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Case Presentation
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Penile Metastasis as Unusual Presentation of Testicular Non-Seminomatous Germ Cell Tumor

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Abstract

Penile metastasis from testicular cancer is a rare condition. To our knowledge, only 11 cases have been described in literature. Patients with non-pulmonary visceral metastases should be considered poor risk, based on the International Germ Cell Cancer Collaborative Group classification. It is debated whether penis lesion is a visceral site. With this clinical case we report our experience with a rare condition, focusing on its unusual clinical presentation, difficult prognostic assessment and identification of the best therapeutic approach.

Introduction

Penile Metastasis (PM) is an uncommon situation and only few data are available from case reports and reviews. In 1870 [1], described the first clinical case of a secondary cancer of the penis, as a consequence of colon-rectum adenocarcinoma [1]. In 2006 [2], published an exhaustive review describing clinical presentation and diagnosis of penile metastases. Among the 372 cases included in the review, only 11 cases of PM from testicular cancer were mentioned [2]. Secondary penile lesion from testicular Non-Seminomatous Germ Cell Tumors (NSGCT) is a rare condition with limited data about management. We describe an interesting case of a penile metastasis as first unusual presentation of a primitive testicular cancer.

Case Presentation

A Caucasian 45-year-old man presented to our clinic for a thickening at the base of his penis, appeared three months before. He had a negative familiar and personal history. Particularly no personal history of genitourinary pathology and of sexually transmitted disease was reported. He had no referred local surgery. Clinical examination revealed a fixed, hard, erythematous nodule, 2.5 cm in diameter, on the proximal third of the penis, without any other clinical signs or symptoms. Ultrasound scan of the penis showed diffusely thickened Corpora Cavernosas (CC). A Magnetic Resonance Imaging (MRI) revealed a single lesion measuring 35 mm x 38 mm of both CC (Figure 1: A, B). A detailed study with a total body computed Tomography (CT) revealed a single nodule in the right lung (17 mm). A fine-needle aspiration biopsy of the penile nodule indicated cohesive groups of pleomorphic epithelioid cells with prominent nucleoli, giving the concluding the diagnosis of metastasis due to germinal carcinoma. The patient underwent standard inguinal right orchiectomy. The tumor measured 1.5 cm, it was composed of embryonal carcinoma (60%), yolk sac tumor (30%) and teratoma (10%). Tunica albuginea infiltrates but does not invade, there is no vascular invasion. Most of the epididymis was replaced by moderately to poorly differentiated adeno carcinoma. Post-orchiectomy tumor markers were: AFP 267.5 ng/mL, βCGH 6529 mUI/ml, LDH 416 U/L. According to the American Joint Committee of Cancer/Union for International Cancer Control (AJCC/UICC), tumor staging was pT1a N0 M1b. Prognostic stratification for this patient, based on the International Germ Cell Cancer Collaborative Group (IGCCCG) the prognostic group was poor [3]. Patients with non-pulmonary visceral metastases should be considered poor risk. It is debated whether penis lesion is a visceral site. Anyway, four courses of BEP (cisplatin 20 mg/m^2 on day 1–5, etoposide 100 mg/m^2 on days 1–5, bleomicine 18 mg/m^2 on days 2, 9 and 16) every three weeks represented the standard of care for both intermediate and poor risk patients. After the administration of only one cycle of BEP tumor markers were considerably reduced: AFP 10.9 ng/mL, βCGH 105 mUI/ml, LDH 363 U/L. Only three cycles of BEP were administered, because of persistent penile infection. Prophylactics Granulocyte Colony-Stimulating Factors (G-CSF) were

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administrated after every cycle. At the end of systemic treatment, serum tumor markers were normalized. Penile MRI and ultrasound showed residual mass of the penis (19 mm x 23 mm x 17 mm) and CT scan described reduction of the lung lesion (5 mm). A multiple-disciplinary discussion was held as to the option of surgical removal of the residual penis disease, as strangely recommended by National and International guidelines for residual mass >1 cm [4,5]. Our patient's desire to preserve the penis was taken in account and they offered him a more strictly observation for the first one year: markers, CT scan and penile MRI every 3 months, than every 6 months. To date, the patient has been followed-up for 40 months and no progression of disease is evident.

Discussion

Penile metastasis from testicular cancer is uncommon. To our knowledge, only 11 cases have been described in literature [2]. With this clinical case we report our experience with a rare condition, focusing on its unusual clinical presentation, difficult prognostic assessment and identification of the best therapeutic approach.

Germ-cell tumor

Germ Cell Tumors (GCTs) are uncommon tumors and represent for 1% of all male tumors [6,7]. GCTs are classified as seminoma or non-seminoma. Non-seminomatous tumors often comprehend multiple cell types, including embryonal cell carcinoma, choriocarcinoma, yolk sac tumor, and teratoma. The 5-year survival for testis cancer is 98% [6,7]. The most common site of metastasis in testicular cancer is the lymph nodes in the abdomen; metastasis to the lung, liver, bones, kidney and brain is also possible [8-10]. In 56% of metastatic non-seminomatous GCTs disease there are normal tumors markers are observed [11]. In their review [2], reported that in the majority of cases Penis Metastases (PM) arise from pelvic primary tumors. Prostate and bladder cancer are the most frequent primary tumor presenting secondary penile lesions: respectively 34% and 30% of 372 penis metastases cases described in literature, followed by recto-sigmoid neoplasm 13% and kidney 8%. As mentioned above, only 11 cases (3%) arise from testicular cancer [2].

Clinical presentation and diagnosis

The most common site of secondary penile lesion is the CC (35% of cases bilateral); most rarely are in Glans Penis (GP), Urethra Penile (PU), Corpus Spongiosum (CS) [12-14]. Most commonly in duration of the penis or a cutaneous lesion are the first presentation. Pain or priapism is described, but less frequently. In 60% of metastatic penile lesion there are multiple infiltrative nodules [15]. Differential diagnosis of penile lesion includes mostly infectious disease, but also pre-malignant conditions should be considered. Among malignant lesions squamous cell carcinoma is the most common type of primary penile cancer. Other epithelial forms of penis cancer, melanoma or sarcoma are less frequent. Synchronous presentation of secondary penile lesions was observed in around one third of patients, while metachronous appearance of lesion occurs after a mean time of 18 months [16]. Ultrasonography and MRI are the gold standards for accurate evaluation of involved anatomic structures of penis. However, histological confirmation is necessary. In our clinical case the penile localization was synchronous with testicular cancer, while the other cases of penile metastasis were metachronous and with a variable interval from the diagnosis of testicular tumor (from 2,5 to 24 month). Clinical presentation represents one of the main points in our case, because about 4 months needed to discover the primary tumor in the testis. Both synchronous and asymptomatic

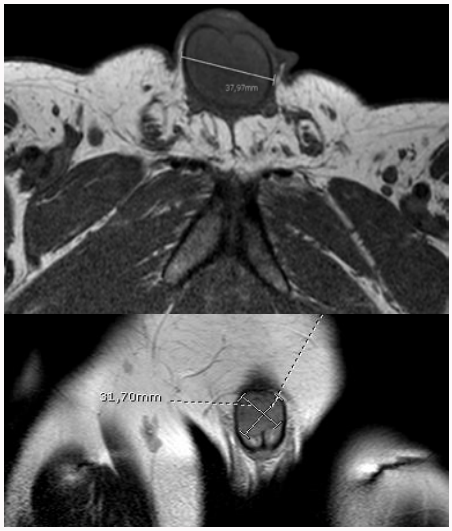

Figure 1: A-B. MRI at diagnosis. Penis metastasis in corpora cavernosas.

presentations certainly contributed to delayed diagnosis.

Metastatic mechanism

It is difficult to understand the mechanism of metastatic spreading to the penis. Indeed, despite the rich Vascularity of corpora cavernosas, secondary lesions of the penis are rare. We briefly listed several proposed mechanisms. Retrograde venous route: the venous drainage of penis is via three main venous systems, composed by superficial dorsal vein of penis, deep dorsal vein (retro pubic venous plexus) and deep circumflex vein, retro chronal plexus and pudendal plexus. Right testicular vein opens into inferior vena cava, where both drainage venous systems are confluent. By a retrograde flow of blood, testicular malignant cells may have spread into penis venous system [14].

Retrograde lymphatic route: the lymphatic drainage of penis is from the bladder base, the posterior surface of the prostate and the lower rectum; drain into the external iliac nodes [14]. The lymphatic drainage of testis is to lumbar and para-aortic nodes. By this way malignant cells may arrive at the penile skin, then the corpora or the glans penis [14]. Hematogenous spread: it is rare, but vascular invasion is a known prognostic factor for NSGCT. Vascular invasion was originally defined as the thrombotic occlusion in blood capillary vessels [17]. The artery supply the penis originates from internal pudendal arteries while testicular artery directly emerged from aorta [14]. Direct invasion or instrumental seeding are less frequent and, however, better recognized when occur [14]. Medical interview is a crucial part in this setting. Surgical history for many common conditions, such as inguinal hernia or cryptorchidism, may suggest iatrogenic anatomic variant to understand spreading tumor way.

Management and treatment

According to IGCCCG prognostic classification, in good prognosis group of patients the 5-years OS rate is 92% [3]. In patients having intermediate prognosis features OS rate is 80% and for the poor prognosis group patients' OS rate is 48% [3]. In patients with intermediate or poor prognosis, the standard treatment is represented by chemotherapy, particularly four cycles of BEP [18]. In this subgroup of patients, complete response rate ranging from 55% to 82% [18]. VIP regimen (Cisplatin, Etoposide and Ifosfamide) can be administrated in cases of contra-indications for the use to

bleomycin, such as high risk of lung injury [3,18]. The administration of prophylactics G-CSF is indicated after every cycle of BEP [19]. In 2014 [19] published a phase III trial (GETUG 13) in patients with poor-prognosis GCT. The patients with AFP and βHCG not declined after one cycle of BEP, underwent to the administration of High-Dose Chemo Therapy (HDCT) regimen. The data suggest that first line HDCT may be effective in poor prognosis patients with slow tumor markers decline after the administration of the first cycle of BEP. HDCT consisting on the infusion of two cycles of paclitaxel (175 mg/m^2 day 1) and BEP plus oxaliplatin (130 mg/m^2 day 10), followed by other two cycles of cisplatin (100 mg/m^2 day 1), ifosfamide (2 g/m^2 on days 10, 12, 14 and mesna), and bleomycin (25 units/day, by continuous infusion for 5 days on day 10 to 14), with G-CSF support. The study met his primary endpoint: 5-year PFS rate was 60% in the HDCT arm versus 47% in the BEP arm (HR 0.65; 95% CI 0.47–0.97; p=0.037). Salvage chemotherapy rate was lower in HDCT treated patients (17% *vs.* 8%; p=0.035) [20]. This approach is still not widely accepted, cause of lacking similar data and the reproducibility of tumor markers decline algorithm.

Surgical residual mass

After the administration of three or four cycles of cisplatin-based chemotherapy, only 60% patients show radiological complete response disease, more than 30% had partial response with the presence of residual masses [21]. The prognosis of this patients depended to serum tumour marker levelsdimensions of disease before systemic treatment, and histological features of the resected masses [22-24]. The presence of residual masses <1.5 cm, masses reduction ≥ 90% after chemotherapy, and the absence of teratoma component in the primitive testicular tumour are predictive of necrosis or fibrosis [22-24]. Several trials showed histologic discordance between Retro Peritoneal (RP) and Extra-Retro Peritoneal (ERP) post-chemotherapy residual masses [22,25]. Histological features of residual mass were necrosis or fibrosis in 45% to 50% of cases, teratoma in 30% to 40% of cases, variable malignant cells (embryonal carcinoma, choriocarcinoma, yolk sac tumour, undifferentiated carcinoma, undifferentiated teratoma, teratoma in malignant transformation) in 10% to 20% of cases. Teratoma and variable malignant cells tumor were related to poor outcomes [26-28]. Removal of residual masses after chemotherapy in NSGCTs remains the standard of care [29]. Resection of RP residual masses has not only a curative objective but also a diagnostic rule [30,31]. The surgery can be done after four weeks at the end of chemotherapy and in men with residual masses with normal serum tumour markers levels [32]. When the primitive tumour shows components of variable malignant cells or teratoma, the aim of surgery treatment is radical excision of residual disease [32]. In fact, teratoma is chemo resistant; it is very aggressive because it may infiltrate adjacent structures [25]. *Devillè et al.* retrospective analysed 51 men underwent surgery after chemotherapy for metastatic NSGCT. Patients with elevated levels of AFP at diagnosis, showed mature teratoma and/or viable malignant cells in residual masses (p: 0.036). Worse outcome was reported in poor prognosis group according to IGCCCG compared with good and intermediate prognosis groups (p: 0.006) [29]. *Steynberg et al.* suggested that the resection of RP residual disease was indicated when tumoral mass reductions after chemotherapy was more than 70% and residual tumoral mass was more than 1 cm to CT-scan [33]. *Carver et al.* reported that poor prognostic risk according to IGCCCG classification and dimension of residual masses were predictive of disease recurrence in patients with residual teratoma at RP lymph node dissection [34]. ERP metastasis is presents in 43% of patients affected of GCT [35]. ERP residual disease is related to poor prognosis if compared to retroperitoneal disease [25]. The most common location of disease recurrence was in the lung, followed by the neck and mediastinum [36-38]. In cases of surgical completely resection of residual disease, mature teratoma or necrosis/fibrosis relapsed less of 10% patients; when in residual disease were found viable malignant cells, the possibility of relapse was around 30% patients before the first 2 years [29]. When residual disease was mature teratoma or variable malignant cells, the administration of two cycles of cisplatin-based chemotherapy (after the surgery) reduced the risks of relapse and improved the PFS and OS [30,31,39].

Follow up

After treatments, men with metastatic NSGCT should be followed for early detection and treatment of relapse. There are no a clear management of this patients. According National and International guidelines, it's indicated a follow-up visit for at least the first 5 years [4,5]. For non-semimoma stage I, clinical examination, serum markers and chest-XR are recommended every 2-3 months for the first two years and every 4-6 months from third and fifth year; abdomen-pelvic CT scan are recommended every 6 months for the first two years and once a year from third and fourth year as clinical indicated [4,5,40]. In metastatic setting, the follow-up schedule provides for a clinical examination, serum markers, and every 2-3 months for the first two year and every six months from third and fifth year. Chest-XR and CT scan every six months for the first two years. CT scan should be done once a year for the third year. Chest-XR should be done once a year from third to fourth year [4,5,40].

Conclusion

To our knowledge, there are limited published data in the literature about non-seminomatous testicular cancer with metastatic localization to corpora cavernosas of penis. It's interesting to observe that in our patient, penis metastases were the first evidence of neoplastic disease with any systemic symptoms. Despite the poor prognosis, after more than 3 years of the end of chemotherapy, he was asymptomatic without clinical evidence of neoplastic disease.

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