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CASE REPORT

PEComa of the colon resistant to sirolimus but responsive to doxorubicin/ifosfamide

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Abstract

A 23-year-old male presented with a three-week-history of crampy abdominal pain and melaena. Colonoscopy revealed a friable mass filling the entire lumen of the cecum; histologically, it was classified as perivascular epithelioid cell tumor (PEComa). An magnetic resonance imaging scan showed, in addition to the primary tumor, two large mesenteric lymph node metastases and four metastatic lesions in the liver. The patient underwent right hemicolectomy and left hemihepatectomy combined with wedge resections of metastases in the right lobe of the liver, the resection status was R0. Subsequently, the patient was treated with sirolimus. After 4 mo of adjuvant mammalian target of rapamycin inhibition he developed two new liver metastases and a local pelvic recurrence. The visible tumor formations were again excised surgically, this time the resection status was R2 with regard to the pelvic recurrence. The patient was treated with 12 cycles of doxorubicin and ifosfamide under which the disease was stable for 9 mo. The clinical course was then determined by rapid tumor growth in the pelvic cavity. Second line chemotherapy with gemcitabine and docetaxel was ineffective, and the patient died 23 mo after the onset of disease. This case report adds evidence that, in malignant PEComa, the mainstay of treatment is curative surgery. If not achievable, the effects of adjuvant or palliative chemotherapy are unpredictable.

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Key words: Perivascular epithelioid cell tumor; Colon; Liver metastases; Mammalian target of rapamycin inhibitor; Sirolimus; Chemotherapy; Doxorubicin; Ifosfamide

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INTRODUCTION

Perivascular epithelioid cell tumor (PEComa) are rare mesenchymal neoplasms for which, according to a World Health Organization classification, histologically and immunohistochemically distinctive perivascular epithelioid cells are diagnostic[1]. Clinical courses are highly variable from benign behaviour to aggressive local tumor growth and seeding of metastases[2]. In this case report, a highly malignant type of PEComa in a 23-year-old male and its response to multimodal therapies is described.

CASE REPORT

A 23-year-old male was admitted to the hospital because of crampy abdominal pain and melaena for three weeks. Colonoscopy revealed a 5.5 cm mass lesion in the cecum surrounding the ileocecal valve (Figure 1). At biopsy, the friable tumor tissue was bleeding easily. An magnetic resonance imaging (MRI) scan showed, in addition to the primary tumor, two mesenteric lymph node metastases (each 5 cm in diameter) and 4 metastatic lesions in the liver (1-2 cm in diameter, segments 1, 2, 4a and 6) (Figure 2). Additional staging procedures at the time of primary diagnosis [abdominal and chest computed tomography (CT), positron emission tomography] revealed no further tumor manifestations.

In a two-stage procedure, the patient underwent right hemicolectomy and, after recovery, left hemihepatectomy combined with atypical wedge resections of hepatic segments 1 and 6 (resection status R0). On the basis of biopsy and resection material, a diagnosis of malignant PEComa was made (see below).

Owing to the aggressive nature of the tumor, both clinically and histologically, the patient received adjuvant treatment with the mammalian target of rapamycin (mTOR) inhibitor sirolimus (2 mg/d). However, after 4 mo the drug had to be discontinued due to two new liver metastases in segments 7 and 8 which were removed by atypical wedge resection. Simultaneously, a local pelvic recurrence of 13 cm × 12 cm × 8 cm with bilateral ureteral obstruction and rectal impression was diagnosed. A debulking operation was performed which resulted in Hartmann's situation (resection status R2); additionally, splints were inserted into both ureters.

Palliative chemotherapy with doxorubicin (75 mg/m^2) and ifosfamide (5000 mg/m^2) every 3 wk was started. This regime was well tolerated until cycle 7 when the dose had to be reduced due to hematotoxicity. Altogether, the patient received 12 cycles of doxorubicin/ifosfamide under which the disease was stable for 9 mo as evaluated by CT scans every 8-12 wk.

Afterwards renewed tumor growth in the pelvic cavity was observed, aggravated by malignant ascites. Three cycles of second line chemotherapy (gemcitabine 900 mg/m^2 on days 1 and 8 combined with docetaxel 100 mg/m^2 on day 8 every 21 d) were administered without measurable effect. The patient died 23 mo after the onset of disease.

Pathology

The specimen obtained at hemicolectomy showed a 5.5 cm measuring mass in the cecum with metastases in 2 of 18 regional lymph nodes, each measuring 5 cm in diameter. The tumor was located in the bowel wall, with broad ulceration of the overlaying mucosa. Histology (Figure 3) revealed a tumor of low to moderate cellularity, with a vague nodular pattern, an epithelioid and solid arrangement of the tumor cells and a sinusoidal vascular pattern without stromal desmoplasia. The tumor cells had a broad clear to granular eosinophilic cytoplasm,

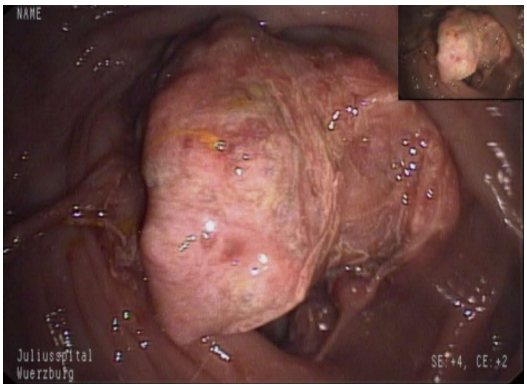

Figure 1 Endoscopic aspect of a soft and friable perivascular epithelioid cell tumor of the cecum.

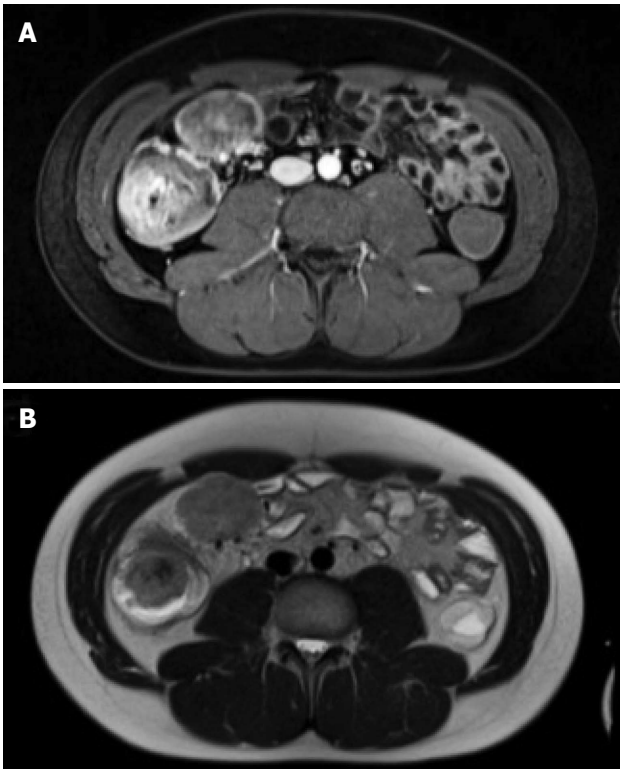

Figure 2 Magnetic resonance imaging of cecal perivascular epithelioid cell tumor and mesenteric lymph node metastasis. A: T2-weighted image; B: T1-weighted image after iv administration of contrast medium.

with moderate PAS positivity. The distinct cellular membranes exhibited some wrinkling. Most tumor nuclei showed moderate nuclear pleomorphism, but there were some highly pleomorphic hyperchromatic tumor cell nuclei. Sixty percent of the tumor area was necrotic. The mitotic rate was 12 per 10 high-power field (HPF). In some areas, the tumor was well demarcated, but there were other areas with a more infiltrative pattern of invasion.

Immunohistochemistry revealed positivity for HMB45 and negativity for melanoma antigen recognized by T cells 1 and microphthalmia-associated transcription factor. There was a weak expression of pankeratin markers (AE1/3, KL1) and CD56 in few tumor cells. Other mark-

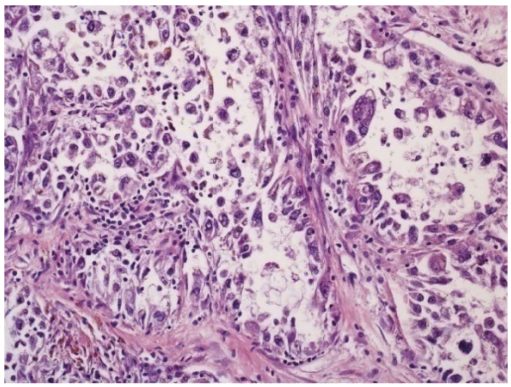

Figure 3 Histologic section of the primary tumor in the cecum. A representative part of the tumor shows epithelioid tumor cells. The cytoplasm exhibits both clear and granular eosinophilic parts. The tumor cells are arranged in large nodules with necrotic debris in the central parts. In the lower left corner, a cytoplasmic brown pigment is seen that upon ultrastructural evaluation turned out to be melanin pigment and melanosomes. There are narrow stalks of collagen-rich stroma with a scant lymphocytic infiltrate (Hematoxylin and eosin, magnification 200 ×).

ers (Synaptophysin, Chromogranin, PanLeu, CD34, CD31, S100, CD117, DOG1, Myogenin, MyoD1, EMA, Actin, Caldesmon, Desmin, CD30) were absent. Ki67 labeled 50%-60% of the tumor cells. PCR analysis of fresh frozen tumor material was negative for translocations suggestive of clear cell sarcoma [t(12;22)], synovial sarcoma [t(X;18)], myxoid liposarcoma [t(12;16)] and alveolar rhabdomyosarcoma [t(2;13)].

The diagnosis of PEComa was suggested in the biopsies obtained at endoscopy. Because of the rarity of this tumor and the missing expression of smooth muscle markers usually found in PEComas, the tissue was sent to a reference pathologist (Fletcher CDM, Boston, MA, United States) who confirmed the diagnosis of PEComa. From the surgical material, a tumor area with brown cytoplasmic pigment (with negativity in the Prussion blue and PAS stains) was selected for electron microscopy; in this sample typical melanosomes could be demonstrated.

The tumor material obtained at the resection of liver metastases did not differ histologically from that of the primary tumor. However, following chemotherapy with doxorubicin/ifosfamide, there was a tremendous increase in nuclear pleomorphism with many extremely large hyperchromatic bizarre tumor nuclei, many tumor cells with nuclear fragmentation and micronuclei, and a decrease in the amount of mitotic figures. These morphologic alterations resemble regressive tumor changes following chemotherapy. However, the area of necrotic tumor cells was 20% at this time point, i.e. most of the tumor contained still viable cells.

DISCUSSION

This report of malignant PEComa has to be seen in the context of other single case descriptions or small case series on an extremely rare tumor entity. Predictors of prognosis in PEComa have been described in a clinicopathologic study on 26 cases by Folpe *et al*[3]: A significant association between tumor size > 5 cm, infiltrative growth pattern, high nuclear grade and cellularity, mitotic rate ⩾ 1/50 HPF, necrosis, vascular invasion and subsequent aggressive clinical behaviour has been seen. In a more recent review article[4] on the basis of 234 PEComas the only pathologic factors of recurrence after surgical resection were primary tumor size ⩾ 5 cm and a high mitotic rate of > 1/50 HPF. All of these "worrisome" pathologic features were present in the 23-year-old patient of the actual case. Additionally, the presence at initial diagnosis of two large metastases in mesenteric lymph nodes (each measuring 5 cm in diameter) and of 4 hepatic metastases had to be considered as clinical indicators of poor prognosis.

PEComas arise from various organs such as uterus and vagina, kidney, digestive tract, retroperitoneum, bone, skin and eye. Intestinal origins include stomach, colon and rectum, peritoneal cavity and falciform ligament. Considering only PEComas of the colon and rectum, there are 4 reports on 7 patients[5-8] in whom the clinical course was benign (5 × operation only, 2 × operation and adjuvant chemotherapy, no evidence of disease at the end of follow-up). These findings are in contrast with the actual case when mesenteric and hepatic metastases were present at the time of diagnosis. The organ of origin, therefore, does not seem to be a predictor of prognosis.

Concerning treatment strategies, Bleeker *et al*[4] stated that cytotoxic chemotherapy and radiation had shown little benefit in malignant PEComa. According to the authors, the emerging role of mTOR inhibitors would raise enthusiasm in the therapy of these rare tumors. The clinical course reported herein reflects the opposite impression: After R0 resection of the primary tumor and mesenteric/hepatic metastases, adjuvant mTOR inhibition with sirolimus given for 4 mo at a dose of 2 mg/d (suitable for liver transplant recipients) failed to prevent a local recurrence and new liver metastases. On the contrary, cytotoxic chemotherapy (doxorubicin/ifosfamide) considered first choice in soft tissue sarcomas was associated with stable disease for 9 mo. Thus, the combination of repetitive surgery with conventional chemotherapy may still be a choice in the palliative therapy of malignant PEComa. The benefit of mTOR inhibition (sirolimus, temsirolimus, everolimus), although theoretically attractive, is at present unpredictable[9,10]. Many other therapies have been tried to control unresectable PEComa, *e.g.*, dacarbacine, epirubicin, paclitaxel, gemcitabine, oxaliplatin, imatinib, α-interferon, thalidomide, alone or in combinations. However, clinical outcomes have been extremely variable and a standard treatment is not in sight.

Some PEComas are associated with phakomatosis and hamartomatous diseases, *e.g.*, the tuberous sclerosis complex (TSC). In these conditions the mTOR signalling pathway is activated which may thus be targeted by sirolimus and related compounds[11]. In the present case of the 23-year-old patient there was no indication of TSC. Due to the paucity of data it is unknown if the presence or absence of TSC can be used as a predictor of susceptibility to sirolimus therapy.

Given the extreme rarity and heterogeneity of PEComas, a comparative study with a focus on optimal treatment will unlikely be performed. Instead, a PEComa registry based at a sarcoma center would be a reasonable option. Well documented clinical courses, histological features and empirical therapies could thus be accumulated and best practice procedures deduced.

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