Preneoplastic and Primary Scrotal Cancer

Updates on Pathogenesis and Diagnostic Evaluation

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KEYWORDS

• Scrotal cancer • Squamous cell carcinoma • Extramammary Paget's disease
• Basal cell carcinoma

KEY POINTS

- Scrotal neoplasm has an annual incidence of approximately 1 per 1,000,000 males. Common histologic types are squamous cell carcinoma (SCC), extramammary Paget's disease (EMPD), and basal cell carcinoma (BCC).
- Scrotal SCC is not currently linked to occupational exposure. Oral psoralen and ultraviolet A photochemotherapy has been confirmed as carcinogenic factors.
- EMPD is classified into primary and secondary neoplasms. Scrotal EMPD is associated with an increased risk of gastrointestinal and genitourinary tumors.
- BCC in the scrotum has carcinogenic pathways other than sun exposure. Histologic classification of BCC is critical for prognosis and treatment.
- Diagnostic evaluation of scrotal cancer depends on pathologic subtypes. Inguinal lymph nodes are common metastatic sites in cases of invasive disease.

INTRODUCTION

The scrotum consists of skin, dartos muscle, and the external spermatic, cremaster, and internal spermatic fascia. The dermis of scrotal skin contains hair follicles and apocrine, eccrine, and sebaceous glands. Early in 1775, Pott[1] described a relationship between soot exposure and a high incidence of scrotal cancer among chimney sweepers. Since then, several occupational exposures have been causally linked to an increased risk of scrotal cancer. With this knowledge, primary preventative cares, including improved hygiene and avoidance of carcinogenic substances, have decreased remarkably the incidence of scrotal cancer. In the modern era, the incidence of scrotal malignancy is as low as 0.9 to 1.8 per 1,000,000 male persons per year.[2] The recent literature included reports on more than 1000 cases of scrotal cancer. However, most of these lack accurate information that can be used for detailed assessment or are hypothesis-generating case reports. The rarity of cases and research impede our understanding of the changing diagram of scrotal cancer. Therefore, this article provides a summary of current knowledge, mainly focusing on pathogenesis and diagnostic evaluation, which may influence the prevention and early recognition of the disease.

PRENEOPLASTIC SQUAMOUS LESIONS AND SQUAMOUS CELL CARCINOMA

Pathogenesis

Bowen's disease and squamous cell carcinoma (SCC) are the most common histologic subtypes of scrotal neoplasm, accounting for 42% of all

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cases in a population-based report from the Netherlands.[2] Historically, SCC was the first malignancy to be linked directly to exposure to occupational carcinogens. In addition to soot, SCC has also been linked to exposure to tar, pith, different types of lubricating and cutting oils, creosotes, gas production, and paraffin wax pressing. Owing to the substantial improvements in working environments, occupational risk factors have not been associated with increased risk of scrotal SCC in the last 2 decades.[3]

Ultraviolet exposure is a well-known risk factor for skin cancer. A nationwide population-based case control study found a near significantly increased risk (odds ratio [OR], 6.7; 95% CI, 1.0–45.6) for scrotal SCC with a cumulative lifetime duration of nude sunbathing of 26 to 150 hours.[4] In addition, the results suggested that the use of sunbeds seemed to increase the risk of scrotal SCC (OR, 3.2; 95% CI, 1.0–10.4). Moreover, iatrogenic ultraviolet radiation for skins diseases was associated with a remarkably high risk of scrotal SCC. In a cohort of men with psoriasis who had been treated with oral psoralen and ultraviolet A photochemotherapy (PUVA) and followed for 12.3 years, Stern and colleagues[5] found a risk ratio of 95.7 (95% CI, 43.8–181.8) for genital SCC in treated patients compared with population incidence data. Notably, the mean age of patients treated with PUVA was 46 years, which is significantly lower than the mean age in sporadic cases (65 in the Surveillance, Epidemiology, and End Results database[6]). The carcinogenic effect of PUVA was also dose dependent: in patients exposed to high levels of PUVA, the incidence of invasive SCC was 16.3 times (95% CI, 9.4–26.4) that of patients exposed to low levels. With a further 10 years of follow-up, Stern and colleagues[7] found a 52.6-fold (95% CI, 19.3–114.6) increase in the incidence of genital SCCs in this cohort compared with that expected for the general white population. Although most of the cohort patients had stopped PUVA treatment or used genital shielding since first publication, long-term follow-up showed a constant incidence of genital tumors after treatment stopped and indicated that PUVA presents a persistent risk. Conversely, the link between PUVA and SCC was not confirmed in European prospective studies with relatively short follow-up periods.[8] However, analysis of a large population-based database with an observation period of at least 14 years showed a relative risk of 5.6 to 6.5 for SCC in European men.[9,10] The male genitalia seem to be more susceptible to the carcinogenic effects of PUVA than nongenital areas. In the PUVA Follow-Up study, genital tumors comprised 3.3% of all invasive and in situ SCCs. In the general population, genital tumors comprised only 0.2% of all nonmelanoma skin cancers. The carcinogenic effects of the PUVA therapy include DNA damage accumulation and immunosuppression.[11] No increased risk of skin cancer has been reported in studies assessing the carcinogenic risk of narrowband UVB, which is used now more commonly for treating psoriasis.[12]

Human papillomavirus (HPV) was previously linked to scrotal SCC in a study of 14 patients at the Mayo Clinic.[13] Out of a 14 total cases, 6 (42%) had a history and histologic evidence of HPV infection. Matoso and colleagues evaluated a total of 29 cases of SCC of the scrotum in 3 North American institutions occurring between 1999 and 2013. Of 26 cases with available tissue, 7 (27%) tested positive for high-risk HPV serotypes using in situ hybridization. Cases associated with HPV-infected disease displayed a predominantly basaloid or warty morphology and were characterized by p16 and Ki-67 immunostaining. Similar morphologic and immunohistochemical results in HPV-infected patients suggested similar a pathogenic pathway proposed for penile SCC.[14] Furthermore, scrotal SCC may be a manifestation of cutaneous carcinoma risk in immunodeficient patients. Matoso and colleagues[15] found that 5 of 29 patients with SCC of the scrotum had immune compromised conditions such as with infection with the human immunodeficiency virus, after transplantation, and in leukemia.

Diagnostic Evaluation

Scrotal SCC lesions present as slow-growing plaques, nodules, or ulcerations. Advanced disease may invade the testes or penis. The diagnosis is confirmed by histologic evaluation, and several areas should be sampled to determine the boundary of extension and depth of invasion. The most commonly used staging system is the Lowe modification of the system proposed by Ray and Whoitmore.[16] It is based on the extent of local disease and the level of metastasis (**Table 1**). The scrotum has the same lymphatic drainage pattern as the penis. Tumors usually spread stepwise from the inguinal lymph nodes to the pelvic lymph nodes. Interestingly, the scrotal lymphatics do not cross the median raphe and drain into the ipsilateral superficial inguinal lymph nodes. Therefore, tumors without involvement of the median raphe rarely metastasize to the opposite inguinal site.[17] Because of similarities in location and histology, the clinical workup of scrotal SCC is quite similar to that of penile cancer. Routine imaging examinations included pelvic/abdominal computed tomography (CT) scans and chest radiographs. Other tests such as chest