PEComa of the colon resistant to sirolimus but responsive to 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. Clinical courses are highly variable from benign behaviour to aggressive local tumor growth and seeding of metastases. In this case report, a highly malignant type of PEComa in a 23-year-old male and its response to multimodal therapies is described.
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/m²) and ifosfamide (5000 mg/m²) 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/m² on days 1 and 8 combined with docetaxel 100 mg/m² 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 overlying 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, 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-
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\(^6\) 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 faliform ligament. Considering only PEComas of  the colon and rectum, there are 4 reports on 7 patients\(^5\)\(^{10}\) 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.\(^6\) 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\(^6\)\(^{10}\). Many other therapies have been tried to control unresectable PEComa, e.g., dacarbazine, 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\(^{10}\). 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.

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.\(^5\): A

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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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REFERENCES

1 Folpe AL. Neoplasms with perivascular epithelioid cell differentiation (PEComas). In: Fletcher CDM, Unni KK, Epstein J, Mertens F. Pathology and genetics of tumours of soft tissue and bone. WHO classification of tumours. Lyon: IARC Press, 2002: 221-222

2 Hornick JL, Fletcher CD. PEComa: what do we know so far? Histopathology 2006; 48: 75-82 [PMID: 16359539 DOI: 10.1111/j.1365-2559.2005.02316.x]

3 Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL, Weiss SW. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. Am J Surg Pathol 2005; 29: 1558-1575 [PMID: 16327428 DOI:10.1097/01.pas.0000173232.22117.37]

4 Bleeker JS, Quevedo JF, Folpe AL. “Malignant” perivascular epithelioid cell neoplasm: risk stratification and treatment strategies. Sarcoma 2012; 2012: 541626 [PMID: 22619565]

5 Baek JH, Chung MG, Jung DH, Oh JH. Perivascular epithelioid cell tumor (PEComa) in the transverse colon of an adolescent: a case report. Tumori 2007; 93: 106-108 [PMID: 17455882]

6 Shi HY, Wei LX, Sun L, Guo AT. Clinicopathologic analysis of 4 perivascular epithelioid cell tumors (PEComas) of the gastrointestinal tract. Int J Surg Pathol 2010; 18: 243-247 [PMID: 19124450 DOI: 10.1177/1066896908330481]

7 Park SJ, Han DK, Baek HJ, Chung SY, Nam JH, Kook H, Hwang TJ. Perivascular epithelioid cell tumor (PEComa) of the ascending colon: the implication of IFN-α2b treatment. Korean J Pediatr 2010; 53: 975-978 [PMID: 21218021 DOI: 10.3345/kjp.2010.53.11.975]

8 Ryan P, Nguyen VH, Ghouloum S, Carpineta L, Abish S, Ahmed NN, Laberge JM, Riddell RH. Polypoid PEComa in the rectum of a 15-year-old girl: case report and review of PEComa in the gastrointestinal tract. Am J Surg Pathol 2009; 33: 475-482 [PMID: 19092636 DOI: 10.1097/PAS.0b013e31819a03d1]

9 Wagner AJ, Malinowska-Kolodziej I, Morgan JA, Qin W, Fletcher CD, Vena N, Ligon AH, Antonescu CR, Ramaiya NH, Demetri GD, Kwiatkowski DJ, Maki RG. Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. J Clin Oncol 2010; 28: 835-840 [PMID: 2048174 DOI: 10.1200/JCO.2009.25.2981]

10 Subbiah V, Trent JC, Kurzrock R. Resistance to mammalian target of rapamycin inhibitor therapy in perivascular epithelioid cell tumors. J Clin Oncol 2010; 28: e415 [PMID: 20567010 DOI: 10.1200/JCO.2010.29.4678]

11 Plas DR, Thomas G. Tubers and tumors: rapamycin therapy for benign and malignant tumors. Curr Opin Cell Biol 2009; 21: 250-256 [PMID: 19297273 DOI: 10.1016/j.ceb.2008.12.013]

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