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Extragonadal retroperitoneal germ cell tumor: evidence of origin in the testis

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Background: The origin of extragonadal retroperitoneal germ cell tumors remains controversial. Whether they develop primarily in the retroperitoneum or whether they are metastases of a primary testicular tumor has long been debated.

Patients and methods: We retrospectively analyzed 26 patients treated as having primary extragonadal retroperitoneal germ cell tumors based upon the findings of testicular palpation by the referring physician. Testicular evaluation was then extended with ultrasonographical and histological examinations.

Results: Biopsy of the extragonadal tumor was performed in 25 patients, confirming diagnosis of extragonadal retroperitoneal germ cell tumor. Prior to treatment patients were clinically evaluated by several physicians and the testes were not considered suspicious for testicular cancer. At urological workup, testes were found to be atrophic and/or indurated in 14 (54%) patients, enlarged in one (4%) and unremarkable in 11 (42%). Ultrasound examination of the testes in 20 patients showed pathological findings in all of them. Histology of the testis was available in 25 of 26 patients and revealed active tumor in three, intratubular germ cell neoplasia in four, scar tissue in 12, sclerosis in three, sclerosis and fibrosis in one, and fibrosis alone in two.

Conclusions: So-called primary extragonadal germ cell tumors in the retroperitoneum are very likely a rare or non-existing entity and should be considered as metastases of a viable or burned-out testicular cancer until proven otherwise. All of our patients with histologically examined testes had pathological finding, 76% of which were either viable tumor or scars.

Key words: burned-out tumor, germ cell tumor, retroperitoneal, testicular tumor

Introduction

The origin of primary extragonadal germ cell tumors is still a matter of debate. These tumors are rare and account for only a small percentage, 1% to 4%, of all germ cell tumors. Although they can arise virtually anywhere, typically they are found in the midline where they present as retroperitoneal, mediastinal or pineal masses [1–3]. It remains uncertain, however, whether such tumors develop primarily at extragonadal sites or represent metastases of a primary testicular tumor.

Systemic chemotherapy is the most commonly used treatment of extragonadal germ cell tumors. Persistent residual malignant tissue in the testes following adequate treatment of the extragonadal lesions has been well documented [1, 2, 4, 5]. The existence of a blood–testis barrier, which would conceivably reduce the effect of chemotherapeutic agents in the germinal tubules, has been suggested, and there is a growing body of evidence that residual neoplastic tissue in the testis may lead to tumor recurrences [6]. Thus, it may be important to actively search for and exclude testicular pathology when treating a so-called primary extragonadal germ cell tumor. We retrospectively analyzed clinical, ultrasonographical and histopathological findings in 26 patients treated for presumed primary extragonadal retroperitoneal germ cell tumors.

Patients and methods

The records of 26 patients with a median age of 36 years (range 19–65) treated between 1974 and 1998 for primary extragonadal retroperitoneal germ cell tumors were evaluated retrospectively. We analyzed only those patients with retroperitoneal masses with or without concomitant tumor sites [3]. Patients with extragonadal germ cell tumors at other sites, e.g. in the mediastinum, without retroperitoneal involvement, were excluded. Data of 14 patients of our previous retrospective analysis [3] were included and updated in this evaluation.

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All patients were diagnosed as having primary extragonadal retroperitoneal germ cell tumors because testicular palpation by several physicians (e.g. medical practitioner, general surgeon or medical oncologist) before treatment was considered not to be suspicious for testicular cancer. In 25 of the 26 patients (96%) the extragonadal mass was biopsied. In one patient, surgical exploration of the extragonadal mass was waived because germ cell tumor was considered to be unequivocally proven by the elevated tumor markers at another hospital.

After initial diagnosis, patients were examined by a urologist during the treatment period. Ultrasound scans were performed and evaluated by a radiologist in 20 of the 26 patients (77%) prior to surgical exploration. Hypo- and hyperechogenic lesions or microcalcifications were defined as being suspicious for active or burned-out testicular cancer. Histology of the testis was obtained by orchiectomy in 23 patients and by open biopsy of the suspicious testis in two.

Twenty patients (77%) were treated with chemotherapy alone, three (11.5%) underwent radiotherapy and three (11.5%) received combined radio- and chemotherapy. Eighteen of the 23 platinum-based chemotherapy regimens (78%) were with and five without bleomycin. Four of the 23 patients received more than one regimen. In half of the patients, chemotherapy was administered before surgical exploration of the testis. Excision of a residual retroperitoneal mass was conducted in 10 patients during follow-up.

Follow-up was available in 23 of the 26 patients (88%). The median follow-up was 51 months (range 2–150). Seventeen of 23 patients (74%) have no evidence of disease. Three patients (13%) are being followed regularly by computed tomography (CT) for residual tumor with a volume <2 cm in diameter. Three patients (13%) have died of disease (Table 1). Follow-up consisted of clinical evaluation, CT, chest X-ray and tumor marker determinations, which were evaluated by a radiologist, medical oncologist and urologist.

Table 1. Patient characteristics

Total number	26
Median age, years (range)	36 (19–65)
Patients with a history of cryptorchidism	3
Site of presentation	
Retroperitoneum alone	18
Retroperitoneum + other sites	8
Biopsy of extragonadal tumor	
Before surgical exploration of the testis	23
After surgical exploration of the testis	2
None	1
Histology of extragonadal tumor (biopsy)	
Seminoma	13
Embryonal carcinoma	6
Embryonal carcinoma + choriocarcinoma	2
Teratoma	2
Suspicious for germ cell tumor	2
None	1
Follow-up	23
Median follow-up, months (range)	51 (2–150)
No evidence of disease	17
Partial remission	3
Death	3

Results

In the 26 patients, 13 seminomas, 10 non-seminomatous germ cell tumors and two tumors suspicious for a germ cell tumor were found at histological examination of the extragonadal mass (Table 1).The primary tumor was on the left side in 10 of 26 patients (38%), on the right side in seven (27%) and bilaterally in nine (35%). None of these patients was suspected of having a testicular tumor by the physicians initially treating them.

At urological workup, palpation of the testis was unsuspicious in 11 of 26 patients (42%), atrophic in 11 (42%), atrophic and indurated in one (4%), indurated in two (8%) and enlarged in one (4%). Ultrasonographical examination was suspicious for tumor in all (20 of 20) patients examined by sonography. A suspicious finding at ultrasonographical examination was the only indication for surgical exploration in 10 of 11 patients with normal testes on palpation and supportive in 10 of 11 patients with suspicious findings on palpation.

At surgical exploration of the testis, pathological findings were located ipsilaterally in 14 of 25 patients (56%) and contralaterally in three (12%) to the site of the primary tumor. Of those nine patients with a bilateral primary tumor, five had pathological findings in the right testis, three in the left testis and one histology of the testis was not obtained.

The histological examination of the explored 25 testes revealed scar tissue in 12 patients (48%), sclerosis in three (12%), sclerosis and fibrosis in one (4%), fibrosis in two (8%), intratubular neoplasia in four (16%) and viable tumor in three (12%) (Figure 1).

Of the 11 patients with an initially non-suspicious testis on palpation, five showed scar tissue, one sclerosis, three intratubular neoplasia and two viable tumor histologically. Of the 15 patients with a suspicious finding on palpation, seven revealed atrophy in the histology, two sclerosis, two fibrosis, one sclerosis and fibrosis, one intratubular neoplasia and one viable tumor.

In the group of patients receiving chemotherapy alone, testicular histology was obtained prior to and after chemotherapy in 10 patients each. After chemotherapy, two of the 10 patients still had viable tumor or intratubular neoplasia (Figure 1). One received vinblastine, bleomycin, cisplatin, cyclophosphamide, etoposide and dactinomycin. We could not retrospectively determine the chemotherapy regimen in detail for the other patient.

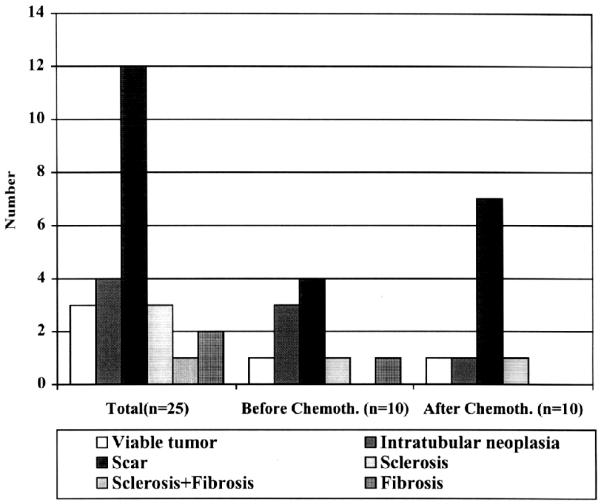

Figure 1. Histology of 25 testes explored in patients with so-called extragonadal retroperitoneal germ cell tumors and divided into those with surgical exploration of the testis before (n = 10) or after (n = 10) chemotherapy.

Discussion

The most widely accepted theory of the development of extragonadal germ cell tumors suggests that these tumors originate from displaced primordial (embryonal) germ cells situated along the midline of the body [2, 3, 5, 7–12]. Whether these tumors are truly extragonadal or synchronous germ cell tumors in the testis and retroperitoneum or metastatic lesions from undetected or regressed (burned-out) testicular carcinoma remains ultimately an open question.

In our series all patients with extragonadal retroperitoneal germ cell tumors had a pathological testis showing either viable tumor or lesions compatible with a burned-out testicular tumor. As early as 1927, Prym [13] had reported testicular scarring in a patient with an extragonadal tumor at autopsy. In the following years further case reports also described such lesions [14, 15]. Azzopardi et al. [16] showed that some palpably normal testes have either scar tissue or small foci of tumor on histological examination. This raised the question of whether a portion of primary extragonadal germ cell tumors may not be metastatic. In 1951, Friedmann [12] found either regressive changes or an overt tumor of the testis in 23 of 29 patients with primary retroperitoneal germ cell tumors. This was confirmed by our earlier report on 14 patients with primary retroperitoneal germ cell tumors [3]. Daugaard et al. [9], in their series, found malignant germ cells in the gonads of 42% of patients with so-called clinically primary tumors in the retroperitoneum.

All of our patients had a pathological finding histologically defined as either viable tumor tissue or regressive changes. Seven patients (28%) showed some form of testicular neoplasia: seminoma (two), teratoma (one) and intratubular neoplasia (four). In 12 (48%) of our patients the histological evaluation revealed testicular scarring. Since trauma could be excluded as a cause in all patients, the suggestion is that such scars should be considered to be residuals of burned-out primary tumors [13–15, 17, 18]. Six patients showed sclerosis, fibrosis or both. This pathological process in the testis may be interpreted in the same way as scar tissue.

The differentiation of a so-called primary extragonadal retroperitoneal germ cell tumor from a primary testicular neoplasm with retroperitoneal metastases strongly depends on the aggressiveness of testicular examination.

Indeed, in our series all patients were clinically evaluated with palpation of the testes by several physicians and palpation was considered not to be suspicious for testicular cancer. Urological workup, however, demonstrated a suspicious finding on palpation in 58% of the patients. Of those patients with unsuspicious testes on palpation, 10 of 11 (91%) became suspicious on ultrasonography.

Ultrasound examination of the testes showed hypo- or hyperechogenic lesions and/or microcalcification in 20 of 20 patients. This is in agreement with Comiter et al. [17] who found intratesticular lesions by ultrasonographical examination in five of six patients with primary retroperitoneal extragonadal germ cell tumors. Fuchs et al. [19] and Medini et al. [20] suggested that normal testes would not require surgical exploration; however, both are small series, with five and eight patients, respectively. Furthermore, in the series of Medini et al., three patients had retroperitoneal masses only. For the other patients it is well known that mediastinal germ cell tumors are another entity and in general do not have concomitant testicular neoplasia [3, 21].

Identification of a primary testicular tumor in patients with a presumed extragonadal germ cell tumor is important because it carries the danger of persistent testicular malignancy in up to 50% of such patients despite systemic chemotherapy [3, 4, 17]. In our series, two patients still had viable tumor or intratubular neoplasia after chemotherapy.

Based on our results the following conclusions may be drawn. (i) So-called primary extragonadal germ cell tumors of the retroperitoneum are probably a rare or non-existing entity. They should be considered to be metastases of a viable or burned-out testicular cancer until proven otherwise. This was found in 76% of our patients. (ii) Intensive urological workup including ultrasonographical examination of the testis, especially of those with unsuspicious findings on palpation, is mandatory. (iii) The presence of viable tumor tissue in the testis after chemotherapy (sanctuary) stresses the need for surgical exploration of all patients with extragonadal retroperitoneal germ cell tumors and a testicular abnormality. (iv) Adequate treatment of the primary testicular tumor is essential for achieving a cure.

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