Small Cell Cancer of the Anal Canal – Case Report of a Rare Tumor

ANDREAS MEYER[1], FRANK BRUNS[1], KLAUS RICHTER[2], VIKTOR GRÜNWALD[3] and JOHANN H. KARSTENS[1]

Departments of [1]Radiation Oncology and [3]Hematology, Hemostaseology and Oncology, Hannover Medical School, Hannover; [2]Institute for Pathology, Berliner Allee, Hannover, Germany

Abstract. *Background: We report on a rare case of small cell cancer located at the anal canal. Case report: A 41-year old woman presented with locally advanced small cell anal cancer and simultaneous hepatic and pulmonal deposits. Due to metastatic disease, chemotherapy with etoposide and cisplatin was performed with mixed response after four cycles of chemotherapy. After application of two additional chemotherapy cycles, locally progressive disease occurred causing symptomatic bowel obstruction. Pelvic irradiation was started and, several days later, additional irradiation of cerebral metastases was initiated due to rapid progression of distant disease. Despite adequate local treatment the patient's condition further deteriorated and irradiation was stopped. The patient died 10 months after initial diagnosis due to rapid tumor progression. Conclusion: In patients with metastatic small cell anal cancer chemotherapy remains the mainstay of therapy. Radiotherapy exerts additional activity and remains a prime choice to gain local control and ameliorate symptoms. Careful histopathological examination, together with immunohistochemistry, is needed to determine the therapeutic strategy to be followed.*

Anal cancer is a rare tumor of the gastrointestinal tract representing only 2% of all anorectal malignancies. A variety of different histologies can be distinguished, including squamous cell cancer, adenocarcinoma, cloacogenic or basaloid carcinoma, melanoma, leiomyosarcoma and small cell cancer (1). This latter type is very rare and is characterized by its aggressive clinical course with a propensity for early distant metastases, rendering this uncommon entity clinically important. In contrast, the predominant squamous cell carcinoma of the anus is treated locally, either by tumor resection and/or fluoropyrimidine-based radio-chemotherapy, which achieves cures in 60-70% of cases (2, 3). In the present report we describe the clinical course of a patient with small cell cancer of the anal canal (SCCA) treated with chemotherapy and subsequent radiotherapy, and discuss the clinical essentials including the histopathological characteristics of this tumor entity.

Correspondence to: Andreas Meyer, MD, Department of Radiation Oncology, Hannover Medical School, Carl-Neuberg-Straβe 1, D-30625 Hannover, Germany. Tel: +49 511 532 3591, Fax: +49 511 532 3796, e-mail: andie.meyer@gmx.net

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Case Report

A 41-year old woman presented with non-specific rectal complaints and gastrointestinal obstruction. The medical history was unremarkable, with the exception of regular smoking. Laboratory findings revealed elevated levels for the tumor markers CA 19-9 and CEA, of 179 kU/l and 7 μg/l, respectively. Screening for HIV-infection was not performed. On rectoscopy, a large tumor localized in the anal canal, 10 cm in diameter, was diagnosed. Histopathological examination revealed a solid malignant tumor with extended necrosis next to tumor proliferates consisting of solid small basophile cells with scant cytoplasm. Immunohistochemically, positive stains were detected for neuroendocrine and epithelial markers, including synaptophysin, chromogranin, Mib1, CK7 and keratin (Figure 1). However, the tumor cells were consistently negative for CK20, LCA, CD3, CD2, MelanA and HMB45. Based on these immunohistochemical results, primary SCCA was diagnosed. On computed tomography, multiple lesions of the liver, lung and paraaortal lymph nodes were detected (Figure 2). Due to maintained defecation, a protective colostomy was not considered appropriate. According to the tumor histology and the disseminated state of disease, chemotherapy was applied consisting of etoposide 130 mg/m^2 given as a 24-h continuous venous infusion (CVI) on day 1, and cisplatin 45 mg/m^2 given as a 24-h CVI on day 2 and 3, repeated every 3 weeks. After 4 cycles of chemotherapy a mixed response was achieved,

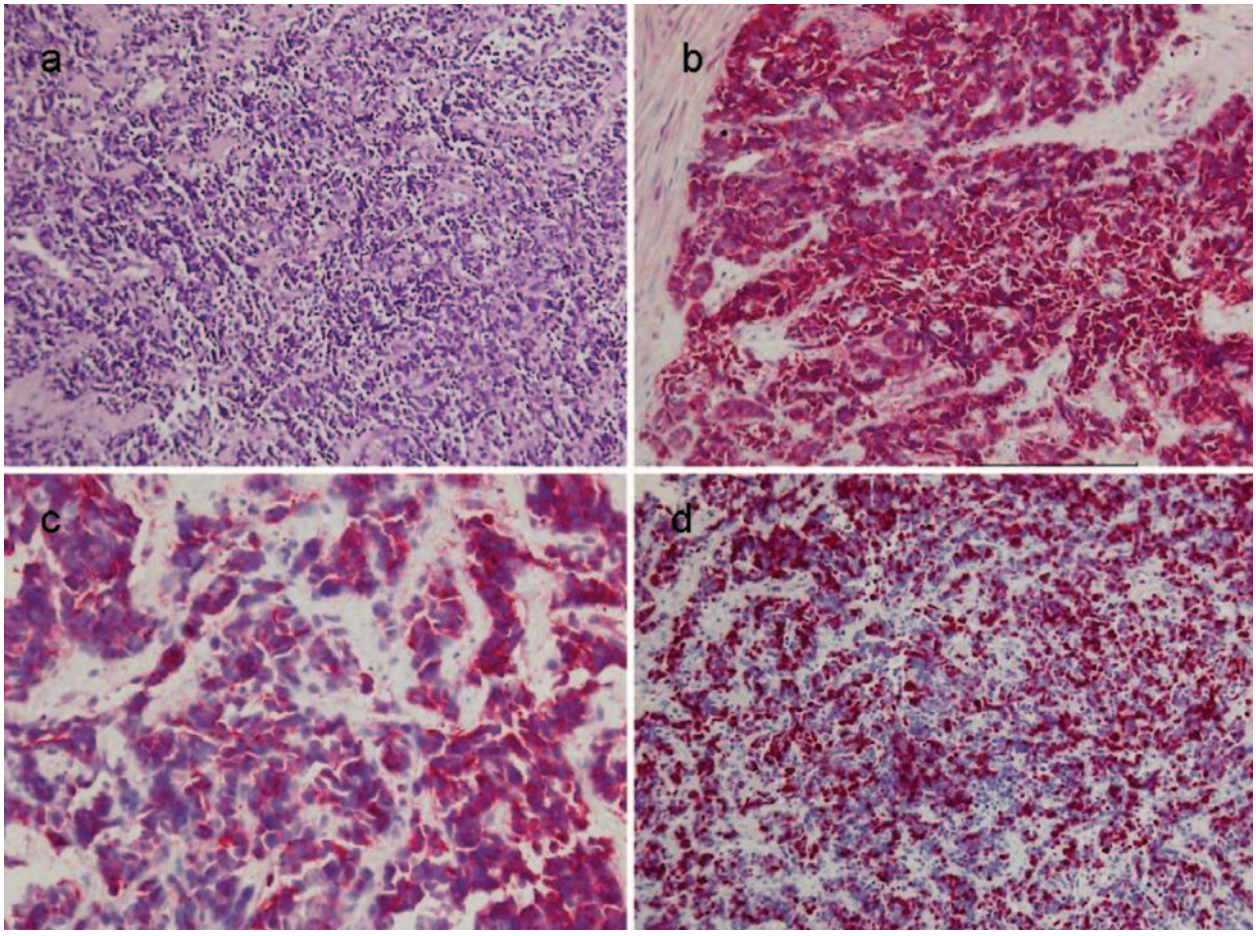

Figure 1. *Biopsy tissue from the upper anal channel showing a small cell carcinoma with neuroendocrine differentiation and diffuse proliferation of anaplastic small tumor cells: a) H&E, x100; b) strong reaction for synaptophysin, x100; c) strong reaction for chromogranin, x100; d) strong reaction for Mib1, x100.*

consisting of a complete remission of pulmonary metastases, near complete disappearance of hepatic metastases and partial remission of the primary tumor, but new bone lesions of the thoracic and lumbal spine arose, which were verified by fine-needle biopsy. Based on the major response of visceral metastases, an additional two cycles of this chemotherapy were given. After the sixth cycle of chemotherapy, the primary tumor was progressive causing symptomatic disease. Radiotherapy of the pelvis was started to treat anal canal stenosis with a single dose of 1.8 Gy. Rapid deterioration with mental and motor deceleration was noted and multiple symptomatic intracerebral metastases were detected by computed tomography. Despite the immediate initiation of irradiation of the CNS with a single dose of 3 Gy, the physical state of the patient rapidly declined and irradiation was stopped. At that time, a total dose of 16.2 Gy was given to the pelvis. The patient died 6 days after the last irradiation, 10 months after initial diagnosis, due to progressive disease.

Discussion

Small cell cancer of the gastrointestinal tract is very rare and accounts for approximately 0.1-1.0% of all gastrointestinal malignancies (4, 5). In a review article published in 2004 by Brenner *et al.,* a total of 544 gastrointestinal small cell cancers had been reported in the English literature (4). Approximately 50% of all small cell tumors of the gastrointestinal tract occur in the esophagus, representing 1-3% of all esophageal cancer cases. The second most common small cell cancer of the gastrointestinal tract is colorectal, which accounts for approximately 0.2% of all colorectal neoplasm (4, 6). SCCA is very rare and few cases have been reported in the literature to date (4, 7).

The pathogenesis of gastrointestinal small cell cancer is largely unknown. Small cell cancer of the gastrointestinal tract is characterized by a variety of histological patterns similar to the other extrapulmonary small cell cancer (8). Approximately 30-40% of the tumors contain non-small cell

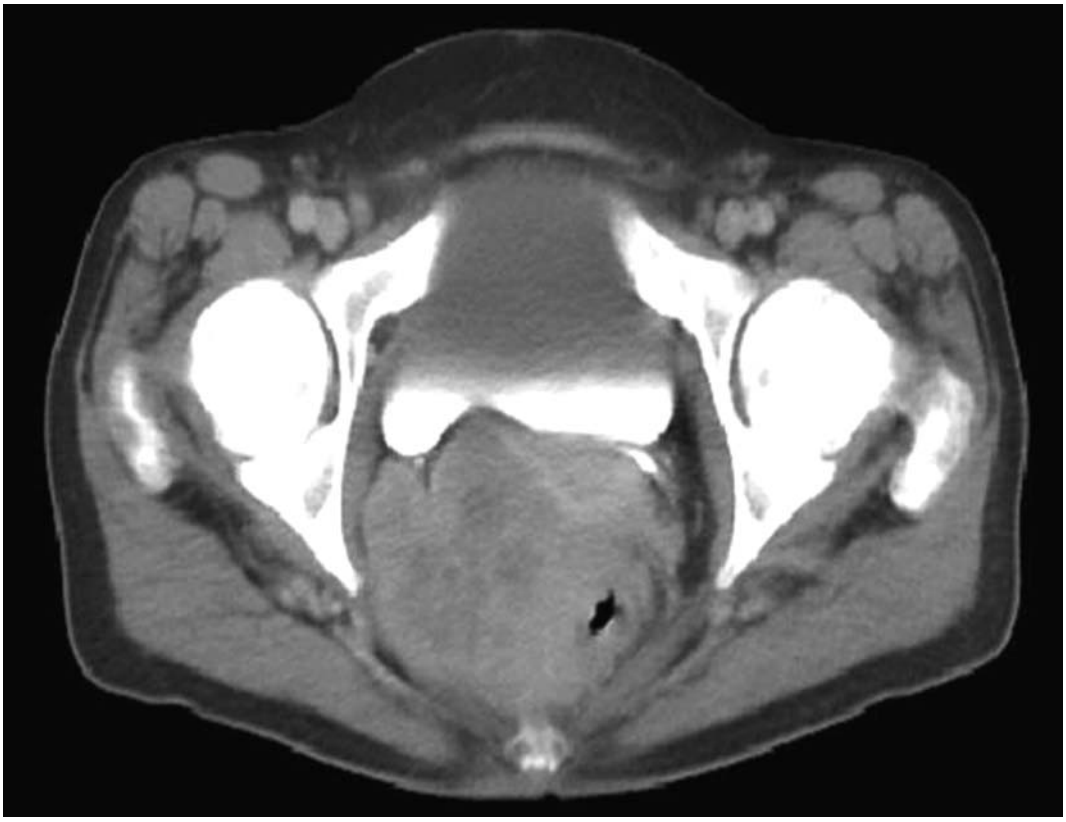

Figure 2. *Computed tomography scan of the pelvis showing the large primary tumor of the anal canal.*

cancer elements, depending on the tumor's location (4, 7, 9). The correct histopathological diagnosis of this rare tumor entity is often biased through artifacts of the tumor specimen. Conventional light microscopy features of small cell cancer do not reveal its organ of origin: specimens from different organs are indistinguishable. Immunohistochemistry is indispensable for the diagnosis of gastrointestinal small cell cancer, in particular the detection of neuroendocrine markers such as chromogranin and synaptophysin are key elements in verifing the diagnosis (10).

Small cell cancer of the gastrointestinal tract exerts an aggressive clinical course with early distant metastases and a very poor prognosis. The clinical presentation of SCCA is dominated by advanced stage at time of diagnosis, at which approximately 50% of patients present with synchronous metastatic disease, predominantly involving the liver (5, 10). In contrast, epidermoid cancers of the anal canal grow aggressively locally and spread to loco-regional lymph nodes, while the rate of distant metastasis remains low (2). Therefore, careful staging examinations are mandatory for SCCA. The role of positron emission tomography (PET) is still under investigation but seems promising for detection of metastatic disease (11).

Due to the rarity of this tumor entity, no standard treatment has been defined for gastrointestinal small cell cancers. Chemotherapy regimens consisting of cisplatin and etoposide are widely used to give palliative therapy and represent the backbone of most of the combinations used (4, 6). Due to its early dissemination, tumor resection or combined chemo-radiotherapy are rarely used to treat SCCA (12). Casas *et al.* reported an improvement in overall survival in chemotherapy-treated patients with esophageal small cell cancers (9). However, response to chemotherapy is usually of short duration. Typically, a good response to initial therapy is shortly followed by relapse or rapid progression with a median survival of only 6-12 months for these patients, as seen in our case (5, 6, 9, 10).

Life expectancy is strongly limited by the disseminated disease itself and not by the primary tumor. The prognosis of patients with small cell cancer of the gastrointestinal tract, even if discovered at an early stage, remains poor despite intensive systemic treatment (4, 6). Boman *et al.* published the largest series of 13 patients with SCCA (7). They clearly demonstrated the aggressiveness of this tumor entity. Five patients presented with metastatic disease, with a median survival of 2.2 months. Seven patients were treated with

surgery with a median interval to recurrence of only 4 months after surgery. They also demonstrated that the small cell variety is, by all parameters, a vastly more virulent disease. Potential prognostic markers consist of the extent of disease, tumor stage, performance status and administration of chemotherapy (9, 10). In a study published by Brenner *et al.* dealing with the outcome of 64 patients with gastrointestinal small cell cancer of various sites, it was demonstrated that anatomic location had no clinical impact and it was concluded that small cell cancer from various gastrointestinal sites can be viewed as one clinical entity (10).

Due to the radiosensitivity of small cell cancers, with the use of radiotherapy good clinical response with local control is usually preserved both for the primary tumor as well as for metastatic lesions. However, in patients with extended disease the radiation therapy is limited to the prevention of or treatment of local tumor occurrence. In our patient, radiotherapy was used as an adjunct to chemotherapy in order to ameliorate symptoms, caused by painful anorectal obstruction and symptomatic cerebral metastases, and to achieve local control.

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