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Case Report

Secondary NK/T cell lymphoma after radiotherapy for non-HPV-related squamous cell carcinoma of the penis: an early warning event and literature review

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Abstract: Squamous cell carcinoma is the most common malignant tumor of the penis. The new World Health Organization (WHO) classifies it into two types: non-HPV-related and HPV-related. There is a certain proportion of recurrence and metastasis after the first operation on the tumor. Radiotherapy is one of the effective methods to improve prognosis, but there is a risk of secondary primary malignant tumor. Primary NK/T cell lymphoma of the penis is rare, and secondary primary NK/T cell lymphoma of penile stump after radiotherapy for penile cancer has not been reported. Here we report a case of a 75-year-old man who was diagnosed with primary non-HPV-related squamous cell carcinoma of the penis five years after the operation of gastric adenocarcinoma. One year after the first penile operation, penile cancer recurred with multiple metastases in the left inguinal lymph nodes, and radiotherapy was performed after re-operation. Secondary primary penile NK/T cell lymphoma was induced 16 months after radiotherapy. Secondary lymphoma after radiotherapy for penile cancer is an accidental event, and the efficacy and risk of postoperative radiotherapy need to be further evaluated.

Keywords: Squamous cell carcinoma, penis, HPV, Radiotherapy, NK/T cell lymphoma

Introduction

Squamous cell carcinoma is the most common type of penile cancer, and the new classification of 2016 WHO has made a major adjustment to this tumor [1]. Mainly according to the correlation between tumor and human papillomavirus (HPV), it can be divided into two categories: non-HPV-related squamous cell carcinoma and HPV-related squamous cell carcinoma. The former mainly includes common differentiation type,verrucous carcinoma, and others. It is often accompanied by overexpression of mutant P53 protein, while P16 protein is negative, and the clinical prognosis is relatively poor. The latter HPV related squamous cell carcinomas include basal type, and condyloma type. This is often accompanied by overexpression of P16 protein and low expression of P53 protein, and the clinical prognosis is good. At present, although the gold standard for HPV-related detection is molecular detection, P16 immunohistochemical markers in the penis can be used as a simple and feasible alternative detection method for HPV [2]. According to the ISUP/WHO grading system, the tumor pathology grading is divided into G1, G2 and G3, corresponding to high, medium and low differentiation. The incidence of squamous cell carcinoma of the penis is obviously different in different countries and regions, and surgery is generally considered to be the preferred treatment [3]. The tumor recurrence and metastasis rates are different after the first operation due to the different surgical methods and surgical scope. For cases of recurrence and lymph node metastasis, postoperative radiotherapy is a necessary adjuvant treatment [4]. Radiotherapy could prolong the survival period and improve the quality of life of patients, but there are differences in the specific treatment methods and individuals, and the treatment effects and complications are also different [5-8]. At present, the literature has reported that complications related to radiotherapy of penile cancer mainly include urethral stricture, soft tissue necrosis, and fibrosis [9-11], while cases of secondary primary malignant tumors of penis induced by

radiotherapy have not been reported so far. The NK/T cell lymphoma of the penis itself is a rare clinical entity [1], and it is rarer as a secondary tumor in the primary site after radiotherapy for penile cancer. This paper reports the first case of secondary primary penile NK/T cell lymphoma induced by radiotherapy for non-HPV-related squamous cell carcinoma of the penis with recurrence and lymph node metastasis. This report reminds us that radiotherapy should be carefully selected after operation for penile cancer, and its efficacy and risk should be comprehensively evaluated according to individual conditions before treatment.

Materials and methods

Clinical data

First admission: A 75-year-old male was admitted to the hospital 3 years ago with a soya bean size mass in the middle of the penis accompanied by itching and pain. After 9 months of conservative drug treatment, the clinical symptoms gradually disappeared, but the mass gradually increased and required further surgical treatment. The patient underwent gastrectomy for gastric cancer in our hospital 8 years prior, and the postoperative pathology was moderately differentiated adenocarcinoma. There was no other medical history or any family history. Specialist examination revealed an ulcer with a diameter of about 0.6 cm at the middle of the penis, with no enlarged lymph nodes in the bilateral groin. The patient underwent "local resection of penile mass" in the same month. During the operation, an ulcer surface of 0.6 cm × 0.5 cm was seen at the junction of the left inner and outer plates of the prepuce of penis. The tumor was completely removed clinically and sent for pathologic examination.

Second admission: One year after the first operation for penile cancer, the patient was readmitted to hospital for a large rice -- sized mass found on the head of the penis again, but without itching and pain. Pelvic enhanced CT revealed multiple enlarged lymph nodes in the left inguinal region, the larger of which was about 1.9 cm in diameter, suggesting penile cancer metastasis. Specialist examination showed that the head of the penis was poorly healed from the incision of the ring operation, and the area was slightly gray. In addition, a number of swollen and hard lymph nodes were palpated in the left inguinal region, the largest about 2.0 cm × 1.5 cm. The second operation was "partial penectomy and left inguinal lymph node dissection".

Third admission: The patient received local radiotherapy (50 Gy-60 Gy/2Gy/25f-30f) 3 weeks after the second operation for penile cancer. Biopsy of the penis stump 10 months after radiotherapy revealed benign lesions. The patient was admitted to hospital for the third time 16 months after radiotherapy, due to an infection at the severed end of the penis after 4 days. The penile incision on physical examination showed poor involution and poor healing with infection and necrosis. A second penile mass biopsy was performed.

Sample process and special staining

Multiple specimens of penile masses were fixed with 4% neutral formaldehyde, paraffin embedded, sectioned and stained with H&E. The two-step method of envision was used for immunohistochemical labeling. The antibodies: CK, P63, LCA, CD3, CD4, CD5, CD8, CD20, PAX-5, CD21, CD56, Granzyme B (Gr B), CD10, Bcl-6, Bcl-2, MUM-1, CD30, ALK, EMA, Ki67 primary and secondary antibodies were all purchased from Beijing Zhongshan Company. In situ hybridization: EBV-RNA (EBER) was detected by ISH method in tissue samples (EBER in situ hybridization kit was purchased from Beijing Zhongshan Biotechnology Co., Ltd.), and the operation procedures were conducted strictly in accordance with the instructions. The positive samples of EBER were used as positive control, and PBS buffer was used as a negative control instead of hybridization solution or primary antibody.

Results

Pathologic findings

The first penile tumor specimen: A patch of gray-red tissue: 2*1.5*0.3 cm, with a shallow ulcer on the focal surface and a diameter of about 0.6 cm. The tumor cells were differentiated under the microscope. The cytoplasm of some tumor cells was rich in red staining, keratinocytes were formed, and nuclear atypia was not obvious (G1 level). The cytoplasm of some tumor cells was moderately red, the nuclei were moderately heteromorphic, and some nucleoli

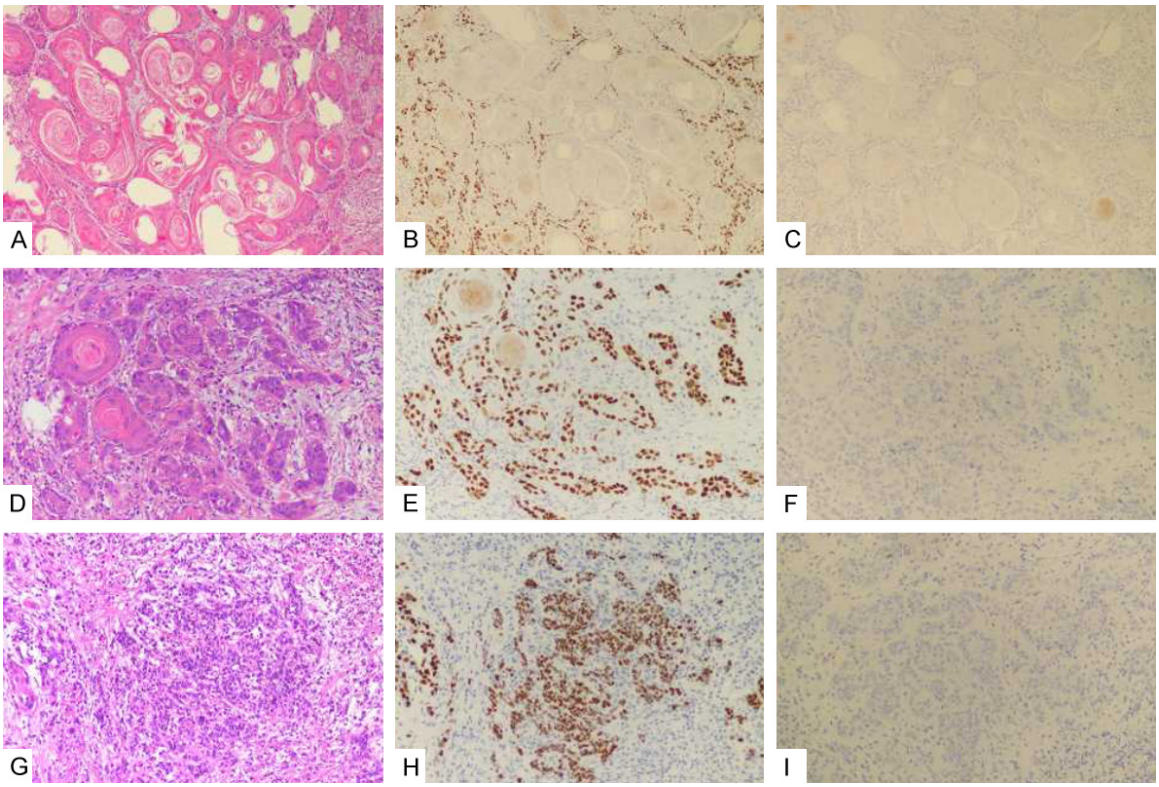

Figure 1. Morphology and immunohistochemical staining of P53 and P16 in the penile biopsy (20 ×): A. H&E image of squamous cell carcinoma of the penis (G1 level). B. The IHC expression of P53 protein in the G1 level region of carcinoma was mutant and strongly positive, but the keratinized area and hyper-keratinized area showed negative expression. C. Negative expression of P16 protein in the G1 region carcinoma. D. H&E image of squamous cell carcinoma of the penis (G2 level). E. Mutant and strongly positive expression of P53 protein in the G2 region of carcinoma. F. Negative expression of P16 protein in the G2 region. G. H&E image of squamous cell carcinoma (G3 level). H. Mutant diffuse and strongly positive expression of P53 protein in G3 region. I. Negative expression of P16 protein in G3 region.

were clearly visible, with occasional mitotic figures (G2 level). Immunohistochemistry: P53 (diffuse strong +), P16 (-) (**Figure 1A-F**). Diagnosis was non-HPV-related squamous cell carcinoma of the penis.

Second penile tumor specimen: A section of penis was 4 cm long, 3 cm in diameter, about 2.5 cm from the severed end. There was a gray area in the original incision with a range of about 0.8 cm × 0.8 cm. Four lymph nodes were found in the labeled left inguinal area with a diameter of 0.8 cm-2 cm. In addition to the above similar highly differentiated and moderately differentiated areas, the focal tumor nucleus/cytoplasm ratio was significantly enlarged, and nuclei was pleomorphic, with visible mitotic figures (G3 level). Immunohistochemistry showed P53 (diffuse strong +), P16 (-) (**Figure 1G-I**). Diagnosis: Combined with the clinical history, recurrence of squamous cell carcinoma of the penis. The resection margin was negative for tumor and 4/4 of the left inguinal lymph nodes had metastasis.

Penile biopsy specimen 10 months after radiotherapy: There were many patches of gray tissue: 0.6 × 0.6 × 0.3 cm. The squamous epithelium of the penile skin showed pseudoepithelioma-like hyperplasia. There were many acute and chronic inflammatory cells infiltrating, with granulation tissue hyperplasia and focal necrosis in the stroma.

Third penile tumor specimen (16 months after radiotherapy): Three small gray-red tissues with a total volume of 1 cm × 1 cm × 0.4 cm. Microscopically, cells were large, with diffuse infiltration of heterotypic lymphocytes, accompanied by necrosis in some areas; the cytoplasm of some cells was transparent and mitotic figures frequent. Vascular invasion and nerve invasion

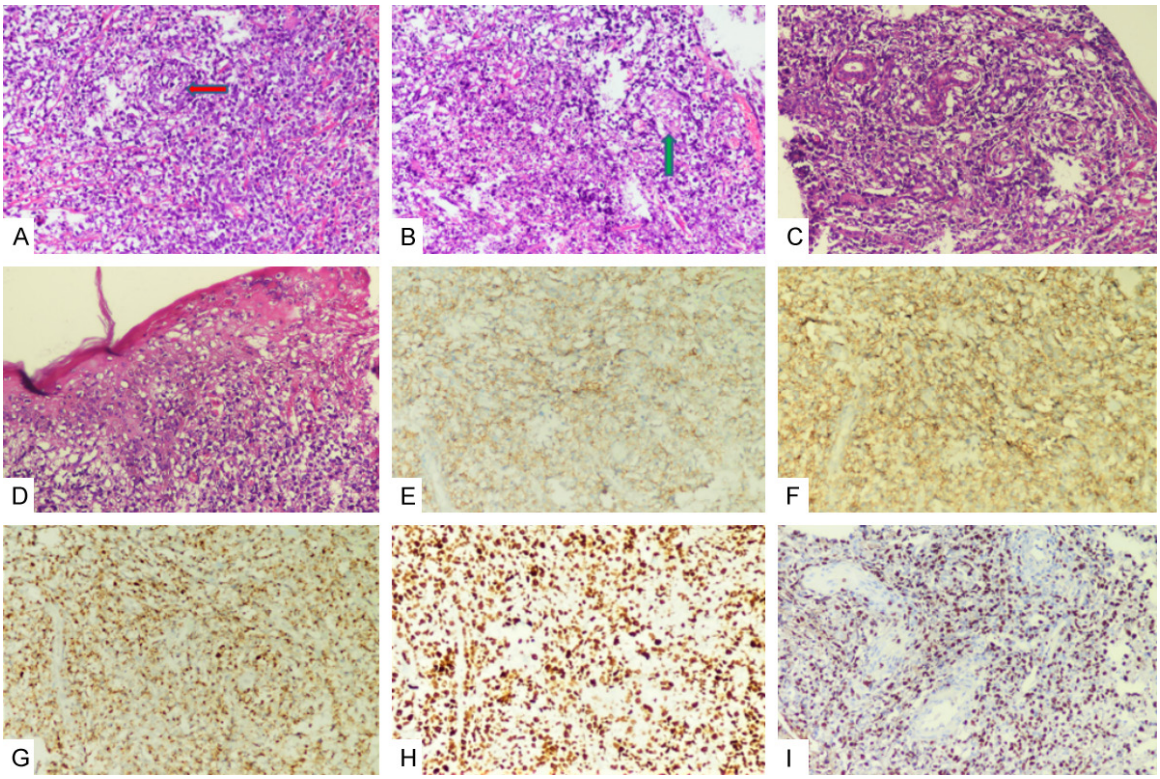

Figure 2. Morphology, immunohistochemistry, and in situ hybridization staining for penile NK/T cell lymphoma (20 ×): (A) Red arrows indicates concentric circles of vascular invasion. (B) Penile NK/T lymphoma nerve invasion (green arrow) and necrotic area. (C) Lymphoma tumor cells invading the skin appendages. (D) Lymphoma tumor cells invading the penile skin surface. Immunohistochemistry of lymphoma tumor cells showed positive expression of CD3 (E), CD56 (F), and GrB (G) in lymphoma tumor cells. (H) High expression of Ki67 in lymphoma tumor cells. (I) In situ hybridization showed EBER positive for lymphoma tumor cells.

were also observed. The tumor dthe skin appendages and penetrated the surface of the penis. Immunohistochemical of tumor cells: CK (-), P63 (-), LCA (+), CD3 (+), CD4 (partly+), CD8 (partly+), CD5 (-), CD56 (+), GrB (+), CD20 (-), PAX-5 (-), CD21 (-), CD10 (partly+), Bcl-6 (-), Bcl-2 (-), CD30 (-), MUM-1 (-), ALK (-), EMA (-), Ki67 positive rate more than 90%. In situ hybridization: EBV-EBER (+) (**Figure 2A-I**). Diagnosis wasenile NK/T cell lymphoma.

Diagnosis and follow up

Non-HPV-related squamous cell carcinoma of the penis with multiple left inguinal lymph node metastases (common differentiation type: pT2N2M0) was diagnosed, followed by secondary primary penile NK/T cell lymphoma induced by radiotherapy for recurrent primary squamous cell carcinoma and lymph node metastasis. After the diagnosis of penile NK/T lymphoma and the positive expression of EBER, it was suggested to further detect EBV infection in the patient's blood. Unfortunately, the patient declined further treatment, left the hospital against advice, and was lost to follow-up.

Discussion

Penile cancer in the male urinary system tumor incidence is low, mainly squamous cell cancer, and occurs in the penis glans, foreskin and coronary sulcus. The early stage of squamous cell carcinoma of penis is mainly manifested as maculopapules, ulcers, or verrucous or vegetated masses, which can be accompanied by erosion, bleeding, malodorous secretions, and other symptoms. Tumors are more common in the elderly, with an average age of about 60 years. The development of squamous cell carcinoma of penis is the result of the synergistic effect of various pathogenic factors. Currently HPV infection is considered to be one of the important exogenous factors causing the disease, and other risk factors mainly include excessive prepuce, phimosis, chronic inflam-

mation, and lichen sclerosus [12, 13]. With the increasing number of patients with HPV infection, which is closely related to clinical prognosis, it is important for classification of squamous cell carcinoma in the new edition of WHO classification. At present, theincidence of non-HPV-related squamous cell carcinoma of penis is higher than that of HPV-related squamous cell carcinoma, and the incidence varies in different countries and regions. The former was further subdivided into *Tp53* mutant isoform and chromosome highly unstable isoform. Among them the *Tp53* mutant isoform is usually invasive and negatively correlated with tumor-specific survival, which needs more clinical attention [14, 15]. Due to the particularity of penile site, different surgical methods and treatment methods should be adopted in the treatment of tumor with different grades and stages. There is a general consensus that patients with low-grade and low-stage tumors can get different organ-sparing surgical treatments, while patients with higher-grade and higher-stage tumors are recommended to undergo radical penectomy. Postoperative adjuvant therapy can prolong survival and reduce the recurrence rate of tumors to some extent [16, 17]. However, early detection and early treatment are the keys to the preservation of penile function and outcome.

Recurrence and metastasis of squamous cell carcinoma of the penis after the first operation are not uncommon, and the prognosis is relatively poor. The metastasis route of penile cancer is mainly lymphatic. Inguinal lymph node is the most common site of metastasis, and lymph node involvement is closely related to the survival rate and subsequent treatment [18]. Imaging examination is helpful for the evaluation of lymph node status, but there is the possibility of false negative results, so there is no consensus on whether inguinal lymph node dissection should be performed at the same time as clinical surgery [19, 20]. However, for patients with high-grade and high-stage penile cancer, radical surgery combined with inguinal lymphadenectomy can significantly improve the survival rate [21]. The selection of treatment method for patients with confirmed penile cancer should be determined according to the individual's specific situation. Currently the adjuvant treatment methods mainly include the following: radiotherapy, chemotherapy, laser ablation, and combination therapy. Local radiotherapy is an effective method for the treatment of penile cancer recurrence and regional lymph node metastasis [22, 23]. The biologic and pathologic features of non-HPV-related squamous cell carcinoma and differences in the effects of radiotherapy and chemotherapy have been well described in the head and neck. However, the incidence of penile tumors is relatively low, and there is not enough literature to guide the implementation of specific radiotherapy programs. With the refinement of the specific classification of penile cancer, the demand for its precise treatment has become high. However, there are few reports on radiotherapy related to the classification of penile cancer [24-26], and the optimal radiotherapy method still needs more research results to provide a reference. Radiotherapy can obviously improve the prognosis of patients and reduce the recurrence rate, but the complications with different severity after corresponding radiotherapy are inevitable, and the most serious one is the induction of malignant tumor. It has been reported that the types of secondary malignant tumors induced by radiotherapy, such as cancer, sarcoma, leukemia and lymphoma, can all occur, and they are related to the site of primary tumor, radiotherapy method, and radiation dose [27, 28]. Among them, radiotherapy-induced lymphoma cases are relatively rare clinically, and the pathologic types are mostly non-Hodgkin's lymphoma [27, 29]. However, the related complications after radiotherapy of the first malignant penile tumor are mainly manifested as various benign lesions. In a few cases, secondary bladder carcinoma of the urothelium occurred after radiotherapy [30], but it has not been reported that lymphoma lesions were induced again in the original site. Although secondary primary lymphoma after radiotherapy for penile cancer is rare, it still occurs.

The incidence of primary lymphoma of the penis is very low, but the mortality rate is high [1]. Statistical data show that the major pathological type of penile lymphoma is diffuse large B-cell lymphoma, while other types are rare and may have worse prognosis [31]. Among them the penile NK/T-cell lymphoma is one of the above-mentioned rare types, which has been very rarely reported in the literature. This tumor belongs to extra-nasal NK/T cell lympho-

mas, which mainly involve the testicular area in males, while most tumors in the penis are reported to be metastases of nasal type NK/T cell lymphoma [32-34]. The histopathologic morphology and immunohistochemical markers of the extra-nasal neoplasms are somewhat different from those of the nasal neoplasms. Currently its pathogenesis and clinical characteristics are still unclear, but the survival rate is relatively lower [32]. The in secondary primary penile NK/T cell lymphoma after radiotherapy for primary penile cancer may have been caused by the following factors: (1) The patient had a tumor predisposition with a history of gastric cancer and penile cancer, (2) The patient was older and has lower immunity and defense function, (3) The patient chose partial penectomy, and there was long-term inflammatory stimulation at the stump, (4) Radiation therapy can induce somatic cell mutation. The main diagnostic criteria for radiation-induced tumor are as follows [35-39]: (1) History of radiation therapy, (2) The secondary tumor must be within the original radiation range, (3) Pathology confirmed that the histologic types of secondary and primary tumors were different, (4) There is a certain incubation period after radiotherapy, but the specific evaluation criteria are not uniform, and two years can also be accepted within the short incubation period. First, this case meets the above requirements for diagnosis of radiation-induced secondary tumor. Second, the pathologic findings of the two interphase biopsy of penile tumor showed benign infective lesions. In addition, there was no evidence of involvement of parenchymal organs or lymph nodes other than the penis. Therefore, it is believed that the pathogenesis of secondary penile NK/T cell lymphoma was mainly related to postoperative radiotherapy of squamous cell carcinoma. It is rare that this tumor is induced by postoperative radiotherapy for primary malignancy of the penis. This report has certain reference significance for guiding the follow-up radiotherapy of penile carcinoma.

In summary, squamous cell carcinoma of penis is a progressive malignant tumor and non-HPV-related squamous cell carcinoma with P53 mutation subtype usually progresses faster, with worse prognosis. When patients find suspicious clinical symptoms early, they should seek medical treatment and early biopsy diagnosis as soon as possible, so as not to delay treatment. For cases of recurrence and inguinal lymph node metastasis, the specific treatment should be based on the individual's actual situation. It is recommended that "radical penectomy with inguinal lymph node dissection" should be the first choice. Postoperative adjuvant treatment should be carefully selected which should be comprehensively considered and accurately formulated according to the patient's specific histologic subtype, pathologic classification, clinical stage, and personal quality. Radiation therapy is one of the recognized adjuvant therapies, but there is a risk of secondary malignancy, which is a major concern for patients. We report the first case of secondary primary NK/T cell lymphoma secondary to penile fracture after radiotherapy for penile cancer, which serves as a warning to us: for some special groups, such as those who are susceptible to cancer or the elderly and the infirm, the choice of surgical method for penile cancer is very important. The complications such as EBV infection should be controlled timely and effectively after operation. The indication and dose of radiotherapy should be strictly controlled. The choice of operation combined with adjuvant therapy, evaluation of curative effect and prognosis, and the risk of complication of penile cancer all need to be further studied.

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Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Disclosure of conflict of interest

None.

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