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Original Article

Metastatic tumor of male genital system from gastric cancer: a case report and review of literature

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Abstract: Spermatic cord (SC) tumor metastatic from gastric cancer (GC) is rare. Here we report a case of left SC metastasis and meanwhile perform a literature review to characterize this rare disease. A 72-year-old male presented with a palpable painful mass in the left groin after one year and a half of remnant GC resection. SC metastasis of signet-ring cell adenocarcinoma was confirmed by trans-inguinal biopsy, and palliative chemoradiotherapy was initiated. The disease remained stable within follow-up 10 months. A total of 27 GC patients with male sex cord metastasis were reviewed according to a literature search from January 1955 to March 2016. In such a cohort, the mean age was 58.3 (range, 23-72) years. The average time interval between primary GC and genital metastasis was 43.2 (range, 2-120) months in 16 (59.3%) metachronous cases, while nine (33.3%) synchronous cases reported. The average size of genital tumor was 3.8 (range, 2.1-9.0) cm in diameter. The major pathological characteristics were signet-ring cell (40.0%, 8/20) and poor differentiation (85.0%, 17/20), with right-side sex cord most commonly involved (48.1%). The incidence of genial metastasis was 74.1% in SC, with 40.7% for epididymis, 33.3% for testis, 14.8% for tunica vaginalis and 3.7% for scrotum. The one-year overall survival rate was 38.7%, with a median survival time of 12 months. Advanced GC metastatic to male sex cord is rare, with poor prognosis. For patients with GC history and groin discomfort or mass, metastatic adenocarcinoma should be suspected, followed by proper diagnosis and treatment.

Keywords: Spermatic cord metastasis, gastric cancer, signet-ring cell, adenocarcinoma

Introduction

Gastric cancer (GC) is one of the most common malignancies all over the world, especially in China [1]. The common metastatic sites of GC include regional lymph nodes, liver, peritoneum, bone marrow and lung, but very rarely involving male genital system (spermatic cord, vas deferens, testis, epididymis and scrotum, etc.) [2, 3]. The prognosis of such a rare metastasis in the male is usually very poor [2] [Alois, 2005 #90]. Herein, we report a case of metastatic tumor in left spermatic cord due to the advanced remnant GC. Meanwhile, we have performed a literature review and summarized the clinical and pathological characteristics of GC metastasis to male sex cord.

Materials and methods

Case report

A 72-year-old male presented with a hard mass complied with persistent pain in his left groin for three months. He had been diagnosed with a remnant GC one-and-a-half years before, and received total gastrectomy and partial resection of transverse colon and left hepatic lobe. Histologically it was described a diffuse, poorly differentiated adenocarcinoma involving the left hepatic lobe and transverse mesocolon, with negative finding for 20 harvested lymph nodes (pathological TNM stage: pT4bN0M0, IIIB). He had received S-1 alone (60 mg/m^2) chemotherapy for six cycles, with no evidence of recurrence within one year of follow-up period.

On physical examination, an 8 cm × 2 cm × 2 cm, hard and tender mass was palpable in the left groin and fossa, with clear in ipsilateral testis, epididymis or scrotum. The left testis was proximally retracted, with no enlarged lymph node found in superficial groin or supraclavicular regions. The digital rectal examination was normal.

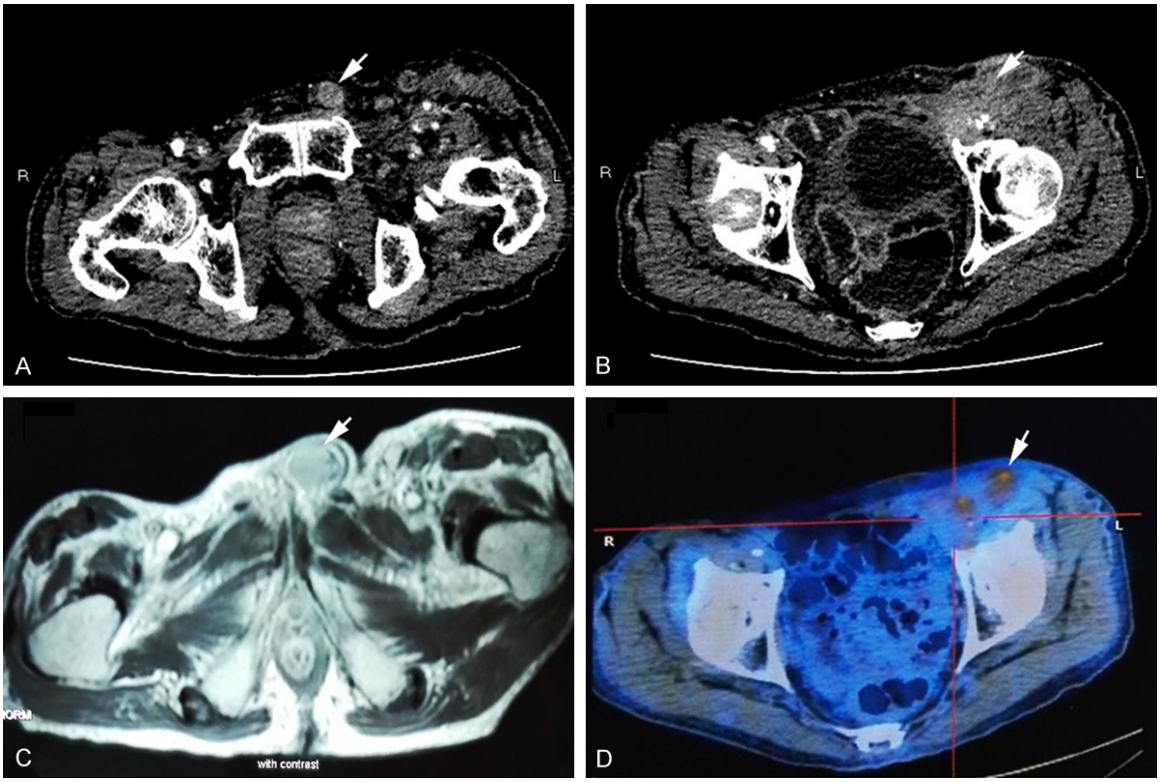

Figure 1. Radiographic findings of the patient after admission. Contrast-enhanced CT scan indicates: (A) The tumor in the left spermatic cord completely surrounds the left external iliac vein (white arrow); (B) Such spermatic cord tumor has heterogeneous density, with irregularly thickening of tumor margin near iliac fossa (white arrow). MRI image (C) shows a spermatic cord metastasis with no evidence of soft-tissue invasion (white arrow). Finally, PET-CT scan (D) confirms that GC metastatic to the sex cord due to significantly high glucose intake.

Pre-operative serum CEA and CA199 were 6.17 μg/L and over 1200 U/ml, respectively. However, values of other tumor markers including PSA, β-HCG, AFP and CA125 were within normal references ranges. Positron emission tomography (PET)-CT imaging revealed an isolated metastatic tumor in the left groin and fossa, with no lymph node and distant organ metastasis identified. Additional magnetic resonance imaging (MRI) indicated a diffuse thickening mass with an irregular margin and heterogeneous contrast enhancement in the left spermatic cord (**Figure 1**). The routinely performed gastrointestinal endoscopy was normal. Afterward, the patient underwent a trans-inguinal exploration with tumor biopsy sampling applied meanwhile. The pathological test using Hematoxylin and eosin staining and specific immunohistochemistry staining detected 18% of gastric signet-ring cell carcinoma from the biopsy sample, which confirmed the spermatic cord metastasis from gastric adenocarcinoma (**Figure 2**).

Subsequently, the patient has received chemoradiotherapy with simplex S-1 again for four cycles and a total radiation of 45 Gy for twenty cycles, respectively. Within a one-year follow-up period, the patient is asymptomatic, without evidence of disease recurrence.

Literature review

We searched possible case reports on male genital metastasis from gastric cancer in PubMed database, between January 1944 and March 2016. The used search terms included “gastric cancer”, “gastric adenocarcinoma”, “stomach neoplasms”, “spermatic cord metastasis”, “testicular metastasis”, “scrotal metastasis”, “inguinal metastasis” and “groin metastasis”. The search was not restricted to English-language literature, with German, Spanish, Chinese, Japanese and Dutch-language publications included. The literature, which had histologically confirmed diagnosis of GC and metastasis in male genital system, was enrolled in

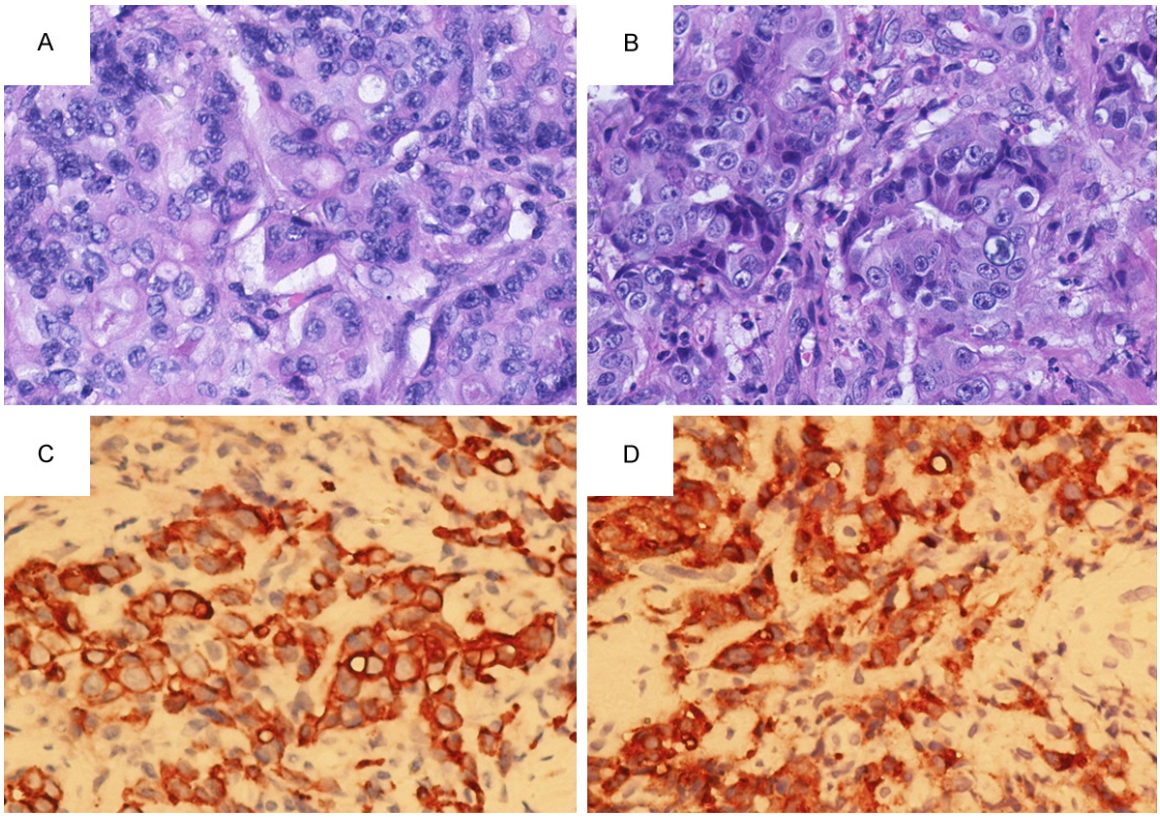

Figure 2. The histopathologic examinations of spermatic cord metastasis from gastric adenocarcinoma. (A) Primary gastric adenocarcinoma detected under Hematoxylin-eosin (HE) staining, original magnification × 400; Poorly-differentiated signet-ring cell carcinoma in the spermatic cord metastasis further confirmed by HE staining (B), CEA (C) and CK (D) immunohistochemistry staining, respectively; magnification × 400.

the current review. Data required for performing analysis were extracted by reading abstract and (or) full-text of included literatures. In sum, 27 GC cases including the reported case were available for subsequent analyses. If not otherwise indicated, categorical variables were expressed as number and percentage of patients, and the other variables were expressed as medians and ranges for non-parametric tests applied and as mean ± standard deviation (SD) for parametric tests applied. Comparison tests, either student's *t-test* or Fisher's exact test, were not applied in the current study. The cumulative overall survival (OS) rate was calculated by the Kaplan-Meier method with log-rank test. All analyses were performed using IBM® SPSS® Statistics (Ver. 23.0; Chicago, IL).

Results

The clinical features and outcomes of 27 cases were summarized in **Table 1**. The average age at diagnosis of genital metastasis was 58.3± 10.8 (range, 23-72) years. Apart from one case without any complaint, the primary symptoms included painless, palpable groin mass with or without involving genital system (37.0%, 10/26), swollen and painful mass in genital system (33.3%, 9/26), pain and swollen genital tract (22.2%, 6/26), and simple hydrocele (3.7%, 1/26). The time interval between GC diagnosis and detection of genital metastasis ranged from 2 months to 10 years (mean, 43.2 months) in 16 (59.3%, 16/27) metachronous cases, while the primary tumor and genital metastasis were diagnosed synchronously in another nine cases (33.3%, 9/27). Of note, such information was not reported in two cases (7.4%, 2/27). The average size of metastatic tumor was 3.8 (range, 2.1-9.0) cm.

The histological differentiation of metastatic tumors included well-differentiated cancer in one case (3.7%, 1/27), with moderately- and poorly-differentiated cancers in two (7.4%, 2/27) and 17 cases (63.0%, 17/27), respec-

Table 1. Characteristics of male genital metastasis from gastric cancer

No.	Author, year	Country	Age	Primary symptoms	Time interval¶ (months)	Size (cm)	Site	Location	Histopathology	Treatment	Outcome, Survival time (months)
1	William [18], 1955	England	57	SC mass, no pain	0	NA	Right	SC & E	PD-MC	No	Died, 1
2	Kagawa [19], 1988	Japan	70	Scrotal mass, no pain	72	NA	Bilateral	SC, E & P	WD-AC	Sex cord resection	Alive, 24
3	Kondo [20], 1988	Japan	63	Groin mass, no pain	11	3.0	Bilateral	SC	AC	Biopsy alone	NA
4	Irisawa [21], 1989	Japan	54	Groin mass, no pain	-2	NA	Right	SC	PD-AC	Radical orchiectomy	NA
5	Kawanishi [22], 1990	Japan	67	Scrotal mass, no pain	84	NA	Right	T, E, TV, T & SC	PD-AC	Radical orchiectomy	NA
6	Nozawa [23], 1995	Japan	39	Scrotal swollen, pain	0	NA	Bilateral	T	AC	No	NA
7	Kageyama [24], 1997	Japan	62	Scrotal swollen & SC mass, no pain	120	NA	Left	SC & TV	Tubular AC	Radical orchiectomy	NA
8	Kato [25], 1999	Japan	70	Scrotal swollen & groin mass, pain	12	2.5	Left	SC	Tubular AC	Orchiectomy	Died, 6
9	Ota [17], 2000	Japan	51	Scrotal swollen, pain	108	2.5	Left	SC, E & TV	PD-AC & SCA	Orchiectomy & chemotherapy	Died, 12
10	Wai [26], 2000	China	50	Hydrocele, no pain	2	NA	Left	TV	PD-AC	Orchiectomy	NA
11	Pozzobon [27], 2001	Italy	69	NA	NA	NA	Right	SC	AC	NA	NA
12	Ozdal [28], 2002	Canada	55	Testicular mass, no pain	NA	NA	Left	E & T	PD-SCA	Radical orchiectomy	NA
13	Alois [2], 2005	Spain	68	Groin mass & scrotal swollen, pain	12	4.0	Right	SC, E & T	PD-AC	Inguinal orchifuniculectomy	Died, 4
14	Yoshida [29], 2005	Japan	62	Scrotal mass, no pain	-5	NA	Right	SC	PD-AC	Radical orchiectomy	NA
15	Qazi [15], 2006	USA	58	Testicular mass, no pain	2	9.0	Left	SC, E & T	PD-SCA	Radical orchiectomy	NA
16	Schaefer [16], 2010	Germany	64	Groin mass & scrotal swollen, pain	-2	3.5	Right	SC & T	PD-SCA	Radical orchiectomy & chemotherapy	Died, 10
17	Yang [13], 2010	China	23	Testicular mass, pain	-2	3.2	Right	T	PD-SCA	Radical orchiectomy & chemotherapy	Alive, 8
18	Lee [9], 2012	Iran	57	Groin mass, no pain	36	4.0	Left	SC	PD-AC	Radical orchiectomy	Alive, 3
19	Xu [14], 2013	China	50	SC mass, no pain	-6	NA	Bilateral	SC, E & T	PD-SCA	Radical orchiectomy	NA
20	Watanabe [30], 2013	Japan	52	Scrotal swollen & groin mass, no pain	24	NA	Right	SC	AC	NA	Died, 12
21	Yoshikazu [31], 2013	Japan	66	Groin mass, pain	12	NA	Right	SC	MD-AC	Radical sex cord resection	NA
22	Kim [10], 2014	England	49	Scrotal swollen & SC mass, pain	84	4.0	Bilateral	SC & E	PD-SCA	Radical orchiectomy & chemotherapy	Alive, 26
23	Kim [10], 2014	England	60	Groin mass, pain	72	3.5	Left	SC	MD-AC	Radical orchiectomy & radiotherapy	Alive, 20
24	Leung [11], 2014	China	66	Testicular mass, no pain	-10	2.1	Right	S	PD-AC	Scrotal exploration & chemotherapy	Alive, 10
25	Matsumura [32], 2014	Japan	66	Scrotal swollen, no pain	-1	2.0	Left	SC	AC	Orchiectomy	NA
26	Li [5], 2015	China	53	Scrotal swollen, no pain	22	4.0	Right	SC, E & T	PD-AC	Orchiectomy & chemotherapy	Alive, 3
27	Our case	China	72	Scrotal swollen & groin mass, no pain	18	4.0	Left	SC	MD-CA & PD-SCA	Biopsy & chemoradiotherapy	Alive, 10

Note: ¶indicates the time interval from primary gastric cancer to confirmed genital metastasis. A negative value means genital tumor was found ahead of primary gastric cancer, with Zero value for synchronously. Abbreviations: SC, spermatic cord; E, epididymis; T, testis; TV, tunica vaginalis; S, scrotum alone; P, peritoneum; PD, poorly differentiated; WD, well differentiated; MD, moderately differentiated; MC, mucinous carcinoma; AC, adenocarcinoma; SCA, signet-ring cell adenocarcinoma. NA indicates data unavailable.

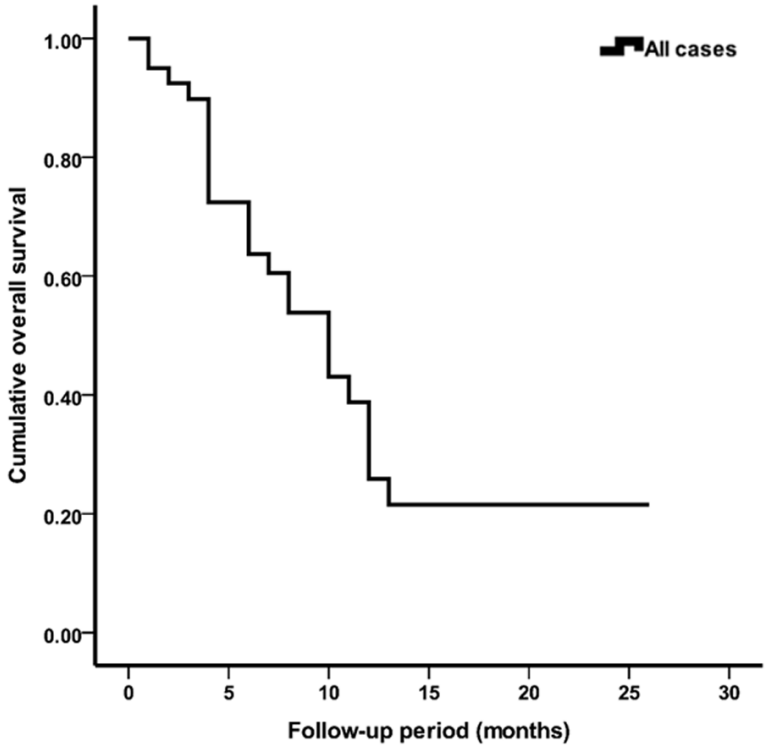

Figure 3. The cumulative overall survival rate of male genital metastasis from gastric cancer since 1955. The survival curve was calculated by the Kaplan-Meier method.

tively. Out of the 20 cases with poorly differentiated disease, eight (40.0%) cases suffered from signet-ring cell cancer. The metastatic sites included unilateral genital tract on the right (48.1%, 13/27) or the left (33.3%, 9/27) side, and bilateral involvement (18.5%, 5/27). The involved genital organs included spermatic cord alone (40.7%, 11/27), spermatic cord with others (33.3%, 9/27), testis with epididymis or tunica vaginalis (11.1%, 3/27), testis alone (7.4%, 2/27), tunica vaginalis alone (3.7%, 1/27), and scrotum alone (3.7%, 1/27). An isolated recurrence in the epididymis was not reported in this review.

A radical orchiectomy was performed in 11 (40.7%) cases, with GC-based chemotherapy and radiotherapy applied in seven (25.9%) cases and one (3.7%) case, respectively. The OS time was reported in 14 cases, with a median value of 12 (range, 1-26) months. Additionally, the actual one-year OS rate for such patients was 38.7%, with 21.5% of OS rate obtained within available follow-up period (**Figure 3**).

Discussion

The male genital system, including spermatic cord, epididymis, vas deferens and testis, is rarely involved due to metastasis of advanced GC. However, the most common origin of a sex cord metastasis is from stomach, followed by prostate, kidney, colon, ileum, appendix and pancreas [2-5]. It has been reported that 28.8% of spermatic cord and epididymis neoplasms were malignant and 8.1% of those were metastatic [6-8].

Metastatic dissemination of gastric adenocarcinoma to the male genital system is also called as “male Krukenberg tumor” [2, 9]. Of note, any Krukenberg tumor must include at least 10% of signet-ring cells according to its definition. Actually, the involved male genital disease would be a rare initial clinical manifestation of gastric cancer [10, 11]. As a result, the lack of awareness to such disease is often attributed to more misdiagnosed and mistreated cases in clinical practice. To our best knowledge, there is no previous attempt to cumulate available data for this rare disease as it is done here. Our findings provide a hint to detect a rare male Krukenberg tumor. Briefly, sex cord symptoms with a recent history of gastric adenocarcinoma are specific signals for the early diagnosis.

In this review, the most common clinical symptom of genital metastasis was a palpable mass in groin and (or) sex cord with or without pain. In addition, scrotal swelling and hydrocele were the second most common clinical symptoms. Those atypical clinical manifestations could easily lead to misdiagnosis and mistreatment as groin hernia or primary tumor of sex cord [12]. In the current literature review, six cases were first misdiagnosed as primary genital tumors, but fortunately, confirmed the primary diagnosis of GC by further examinations. In some specific cases, a metastatic tumor in groin with or without pain might be the first sign

of a primary gastric cancer [4, 11, 13]. Therefore, this rare metastatic tumor from non-genital origins, especially from the stomach, should never be neglected for patients complaining of groin pain or palpable mass. Nowadays, routine imaging tests such as CT, MRI and PET-CT, combined with CEA, CA199 and other tumor markers, could make more precise diagnosis to genial tract metastasis [9-11, 13, 14]. Of note, laparoscopic exploration is not performed routinely; however, it is helpful to identify peritoneal dissemination and regional invasion [10]. Moreover, immunohistochemically examinations, such as CK, CK7, CK20, CEA and P53, are specifically positive in gastrointestinal tumors and quite useful to identify the primary origin of metastatic tumor [9, 10, 13, 15, 16].

The average time interval between GC diagnosis and identification of genital metastasis was 43.2 (range, 2-120) months in 16 metachronous cases, with eight synchronous cases and three unclear cases also observed. A radical orchiectomy with wide local excision remains the recommended treatment for metastatic genial tumors, with adjuvant chemotherapy or radiotherapy considered in specific cases. Overall, the prognosis of metastatic genital tumor from gastric adenocarcinoma is very poor as previously reported. In this review, the actual one-year OS rate was 38.7%, with a median follow-up duration of 12 (range, 1-26) months. Note that four patients with late-onset metastasis (greater than 6 years) have much longer survival time than others. Within a mean follow-up period of 20.5 months, three of four patients have undergone radical orchiectomy and been survived without recurrence. If the metastatic tumor is localized and resectable, a radical resection followed with chemoradiotherapy can achieve survival benefits for such rare disease [9, 10].

At present, the concrete mechanism of cancer metastasis to the sex cord has not been accurately elucidated. However, several routes by which gastric cancer cells may disseminate to the sex cord have been proposed [2, 4, 5, 9, 10, 13, 17]. Briefly, those routes include (1) retrograde venous extension or embolism, (2) peritoneal carcinomatosis or direct invasion along the sex cord, and (3) retrograde lymphatic extension. To our best knowledge, spermatic cord tumors are most likely metastatic from gastric adenocarcinoma through hematogenous or lymphatic routes.

In conclusion, a metastatic tumor in the male genital system should not be neglected in patients with palpable mass in the sex cord, especially for those with history of gastric adenocarcinoma. The current systematic literature review indicates that such rare tumor is more associated with poorly-differentiated GC, and more commonly presented as a palpable mass in a unilateral side of genital tract. Although the prognosis is poor, successful resection of such a metastasis followed by chemoradiotherapy would achieve some survival benefits.

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Disclosure of conflict of interest

None.

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