymphoid Tumors
    1. Malignant lymphoma
    2. Leukemia
- VI. Secondary tumors

VAGINA NEOPLASIA:

- I. Epithelial neoplasms
  - A. Squamous Tumors and precursors
    1. Squamous cell carcinoma not otherwise specified
    2. Squamous intraepithelial neoplasia
    3. Benign squamous lesions (condyloma acuminatum, squamous papilloma, fibroepithelial polyp)
  - B. Glandular lesions
    1. Adenocarcinoma, NOS
    2. Clear cell adenocarcinoma
    3. Endometrioid adenocarcinoma
    4. Mucinous adenocarcinoma
    5. Mesonephric adenocarcinoma

6. Mullerian papilloma
7. Adenoma not otherwise specified

C. Other epithelial Tumors
1. Adenosquamous carcinoma
2. Adenoid cystic carcinoma
3. Adenoid basal carcinoma
4. Carcinoid
5. Small cell carcinoma
6. Undifferentiated carcinoma

- II. Mesenchymal Tumors
1. Sarcoma botryoides
2. Leiomyosarcoma
3. Endometrioid stromal sarcoma, low grade
4. Undifferentiated vaginal sarcoma
5. Alveolar soft part sarcoma
6. Leiomyoma
7. Deep angiomyxoma
8. Post-operative spindle nodule

- III. Mixed epithelial and mesenchymal Tumors
1. Carcinosarcoma (Malignant Mullerian Mixed tumors; metaplastic carcinoma)
2. Adenosarcoma
3. Malignant mixed Tumors resembling synovial sarcoma
4. Benign mixed Tumors

- IV. Melanocytic Tumors
1. Malignant melanoma
2. Blue naevus
3. Melanocytic naevus

- V. Miscellaneous Tumors

A. Tumor of germ cell type
1. Yolk sac Tumor
2. Dermoid Cyst

B. Others
1. Peripheral primitive neuroectodermal Tumor/Ewing sarcoma
2. Adenomatoid Tumor
3. Malignant lymphoma
4. Granulocytic sarcoma

- VI Secondary Tumors

Clinics and pathology

Disease

Tumor of the vulva and vagina

Note: Benign and malignant solid tumors at these sites are rare. The malignant lesions may have epithelial (squamous and glandular) and mesenchymal (soft tissue) origin.

Etiology

The high-risk (HR) human papillomaviruses (HPVs) infections have been identified as an essential although not sufficient factor in the pathogenesis of vulval and vagina carcinoma. It has been demonstrated that HPV integration sites are distributed over the whole genome, with a preference for genomic fragile site. It has been also hypothesized that, at the early stages of infection, the virus genome, still in an not integrated state, expresses oncoproteins E6 and E7 which interfer with the mechanisms of chromosome segregation during mitosis. This phenomenon, would favour the virus genome integration into chromosomal DNA. However, no evidence for targeted disruption of critical cellular genes by the integrated viral sequences has been found. According to this, two categories of affected patients can be distinguhished:

Malignant lesions of the vulva

Older age (mean 77): no vulva intraepithelial neoplasia (VIN) pre-existing pre-malignant condition, not Human Papilloma Virus (HPV) related, unknown etiology.

Younger age (mean 55): usually associated with VIN, HPV-related (usually type 16).

Malignant lesions of the vagina

The strongest association is between squamous cell carcinoma and HPV types 16 and 18 infection.

Association with a pre-malignant lesion, known as vaginal intraepithelial neoplasia (VAIN), was reported.

Association with previous history of cervical intraepithelial neoplasia (CIN), invasive cervical carcinoma, or invasive vulvar carcinoma has been reported.

Epidemiology

Malignant neoplasms of the vulva together with neoplasms of the vagina account for less than 5% of all genital tract cancers. Squamous cell carcinoma (approximately 90% and 80% of the malignant neoplasms of the vulva and the vagina, respectively) is the most commonly found, and it is primarily a disease of elderly women, although it may be also observed in premenopausal women. Pigmented vulvar and vaginal lesions may occur, including nevi and melanoma, which accounts for 9% of vulvar and 5% of vaginal malignant lesions. Diethylstilbestrol (DES)-Associated Disease of the vagina are described: DES is a synthetic non-steroidal estrogen used in the early 1970s to prevent miscarriage. The female fetuses delivered by the mothers taking DES suffered from severe vaginal lesions including vaginal adenosis (benign) and clear cell adenocarcinoma. Malignant mesenchimal tumors of the vulva or vagina are rare: leiomyosarcoma is the most common vulvar lesion (mean age 35), dermatofibrosarcoma is one of the rarest: 25 cases reported, mean age 54.

Clinics

Cancer of the vulva and vagina at the very early stages tends to be asymptomatic. Delay in diagnosis is common, partially due to disease rarity and to delay in relating patient symptoms to the disease origin.

Vulva. Major symptoms are: painless bleeding unrelated to the menstrual cycle, appearing of vulvar skin white and rough.

Vagina. Major symptoms are painless vaginal bleeding (65-80% of all cases), difficult or painful urination,

pain in the pelvic area. Mainly post-menopausal women (70%) are affected. Many vulvar or vaginal growths are not neoplastic and may be treated by monitoring or simple excision. Suspicious growths require diagnostic biopsy and in case of cancer diagnosis surgical ablation is mandatory.

Pathology

The histopathology of vulva and vagina neoplasms reflects the different cell origins of the Tumors (see classification). Examples of both gross and microscopic images of these clinical entities can be viewed at http://www.gfmer.ch/selected_images_v2/level1.php?cat1=8 & stype=n Immunohistochemical studies demonstrate that monoclonal antibodies to MIB-1 (Ki67), a proliferation-associated marker, distinguish two different labeling patterns in the vulvar lesions : diffuse pattern, associated with poor prognosis, or localized pattern.

Treatment

Vulva. Small primary lesions less than 2 cm in diameter with superficial invasion are usually treated with wide local excision with adequate surgical margins For tumors larger than 2 cm, or deeply growing into the underlying inguinal, lymphadenectomy is performed in order to plan a further partial or total vulvectomy. Radiation, with or without chemotherapy, may be used to treat advanced tumors or tumor recurrences, although there is not general consensus on the advantage of post-operative radiation therapy.

Vagina. According to the FIGO, a vaginal lesion arises solely from the vagina : a vaginal lesion involving the external os of the cervix should be considered cervical cancer, and a tumor involving both vulva and vagina should be considered vulvar cancer, and they should be treated as such. Radiotherapy is the most commonly used treatment for cancer of the vagina. Indication for diverse surgical interventions (radical hysterectomy, total or subtotal vaginectomy, vulvectomy, inguinal lymphadenectomy, etc), often accompained by radiation therapy, depends on the lesion type, stage, location, size and patient's history.

Prognosis

Vulva. As with many other types of cancer prognosis depends on several factors, including the histological type of the lesion. In general, patients with increasing tumor stage have a lower rate of survival. The overall 5-year survival rate ranges from 90% to 33%, depending upon whether and how many lymphonodes are involved (not in a directly proportional way). Recurrences are seen in a high percentage of patients within the first two years of follow-up.

Vagina. The histologic type, size (Tumors less than 4cm seem to be associated with a significantly better survival rate), stage and grade and location of the tumor influence the survival rate. The overall 5-year survival rate is about 61%, with about 54% survivig for 10 years or more.

Cytogenetics

Cytogenetics morphological

Data on cytogenetics of vulva and vagina cancer are scarse. Epithelial malignancy of both lesions show cytogenetic abnormalities, although no specific chromosome markers have been identified so far, and no consistent association between cytogenetic subgroups and histological differentiation have been observed. Complex karyotypes are frequent, however simple karyotypes have been observed in a number of cases as well. Cytogenetically unrelated clones, as well as closely related clones, were found in both in situ and infiltrating squamous cell carcinoma (SCC). Structural changes of chromosome 3, 8, 9, 11, 13, 14, 19 and 22 have been frequently observed. Cytogenetically unrelated, abnormal clones, characterized by simple changes (chromosome X and 7 aneuploidy) have been described in Paget's disease. The karyotypes of melanoma and dermatofibrosarcoma protuberans, arising in the vulva and/or vagina, substantially do not differ from the karyotypes of the same entities arising at other sites. A single case of vagina leiomyoma has been reported recently and a t(7;8)(p13;q11.2) translocation without PLAG1 alteration has been described.

Cytogenetics molecular

Fluorescence in situ hybridization (FISH) supports the cytogenetic pattern observed by conventional techniques, confirming the gain of chromosome 3q as an early and consistent change in carcinomas of the vulva, and the presence of EWS/FLI-1 fusion in extraosseous Ewing's sarcoma/peripheral neuroectodermal tumors of both vulva and vagina.

CGH profiles are also confirmatory: chromosome imbalance with gains from the long arm of chromosome 3, 5, 8, 9 and losses from the 11q have been frequently observed. A comparison between papillomavirus-negative and papillomavirus-positive vulvar cancer indicated that chromosome 8q was more commonly gained in the positive cases.

Genes involved and Proteins

Note: No specific genes involved in vulva or vagina carcinogenesis have been found so far. An isolated study indicated a prominent role of the common IL1RN intron 2 polymorphism in vulvar carcinogenesis.

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