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Presentation of a rare, highly aggressive peritoneal disease: desmoplastic small round cell tumor and its therapeutic options

Jan Philipp Ramspott · Tarkan Jäger · Daniel Neureiter · Klaus Emmanuel · Philipp Schredl

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Summary
Background Desmoplastic small round cell tumor is a rare highly aggressive peritoneal disease (sarcoma) with mortality rates up to 70% in the first 3 years after diagnosis. It mainly affects young men. Patients clinically complain about diffuse abdominal pain.
Methods This case report describes the clinical course of a 69-year-old man who presented with recurrent abdominal pain. Physical examination, laboratory testing, imaging, and gastroscopy were performed. Intra-abdominal peritoneal biopsies were taken during diagnostic laparoscopy.
Results Physical examination was unremarkable. Laboratory results showed elevated white blood cells, C-reactive protein, and negative tumor markers. Computed tomography and positron emission tomography scan revealed extensive peritoneal metastases with diffuse intra-abdominal signal intensities and ascites. Gastroscopy was unremarkable, whereas diagnostic laparoscopy confirmed imaging results with a peritoneal cancer index of 39. Extensive immunohistochemical and consecutive molecular investigations led to the diagnosis of an intraperitoneal desmoplastic small round cell tumor.
Conclusion Our case report demonstrates a very rare cause of recurrent abdominal pain. Desmoplastic small round cell tumor is a rare and highly aggressive undifferentiated sarcoma, which mainly affects young men. Treatment options include chemotherapy, radiotherapy, cytoreductive surgery, and/or hyperthermic intraperitoneal chemotherapy. Standardized treatment protocols are still lacking because only a few cases have been described so far. Differential diagnoses include all malignancies with peritoneal masses.

Keywords Peritoneal malignancy · Sarcoma · Cytoreductive surgery · Hyperthermic intraperitoneal chemotherapy · Chemotherapy

Main novel aspects

- In case of unspecific abdominal pain rare diseases should be included in the differential diagnoses.
- The combination of young male patients and massive peritoneal tumor masses with unknown primary tumor may help in the diagnosis of desmoplastic small round cell tumor.
- Therapeutic guidelines for desmoplastic small round cell tumor are still lacking because only a few cases have been described so far. Individual treatment strategies are necessary.

Introduction

Desmoplastic small round cell tumor (DSRCT) is a rare highly aggressive form of sarcoma [1]. The entity was first described by Gerald and Rosai in 1989 [2] and mainly affects young men. DSRCT is associated with a very poor prognosis with mortality rates up to 70% in the first 3 years after diagnosis [3]. It mostly originates and spreads on peritoneal

J. P. Ramspott · T. Jäger (✉) · K. Emmanuel · P. Schredl
Department of Surgery, Paracelsus Medical University, Salzburger Landeskliniken (SALK), Salzburg, Austria
ta.jaeger@salk.at

J. P. Ramspott
Department of Gynecology and Gynecologic Oncology, Ev. Kliniken Essen-Mitte (KEM), Essen, Germany

D. Neureiter
Institute of Pathology, Paracelsus Medical University, Salzburger Landeskliniken (SALK), Salzburg, Austria

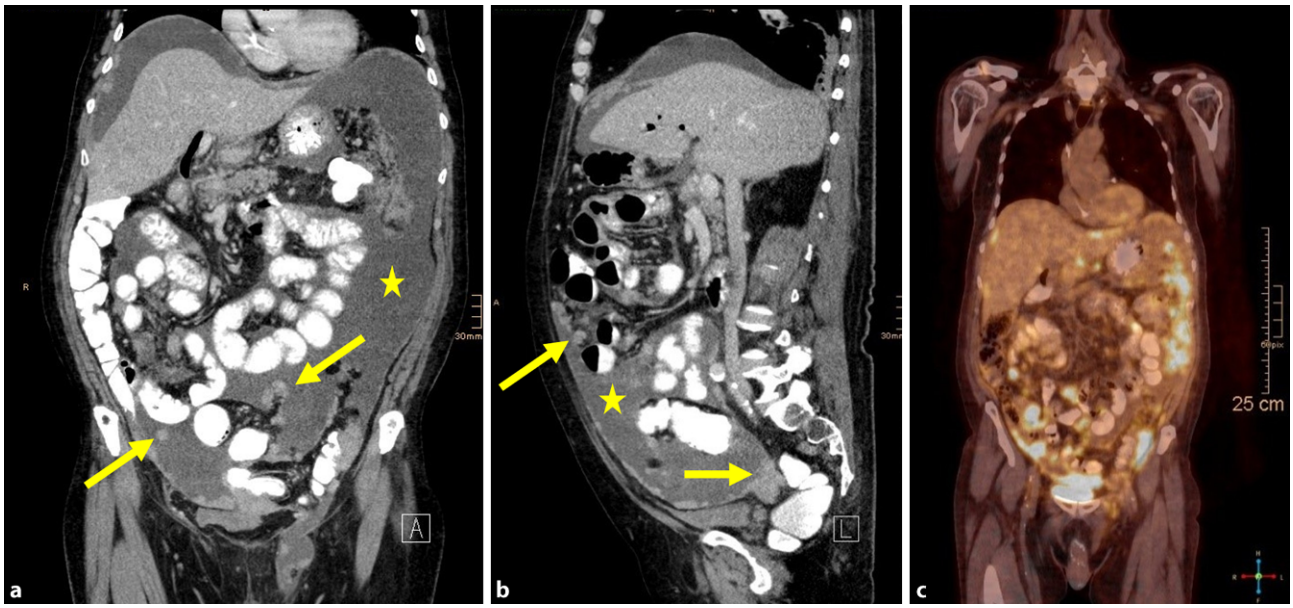

Fig. 1 Coronal (**a**) and sagittal (**b**) contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis showing diffuse soft-tissue masses (*arrows*) and ascites (*stars*) in the peritoneal cavity. Color-fused coronal positron emission tomography (PET)-CT scan (**c**) showing diffuse peritoneal nodules with enhanced fluorodeoxyglucose (FDG) uptake

surfaces in the abdominal and pelvic cavity. Patients complain about diffuse abdominal pain, obstipation, and increased abdominal girth caused by ascites [4]. Liver metastases can already be present at diagnosis. Lymph nodes, lungs, brain, and bones can also be affected. Computed tomography (CT) scan, magnetic resonance imaging (MRI), and positron emission tomography (PET) scan with fluorodeoxyglucose (FDG) are used as preoperative diagnostic modalities revealing multiple soft-tissues masses [5]. Final diagnosis can only be revealed by tissue biopsy following complex immunohistochemical and molecular analysis. DSRCT is characterized by a translocation involving fusion of the Ewing sarcoma (EWS) and Wilms tumor (WT1) gene leading to formation of a chimeric protein [6]. Therapeutic options for treatment of DSRCT include chemotherapy, radiotherapy, cytoreductive surgery, and/or hyperthermic intraperitoneal chemotherapy (HIPEC) [1]. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) can be considered as a new possibility as an individualized treatment strategy.

Case report

We report the case of a 69-year-old man who presented to our emergency department with recurrent severe abdominal pain for 1 week (numeric rating scale [NRS] 7/10). Six months previously, the patient had suffered from a similar episode. A colonoscopy had not revealed any significant findings. The patient denied any fever, dysuria, change in bowel habit, or weight loss. His past medical and surgical history were unremarkable.

On physical examination, his abdomen was soft without any tenderness. Laboratory results showed elevated white blood cells 10.41×10^9/l (reference $3.5–9.8 \times 10^9$/l) and C-reactive protein 4.3 mg/dl (reference < 0.6 mg/dl). Abdominal X-ray was unremarkable. To rule out an acute abdominal process we performed a computed tomography (CT) scan. Extensive lobulated peritoneal soft tissue masses with a large amount of ascites were detected (Fig. 1a, b). Furthermore, a 25 × 16 mm hypodense structure was found in the pancreas. Positron emission tomography (PET)-CT scan showed diffuse intra-abdominal signal intensities (Fig. 1c).

Next, we performed a gastroscopy without any significant findings. Serological tumor markers (carcinoembryonic antigen [CEA], carbohydrate antigen [CA] 19-9, and CA 72-4) were all negative. Ascites was drained and cytological analysis revealed reactive-inflammatory cells. As the diagnosis was still unclear, we performed a diagnostic laparoscopy. Here, we saw multiple tense and spherical tumors on the parietal and visceral peritoneum (size: 1–5 cm; Fig. 2). The peritoneal cancer index (PCI) was 39.

Histopathological analysis of laparoscopic biopsies revealed solid nests of round cells surrounded by cellular desmoplastic stroma. In addition, pleomorphic nuclei (hematoxylin–eosin staining) without any clear cell differentiation were detected. The proliferation index Kiel (Ki)-67 was about 40–50%. Further immunohistochemical analysis showed slightly positive epithelial markers (pan-cytokeratin CAM 5.2, cytokeratin [CK] 7, CK 20, epithelial membrane antigen [EMA], and Ber-Ep4). In contrast, mesothelial markers (thrombomodulin, podoplanin, calretinin, and Wilms tumor protein 1 [WT1]), neuroendocrine

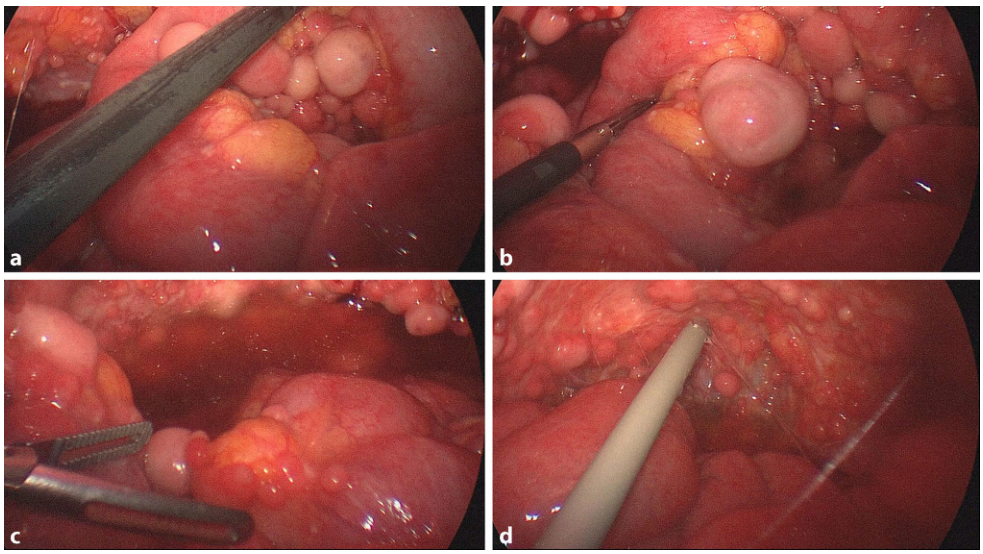

Fig. 2 Diagnostic laparoscopy revealed diffuse 1–5 cm tense and spherical tumors in the mesentery (**a** and **b**), right paracolic gutter (**c**), and in the pelvis (**d**)

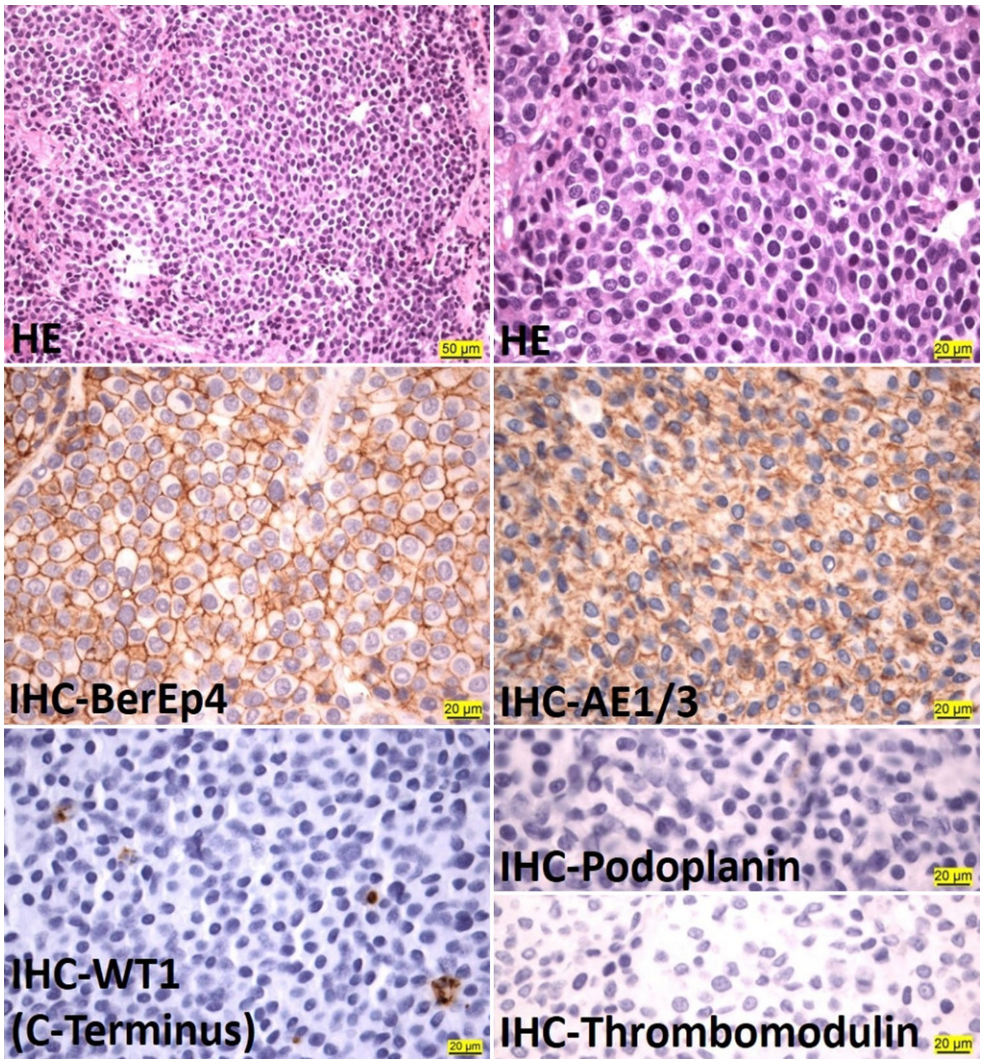

Fig. 3 Hematoxylin–eosin (HE) staining and exemplary immunohistochemical (IHC) stainings (BerEp4, AE1/3, Wilms tumor protein 1 [WT1], podoplanin, thrombomodulin) of intraperitoneal biopsies. *Scale bars* are indicated

markers (synaptophysin, chromogranin, and cluster of differentiation [CD]56), neurogen, and melanocytic markers (neuronspecific enolase [NSE], S-100, and Melan A), mesenchymal markers (myogenin-D1, desmin, and CD99), and lymphatic markers (among others CD34, CD45, CD68, CD117) were all negative (Fig. 3). Finally, fluorescence in-situ hybridization (FISH) revealed a translocation in the Ewing sarcoma breakpoint region 1 gene (EWSR1), which led to the diagnosis of an intraperitoneal desmoplastic small round cell tumor (DSRCT).

After laparoscopy, the patient became more and more immobile and suffered from diffuse abdominal pain with irregular bowel habits. In the interdisciplinary tumor board, palliative chemotherapy with doxorubicin, cyclophosphamide, and vincristine was scheduled. Cytoreductive surgery and heated intraperitoneal chemotherapy (HIPEC) were rejected because of multiple comorbidities (Eastern Cooperative Oncology Group [ECOG] 3). A few weeks after the primary diagnosis, the patient died during the palliative chemotherapy due to tumor toxic cardiovascular failure.

Discussion

DSRCT is a rare, aggressive form of sarcoma causing diffuse abdominal pain in mainly young men. Different preoperative imaging modalities are used for diagnosis to evaluate locoregional and extra-abdominal disease extent. Imaging studies show multiple soft tissue masses throughout the abdomen without any clear primary tumor source [5]. Histological analysis of tissue biopsies reveal round tumor cell nests separated by desmoplastic stroma [7]. Further immunohistochemical analysis show a heterogeneous pattern with positive epithelial and neural markers [6]. Finally, only the translocation (11;22)(p13;q12) in which the Wilms tumor (WT)1-gene is fused to the EWSR1-gene characterizes DSRCTs and distinguish them from Ewing sarcoma or other sarcomas which often appear similarly [1, 5]. As DSRCT are highly sensitive to chemotherapy, patients should be initially treated with six cycles of systemic chemotherapy (mostly combination of vincristine, doxorubicin, and cyclophosphamide). If tumor masses decrease to a minimum of 20% after six cycles, chemotherapy should be completed with 8–12 cycles. In case of tumor progression second-line chemotherapy (temozolomide/irinotecan, cyclophosphamide/topotecan, and high-dose ifosfamide) should be considered. CRS combined with or without intraperitoneal chemotherapy is only recommended if complete cytoreduction is predicted after completion of chemotherapy. Adjuvant chemotherapy may be considered after complete cytoreduction. Patients with progression after therapy or extraperitoneal disease extent should be enrolled in clinical trials, should be considered for whole abdominal radiation therapy, or should be offered salvage and/or palliative chemotherapy [1]. Cytoreductive surgery includes peritonectomy and visceral resections to achieve no macroscopic residual disease. HIPEC regimens often include cisplatin which showed a 30-month overall survival rate of 78% in a recent phase 2 trial [8]. In our case, the poor general condition of the patient only enabled initiation of palliative chemotherapy.

Conclusion

We present a very rare cause of recurrent abdominal pain caused by DSRCT. Especially in men presenting with unspecific abdominal pain and massive intra-abdominal tumor masses without any clear origin, DSRCT should be included in the differential diagnosis. All other possible malignancies with peritoneal masses (rhabdomyosarcoma, lymphoma, neuroblastoma, neuroectodermal tumor, mesothelioma, and tumors of gastrointestinal or ovarian origin) have to be included in the differential diagnosis and should be excluded with extensive immunohistochemical and consecutive molecular investigations [5]. Because only rare cases have been described so far, clear therapeutic guidelines are lacking. Therapeutic approaches include chemotherapy, radiotherapy, cytoreductive surgery, and/or hyperthermic intraperitoneal chemotherapy (HIPEC).

Author Contribution All authors contributed to the conception, design, performed material preparation, and data collection. The manuscript was written by J. P. Ramspott. D. Neureiter performed the histological analysis. T. Jäger and P. Schredl supervised the project. All authors read and approved the final manuscript.

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Declarations

Conflict of interest J. P. Ramspott, T. Jäger, D. Neureiter, K. Emmanuel and P. Schredl declare that they have no competing interests.

Ethical standards All procedures performed in studies involving human participants or on human tissue were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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