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CASE REPORT

V. Delvaux · R. Sciot · B. Neuville · P. Moerman
M. Peeters · L. Filez · D. Van Beckevoort · N. Ectors
K. Geboes

Multifocal epithelioid angiosarcoma of the small intestine

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Abstract A 67-year-old man presented with weight loss, intermittent severe abdominal pain and melaena. Initial radiology (including abdominal ultrasonography), gastroscopy and colonoscopy did not demonstrate any lesions that could explain the complaints. Three weeks later, upper gastrointestinal and small-bowel barium studies revealed two areas in the small intestine with an abnormal mucosal pattern. Explorative laparotomy revealed three tumoral lesions. Three partial enterectomies were performed. Gross examination showed centrally depressed dark reddish tumoral lesions extending from the mucosa throughout the full thickness of the bowel wall (diameter varying between 1.6 cm and 2.2 cm). The tumours, composed of large, plump, polygonal cells showing little architectural differentiation, were mainly situated in submucosa and muscularis propria. The growth pattern appeared rather solid. The epithelioid cells showed pronounced nuclear pleomorphism and atypia with central large nucleoli. There were several small blood vessels with occasional anaplastic endothelial cells. Immunohistochemical staining demonstrated an intense expression of CD 31, CD 34, factor VIII related antigen and keratin. This supported the diagnosis of an epithelioid angiosarcoma. The patient died 3 months after diagnosis. Tumours of the small intestine are very rare, and angiosarcomas of the small intestine are even more rare. Epithelioid variants have only been described in two patients and only one of these had a multifocal presentation. The prognosis is very poor. Because of the epithelioid growth pattern and the cytokeratin expression, these tumours may erroneously be diagnosed as a carcinoma.

Key words Small intestine · Epithelioid angiosarcoma

V. Delvaux (✉) · R. Sciot · P. Moerman · N. Ectors · K. Geboes
Department of Pathology, University Hospitals Leuven,
Minderbroedersstraat 12, B-3000 Leuven, Belgium
Tel.: +32-16-336630, Fax: +32-16-336548

B. Neuville · M. Peeters
Department of Internal Medicine, University Hospitals Leuven,
Leuven, Belgium

L. Filez
Department of Abdominal Surgery, University Hospitals Leuven,
Leuven, Belgium

D. Van Beckevoort
Department of Radiology, University Hospitals Leuven, Leuven,
Belgium

Introduction

Although the small intestine represents about 75% of the gastrointestinal tract, only 1–1.6% of all gastrointestinal malignancies originate in this part [2, 4, 20]. The three most frequent malignant tumours are neuro-endocrine tumours, adenocarcinomas and leiomyosarcomas [4, 20]. Angiosarcomas represent 1–2% of all sarcomas and most frequently occur in the skin and subcutis [6, 9, 10, 13, 22]. Intra-abdominally, they occur often in spleen and liver. Primary gastrointestinal angiosarcomas are very rare [6, 7, 13, 15, 16, 17, 19, 22]. The patients present with atypical symptoms such as abdominal pain, gastrointestinal bleeding, nausea, vomiting and a mass. The diagnosis is difficult and often made in the advanced stage of disease with the presence of metastases. Histologically, the tumour can be mistaken for a (metastatic) carcinoma, lymphoma or malignant melanoma. Immunohistochemical stainings are a mandatory tool to establish the diagnosis.

The treatment generally consists of surgery, sometimes followed by neo-adjuvant chemotherapy. The prognosis is very poor. Only two cases of intestinal epithelioid angiosarcoma have previously been described [19]. Only one of them had a multifocal presentation (duodenum and upper jejunum). The tumour of the other patient was localised in the sigmoid. Histologically, the growth pattern of the tumour was dominantly solid and epithelioid. Both tumours co-expressed endothelial and epithelial markers.

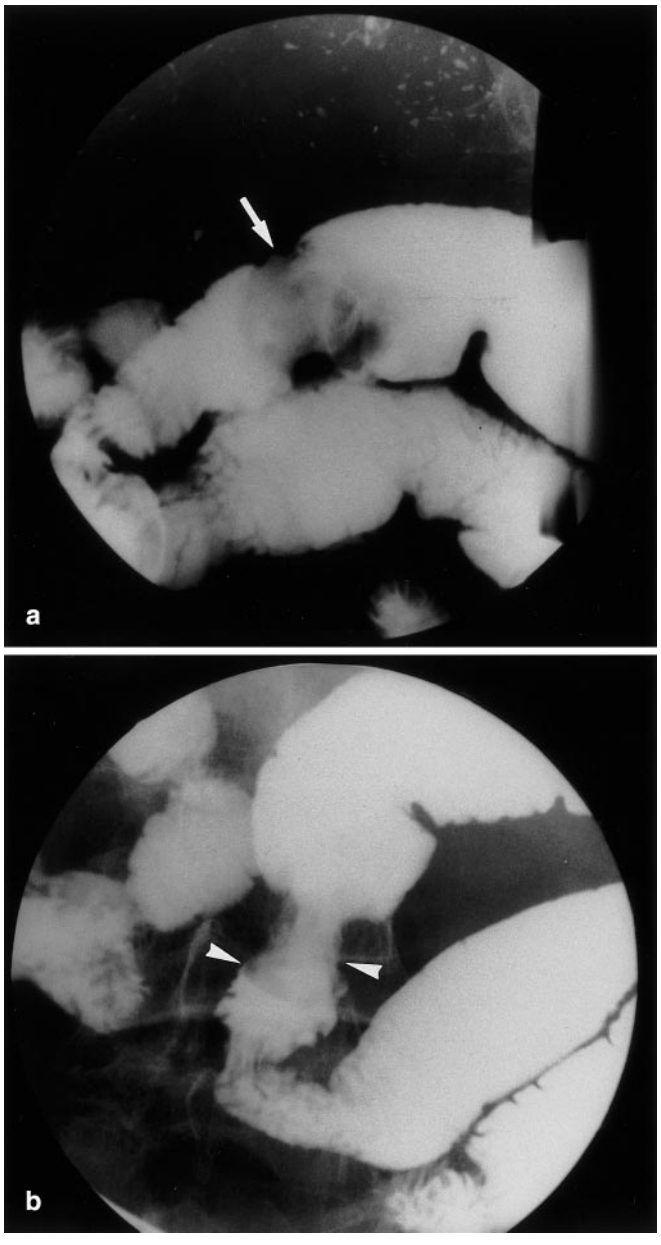


Fig. 1 **a** Small-bowel follow-through study demonstrates a small segmental narrowing with alterated mucosa in distal jejunal loop (*arrow*). **b** A similar lesion is present in an ileal loop (*arrowheads*)

Case report

Clinical history

A 67-year-old man was admitted to the hospital with episodes of melaena and abdominal distension associated with cramping abdominal pain. Symptoms had been present for the last 3 months. For chronic back pain, he took bisoprolol, bromazepam and naloxon hydrochloride. Clinical examination revealed no abnormalities. Laboratory examination was normal, including tumour markers CEA and Ca 19.9. Because of the history of intermittent melaena, endoscopic examination was performed. A gastroscopy showed superficial erosions in the antrum, without signs of active bleeding. Colonoscopy showed uncomplicated diverticulosis of the sigmoid. On abdominal computed tomography (CT) scan, mul-

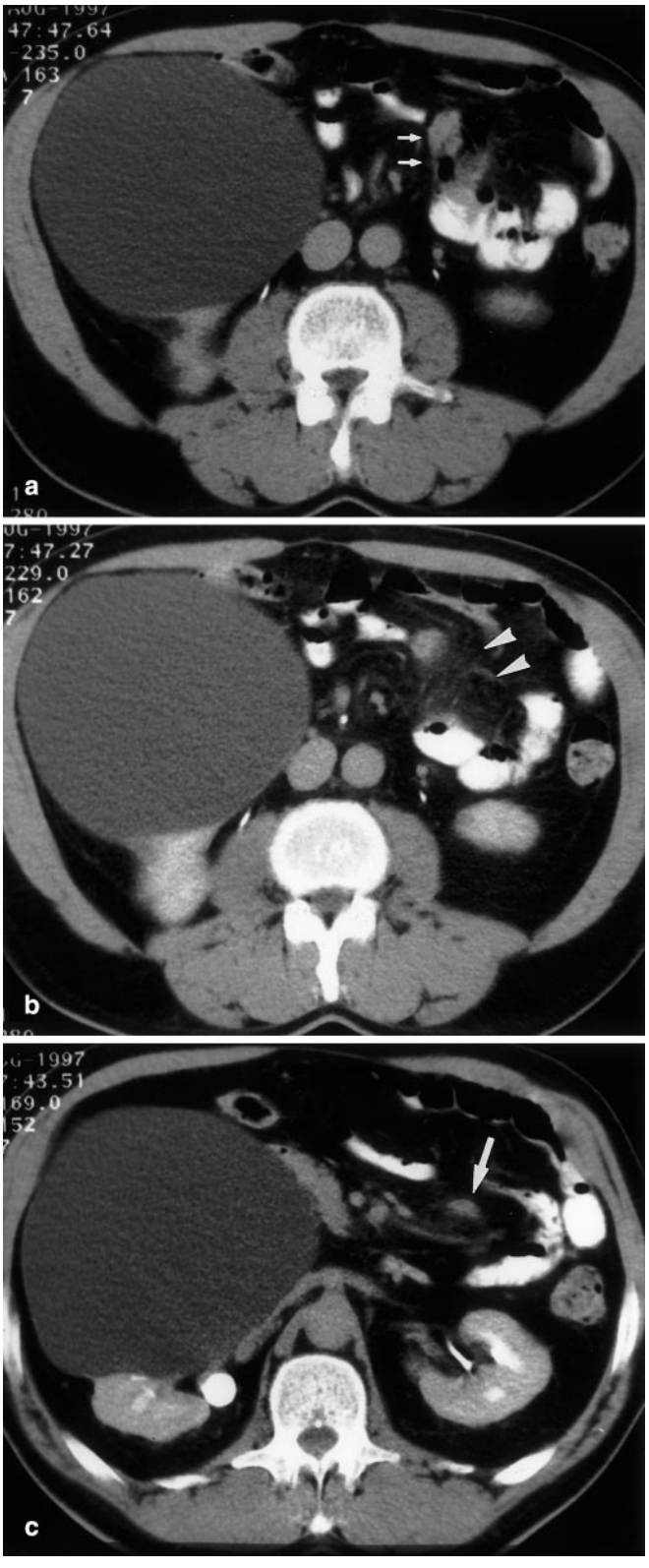


Fig. 2 **a, b** Moderate segmental wall thickening (*small arrows*) of a small-bowel loop with streaky infiltrations in the adjacent mesenteric fat (*arrowheads*) is seen on computed tomography. Note also a large benign renal cyst in the right kidney. **c** On a higher section, a small perivascular adenopathy (*large arrow*) is present

Table 1 Immunohistochemical stains performed and results obtained. *ND* not done; – negative; + weak positivity; ++ moderate positivity; +++ strong positivity. *CEA* carcino embryonic antigen; *α-SMA* alpha smooth muscle actin; *β-HCG* beta-human chorionic gonadotrophin; *LCA* leucocyte common antigen; *CD 34* anti-HPCA-1

Antibody	Source Paraffin/frozen	Dilution		Results	
		Paraffin	Frozen	Paraffin	Frozen
Keratin	Immunotech (France)	1/50	1/50	–	++
Cytokeratin 7	Dakopatts (Denmark)	1/50	1/50	–	ND
Cytokeratin 20	Dakopatts (Denmark)	1/50	1/50	–	ND
CEA	Dakopatts (Denmark)	1/300	1/300	–	ND
Desmin	ICN(USA)/ Boehringer Mannheim	1/20	1/20	–	–
α-SMA	Sigam (USA)	1/400	1/400	++	–
β-HCG	Dakopatts (Denmark)	1/200	1/200	–	ND
Neurofilament	Monosan (Sanbio-Holland)	1/20	1/10	–	ND
LCA	Dakopatts (Denmark)	1/50	1/50	–	–
Vimentin	Amersham (UK)	1/20	1/20	+	+
S-100	Dakopatts (Denmark) (not on frozen)	1/300	–	–	ND
HMB 45	Bio-Genex (USA)	1/100	1/100	–	–
CD31 (JC70 A)	Dakopatts (Denmark)	1/50	1/50	–	+++
CD34	Becton Dickinson	1/10	1/5	–	+++
Factor VIII related antigen	Dakopatts (Denmark)	1/30	1/30	–	+++

tiple nodular structures were seen in the mesenterial fat, most of them located in the left hypochonder (Fig. 1). No differentiation between primary small intestinal pathology or lymphatic metastases could be made. An RX small-bowel transit revealed at least two areas of abnormal mucosal folds, suggestive of intraluminal pathology (Fig. 2). An explorative laparotomy was performed. Three separate lesions in the small bowel, with fixation of the omentum and pathologic mesenterial adenopathies, were found. For each of them, a partial enterectomy with terminoterminal anastomosis was performed. The postoperative period was uncomplicated. Two months later, he returned to the hospital because of heavy cramping abdominal pain. Investigation by CT scan revealed a mesenterial relapse and multiple lung metastases. Subsequently, there was rapid deterioration of his general condition. He finally developed fulminant respiratory failure and died 1 month later.

Materials and methods

Biopsies from all three surgical enterectomy specimens were freshly frozen in liquid-nitrogen-cooled isopentane and stored at –70°C. The remainder was formalin fixed and embedded in paraffin. Sections were stained with haematoxylin and eosin, periodic acid/schiff base (PAS) and PAS after amylase pre-treatment.

Immunohistochemical stains were performed on freshly frozen tissue and on paraffin embedded tissue. An avidin-biotin-complex technique was applied on 5-µm-thick sections. The antibodies used are listed in Table 1.

Pathological findings

The length of the three partial enterectomy specimens varied from 3 cm to 6 cm. Grossly, all three contained in the centre a slightly depressed dark reddish tumoral lesion, measuring between 1.6 cm and 2.2 cm. Each lesion extended macroscopically from the mucosa throughout the full thickness of the bowel wall.

On microscopic examination, the tumour was principally situated in the submucosa and muscularis propria. There was limited extension of the tumour in the mucosa with focal destruction and ulceration. The tumour was composed of large, plump, polygonal cells showing little architectural differentiation. The growth pattern appeared rather solid. The epithelioid cells showed pronounced nuclear pleomorphism and atypia with vesicular aspect of the nucleus and central large nucleoli. Some tumour cells showed cytoplasmic vacuolisation suggesting vasoformative properties (Fig. 3).

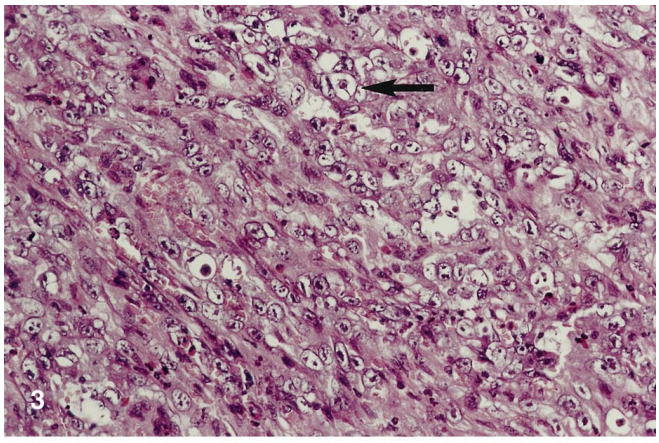
Several small blood vessels were admixed to the individual tumour cells with a possible lining of some of these vessels by anaplastic cells.

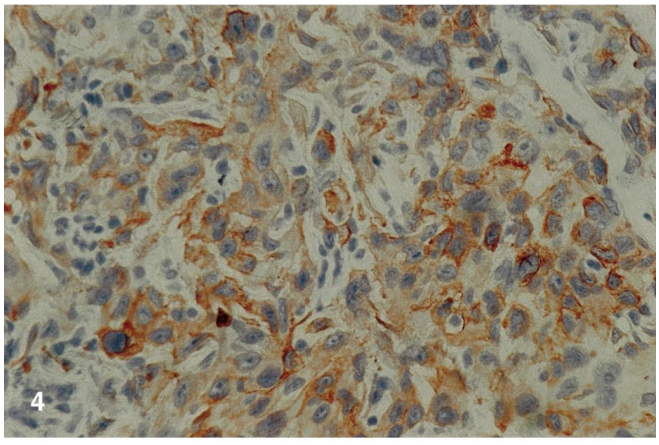
The most important results of the immunohistochemical stains were the co-expression on the frozen tissue of three endothelial markers and one epithelial marker (Table 1, Fig. 4 and Fig. 5). These immunohistochemical features, combined with the morphology, allowed the diagnosis of an epithelioid angiosarcoma.

At autopsy there were bilateral hemorrhagic pleural effusions within the parenchyma and especially subpleurally numerous whitish to dark red small nodules. Similar lesions were seen in the liver. The gastrointestinal mucosa was focally hemorrhagic but without evidence of residual tumour. In the mesentery of the small bowel, a large tumoral mass was found with a diameter of 17 cm extending into the head of the pancreas. Enlarged lymph nodes were present next to the portal vein. Histology confirmed the tumoral nature of the lesions described above. All foci showed features of an epithelioid angiosarcoma.

Discussion

Angiosarcoma of the gastrointestinal tract is a very rare tumour, mostly seen in elderly patients. In the last two decades, 12 cases have been reported [6, 7, 13, 15, 16, 17, 18, 19, 22] in literature. Angiosarcomas show mostly a double growth pattern, vasoformative and/or solid. The vasoformative structures can range from well-formed vessels over vascular spaces with papillary projections to slit-like anastomosing vascular channels. These vessels are lined by spindle or plump anaplastic endothelial cells with slight or moderate nuclear pleomorphism and multilayering. The solid growth pattern consists of two cell types: sheets of spindle-shaped cells or large, polygonal epithelioid-type cells with abundant amphophilic or eosinophilic cytoplasm. These epithelioid cells often show moderate to marked nuclear pleomorphism with vesicular nuclei and large, central nucleoli. Intracytoplasmic vacuolisation is observed in some cases. The mitotic rate is high.





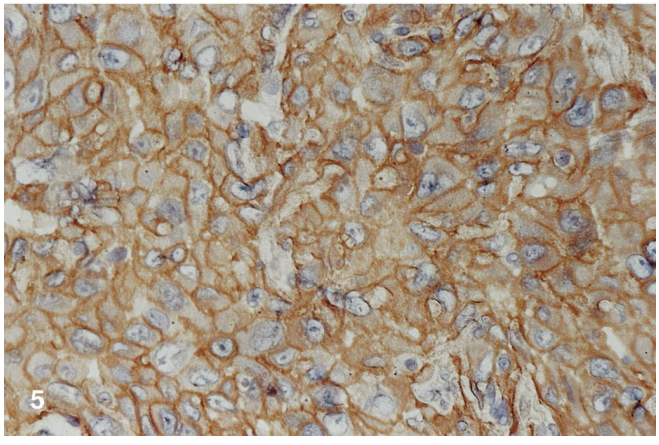


Fig. 3 A dominantly solid growth pattern is seen, with large epithelioid cells with vesicular nuclei and a central nucleolus. Note cytoplasmic vacuolisation of some cells (*arrow*). Haematoxylin and eosin, ×25

Fig. 4 A focal expression of keratin is present on the frozen tissue, ×40

Fig. 5 The tumour cells display diffuse and strong positivity for CD 31 on the frozen tissue, ×40

Because of the variegated histological features, the diagnosis may be difficult to reach based on pure morphology. An epithelioid angiosarcoma can mimic a primary or metastatic carcinoma, a malignant melanoma, a lymphoma and many sarcomas with epithelioid features. Immunohistochemical staining with expression of endothelial markers (factor VIII related antigen, CD31, CD34) is needed to allow definite diagnosis [1, 5]. In the absence of these stains, epithelioid angiosarcoma can easily be misdiagnosed as a carcinoma, since keratin is often expressed in epithelioid angiosarcoma. Moreover, some carcinomas, especially those arising in the breast, thyroid or skin, may have a pseudoangiomatoid appearance and may even demonstrate immunohistochemical overlap [3, 8, 12, 14]. In those cases, electron microscopy is an important adjunct [3].

There is an overlap between epithelioid hemangioendothelioma and epithelioid angiosarcoma. In its pure form, epithelioid hemangioendothelioma is characterised by cords and strands of vacuolated epithelioid cells, embedded in a myxohyaline matrix [21]. Recently, soft tissue tumour pathologists have become aware of epithelioid vascular lesions that fall into the gray zone between epithelioid hemangioendothelioma and epithelioid angiosarcoma. Most probably both tumours represent, in their pure form, both ends of a spectrum of malignant epithelioid vascular neoplasms [11].

Until now, only two cases of a gastrointestinal epithelioid angiosarcoma have been described, one of which was multifocal [19]. The first patient was a 70-year-old woman with a tumour of 1.7 cm in the sigmoid without metastases. She underwent a sigmoid resection and the post-operative course has been uneventful for 2 years. The second patient was a 64-year-old man with a tumour of 3 cm in the duodenum and one of 4 cm in the upper jejunum. Partial duodeno-jejunectomy was performed. He died of pulmonary metastases 1 year afterwards. Permission for autopsy was not granted.

Histologically, the tumours had a solid growth pattern and consisted of large, epithelioid cells with focally formation of vasoformative structures. Intracytoplasmic vacuolisation was present in both cases. Both tumours expressed anti-endothelin-1, vimentin and two epithelial markers (AE1, NCL-5D3). One tumour was intensely positive for CD31 and Ulex Europaeus Agglutinin I and weakly positive for factor VIII related antigen.

Although epithelioid angiosarcomas are rare tumours, they should be taken into consideration when confronted with an undifferentiated epithelioid malignant tumour especially in elderly patients. Immunohistochemical investigation and eventually electron microscopy are mandatory to allow a correct diagnosis.

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