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BRIEF REPORT

CIC fusion-positive sarcoma of the spermatic cord

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Abstract

In addition to germ cell tumors and tumors of the sex cord stroma, the WHO classification of testis and paratesticular tumors also contains malignant soft tissue tumors. Among them, liposarcomas of the spermatic cord are the most common entities. Other mesenchymal tumors with smooth muscle, skeletal muscle, fibroblastic/myofibroblastic, or nerve sheath differentiation are rare. Ewing sarcoma is composed of uniform small round cells and typically characterized by translocations of the *EWSR1* gene. In rare cases, Ewing sarcoma-like tumors lack an *EWSR1* gene fusion. Some of these tumors harbor a specific *CIC* translocation. However, Ewing-like sarcoma has up to now never been described in the testis or spermatic cord. The present case describes the first *EWSR1*-negative, undifferentiated round cell sarcoma with *CIC* translocation of the spermatic cord. Potential differential diagnoses are discussed.

Keywords CIC translocation · Spermatic cord · Testis · Ewing-like sarcoma

Introduction

The WHO classification of tumors of the testis and paratesticular tissue contains not only germ cell tumors and tumors of the sex cord stroma but also mesenchymal tumors. The most common entities of mesenchymal tumors are adipocytic tumors, which are typically localized in the spermatic cord [1]. Other mesenchymal tumors such as smooth muscle, skeletal muscle, fibroblastic/myofibroblastic, or nerve sheath tumors are rare. Only few cases of tumors with small round blue cell morphology, mostly in young patients, have been reported in this anatomic location [1–4]. Many of these cases of tumors with small round blue cell morphology such as extraskeletal myxoid chondrosarcoma, Ewing sarcoma/PNET, or desmoplastic small round cell tumor show a *EWSR1* translocation [5]. Recently, a group of sarcomas without *EWSR1* translocation but with *CIC* translocation could be identified [6–9]. Here, we present a case of an Ewing family tumor (EFT) with a *CIC* translocation as an example of a round cell tumor, and we discuss potential differential diagnosis.

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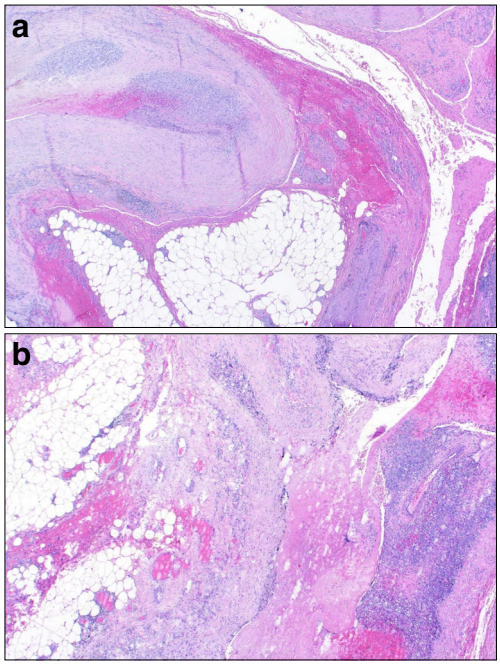

Fig. 1 The paratesticular region and spermatic cord shows infiltration by a cell-rich undifferentiated tumor (**a**) with hemorrhagic zones (**b**)

Material and methods

Immunohistochemical and fluorescence in situ hybridization analyses were performed on 4-μm sections of formalin-fixed and paraffin-embedded tissue. The immunohistochemical analysis included vimentin, CD56, CD99, keratin, CK20, EMA, synaptophysin, CD30, myogenin, desmin, caldesmon, actin, S100, CD34, CD45, CD3, CD4, CD8, myeloperoxidase, CD20, CD68, granzyme B, CD57, and OCT3/4 (all from Dako, Glostrup, Denmark) as well as chromogranin, perforin, and SALL4 (Cell Marque, Wedel, Germany), TLE1 (Santa Cruz, Heidelberg, Germany), and INI1 (BD biosciences). Chromosomal translocations with chromosome 19q13.2 (*CIC*) as a translocation partner were investigated using fluorescence in situ hybridization (FISH) with the SureFISH CIC 5′ BA probe and the SureFISH CIC 3′ BA probe (Agilent Technologies, Cedar Creek, USA). The cut-off was set at 20% nuclei with break-apart signals. FISH analysis of the *EWSR1* gene locus was carried out using the ZytoLight SPEC *EWSR1* Dual Color Break Apart probe set (ZytoVision, Bremerhaven, Germany).

Case presentation

A 70-year-old man was examined at the urological clinic due to an increasing scrotal mass. On clinical examination, a tumor on the right spermatic cord was palpable. Sonographic examination revealed a maximally 8-cm-sized tumor. Tumor markers were not elevated. Up to that time, no lymph node or organ metastases were detectable.

Based on the diagnostic findings, an orchiectomy was performed. At surgery, an 11 × 5 × 4-cm-sized mass within a 5 × 3 × 3-cm-sized inconspicuous testis and epididymis was removed. The spermatic cord measured 7 × 2 cm. In the range of the spermatic cord, an 8 × 8 × 2.5-cm-sized tumor was

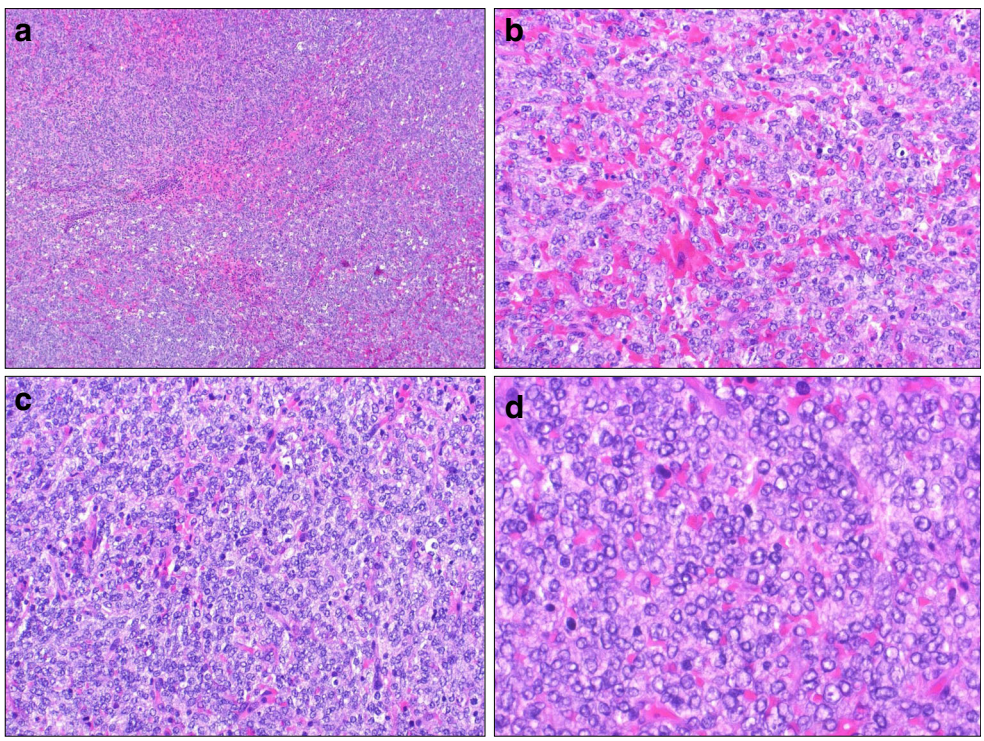

Fig. 2 The small round tumor cells (**a**) have an eosinophilic cytoplasm and blurred cell boundaries (**b** + **c**). The tumor cell nuclei show vesicular chromatin and prominent nucleoli (**d**)

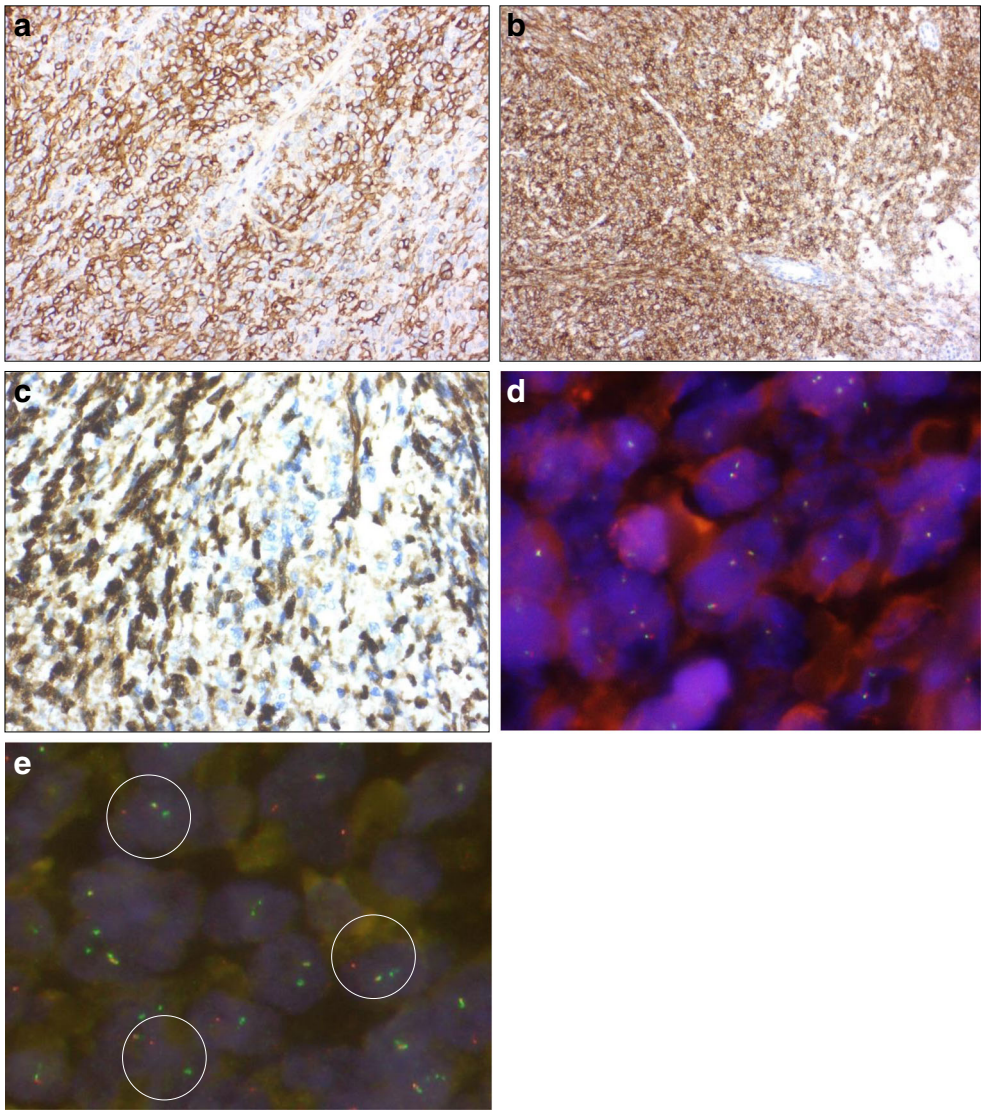

Fig. 3 Immunohistochemical analysis revealed strong expression of CD99 (**a**) and variably strong expression of CD56 (**b**). The cytoplasm and the nucleus are positive for WT-1 (**c**). EWSR1-FISH with two fusions signals indicating *EWSR1*-negativity (**d**). CIC translocation demonstrated by a FISH break-apart. The split of the green-orange (red) fusion signal indicates the translocation (circles, **e**)

detectable. The tumor showed a whitish, solidified, partly necrotic, and bloody cut surface.

Histological examination revealed tissue of the paratesticular region and spermatic cord that was infiltrated by an undifferentiated cellular tumor (Fig. 1a) which was partially inoculated and necrotic. In addition, the tumor contained hemorrhagic zones (Fig. 1b). The small- to medium-sized round tumor cells had an eosinophilic cytoplasm and blurred cell boundaries (Fig. 2a–c). Furthermore, the tumor cells showed vesicular chromatin and prominent nucleoli (Fig. 2d). In ten HPF, eight mitoses were seen.

Immunohistochemically, the tumor cells were found to express CD99 (Fig. 3a), CD56 (Fig. 3b), nuclear WT-1 (Fig. 3c), and vimentin but were negative for keratin, CK20, EMA, synaptophysin, CD30, myogenin, desmin, chromogranin, caldesmon, actin, S100, CD34, CD45, CD3, CD4, CD8, myeloperoxidase, CD57, granzyme B, perforin, and CD20. Scattered CD68-positive macrophages were seen. No expression of SALL4, OCT3/4, TLE1, or loss of INI1 expression was noted.

Molecular analyses were performed using fluorescence in situ hybridization (FISH), but no translocation of the *EWSR1* gene was found (Fig. 3d). However, analysis of the *CIC* gene by FISH showed aberrant break apart signals in 88% out of 50 evaluated tumor cell nuclei. Thus, a translocation with chromosome 19q13.2 as translocation partner was observed (*CIC* fusion-positive) (Fig. 3e, circles).

In conclusion, the diagnosis of an Ewing-like sarcoma with *CIC* fusion of the spermatic cord was made on the basis of morphological, immunohistochemical, and molecular findings.

Discussion

EFT are composed of uniform small round cells and characterized by translocations of the *EWSR1* gene [5, 10].

Table 1 Summary of selected published cases of CIC-translocated sarcoma with respect to age, size, location, and follow-up. (NA not available, DOD died of disease, OS overall survival)

Diagnosis	Age	Localization	Size	Follow-up	Reference
Sarcoma with CIC-DUX4 gene fusion	38 years	Deep abdominal wall	7 cm	DOD 2 months after surgery	[1]
Sarcoma with CIC-DUX4 gene fusion	35 years	Biceps femoris muscle	18 cm	DOD 6 months after diagnosis	[2]
Sarcoma with CIC-DUX4 gene fusion	40 years	Thigh	NA	DOD 14 months after diagnosis.	[3]
Sarcoma with CIC/DUX4 gene fusion	19 years	Gluteus	16 cm	7 months after diagnosis the patient is refractory to chemotherapy, with persistent metastatic disease	[4]
57 cases with CIC gene break-apart signal	Median of 31 years	Soft tissue, viscera, bone	0.7 to 23 cm	The patients showed a 53% 2-year OS and a 43% 5-year OS rates	[5]
16 cases with CIC gene break-apart signal	Median 28.5 years	Head and neck soft tissue, scalp, submandibular region, tonsil	Median 4.8 cm	Three patients DOD after 13, 17, and 27 months, the other patient were alive (with and without recurrence) or follow-up was NA	[6]

Nearly all EFT demonstrate immunoreactivity for CD99 [11]. However, a small portion of cases with Ewing sarcoma morphology and CD99 expression lacks the characteristic *EWSR1* translocation. Recently, a rearrangement of the *CIC* gene was shown in these tumors [8, 12–14]. In our case, the tumor presented with characteristics of small round blue cell morphology and immunohistochemical positivity for CD99, CD56, nuclear WT-1, and vimentin. Specht et al. used histochemical analysis to compare *CIC* translocated sarcomas with *EWSR1*-rearranged sarcomas and could demonstrate *CIC*-rearranged tumors with variable (in 84%, 23% of which were diffuse) or no (16%) expression of CD99. In contrast, most cases of *EWSR1*-rearranged Ewing sarcomas show diffuse and strong expression of CD99 [9]. The authors also demonstrated that *CIC*-rearranged sarcomas express WT-1 in cytoplasm as well as nuclei, which is in line with the present case in which diffuse CD99 and nuclear WT-1 positivity were observed (Fig. 3 a, c).

The anatomic localization of the spermatic cord in this case is an unusual finding. Antonescu et al. analyzed 115 cases of sarcomas with *CIC* rearrangements. The anatomic location of 111 of these sarcomas was known: in 95 cases in the soft tissue (86%; 39 in the trunk, 31 in a lower extremity, 7 in an upper extremity, 12 in the head/neck, 6 in the retroperitoneum/perineum/pelvis), 13 cases in the viscera (12%; 1 in the stomach, 5 in the small or large intestine, 4 in the kidney or prostate, 3 in tonsils/parapharyngeal), and three cases in the pelvic bones (3%). To our knowledge, only four cases have been reported in the genitourinary location (kidney and prostate) thus far [6], and never before has a *CIC*-rearranged sarcoma of the spermatic cord been described.

There is a wide range of differential diagnoses of Ewing sarcomas. Many of these entities show a CD99 expression such as T lymphoblastic lymphomas (92%), poorly differentiated synovial sarcomas (50%), small-cell osteosarcomas (23%), rhabdomyosarcomas (21%), desmoplastic round cell tumors (16%), small-cell carcinomas (9%), and Merkel cell carcinomas (9%) [15].

CIC-rearranged sarcomas are found in men and women, with slight predominance in men. The mean age in 115 cases in the study by Antonescu et al. was 32 years [6]. The patient in our case was 70 years old. This is unusual; nevertheless, the study by Antonescu et al. included patients up to 81 years of age. Taken together, it should be noted that *CIC*-rearranged sarcomas typically occur in young patients but can also be found in older patients. The prognosis for patients with *CIC*-rearranged sarcomas compared with Ewing sarcomas is very poor (Table 1, [6, 7, 16–19]).

In conclusion, *CIC*-rearranged sarcomas are generally rare findings. Our present case is the first description of *CIC* fusion-positive sarcoma of the spermatic cord available in the literature. Therefore, CIC fusion-positive sarcoma of the spermatic cord should now be considered as a potential differential diagnosis of small round blue cell tumors in this anatomic region. When CD99-positive and *EWSR1*-negative small round blue cell tumors are present in this lesion, an analysis of *CIC* translocation is indicated due to the tumor classification and its poor prognosis.

Author contributions F.B. A.F., and P.S. were responsible design of the study, interpretation of the results, and writing the manuscript. L.L. and H.U.S. were responsible for FISH experiments. R.T., A.F., R.I. and F.B. contributed critical discussion of the experiments and results. F.B., A.F., P.S., and H.U.S. reviewed the manuscript.

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Compliance with ethical standards

The case report was approved by the ethics committee of the University Medical Center Göttingen (applicant number: 7/2/18An). The patient gave his formal consent to the publication of the data.

Conflict of interest The authors declare that they have no conflict of interest.

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