Virchows Arch (2001) 438:398–403
DOI 10.1007/s004280000324

CASE REPORT

K. Cokelaere · J. Vanvuchelen · P. Michielsen · R. Sciot

Epithelioid angiosarcoma of the splenic capsule

Report of a case reiterating the concept of inert foreign body tumorigenesis

Received: 19 June 2000 / Accepted: 12 September 2000 / Published online: 31 October 2000

Abstract We report an epithelioid angiosarcoma involving the splenic capsule. This neoplasm developed because of a gauze sponge, retained for 38 years following left-sided nephrectomy. Clinical, radiological, and histological features of this angiosarcoma add to the validity of the concept of inert foreign body tumorigenesis in humans.

Keywords Epithelioid angiosarcoma · Splenic capsule · Foreign body tumorigenesis

Introduction

Primary peritoneal angiosarcomas are rare tumors, with few well-documented cases in the literature [14, 15, 20, 24]. Some of these neoplasms involve the serous membranes in a peculiar surface-spreading manner, mimicking mesothelioma, both clinically and grossly [15, 19, 24]. Differentiation from epithelial mesothelioma using light microscopy can be challenging, especially with angiosarcomas exhibiting epithelioid features [12, 19, 30]. Similar tumors occur in the pericardium or pleura [16, 20, 35]. By analogy with the so-called pseudomesotheliomatous adenocarcinoma [19], the term pseudomesotheliomatous angiosarcoma has been suggested for this entity [20].

Retained foreign material has been implicated as an etiological factor in the development of a variety of sarcomas, both in experimental animal studies and in humans [5, 6]. Angiosarcomas could also develop through this mechanism of inert foreign body tumorigenesis [3, 13, 15, 33, 38]. This report describes the clinical, radiological, and pathological features of a primary epithelioid angiosarcoma encasing the spleen. The rareness of this neo-

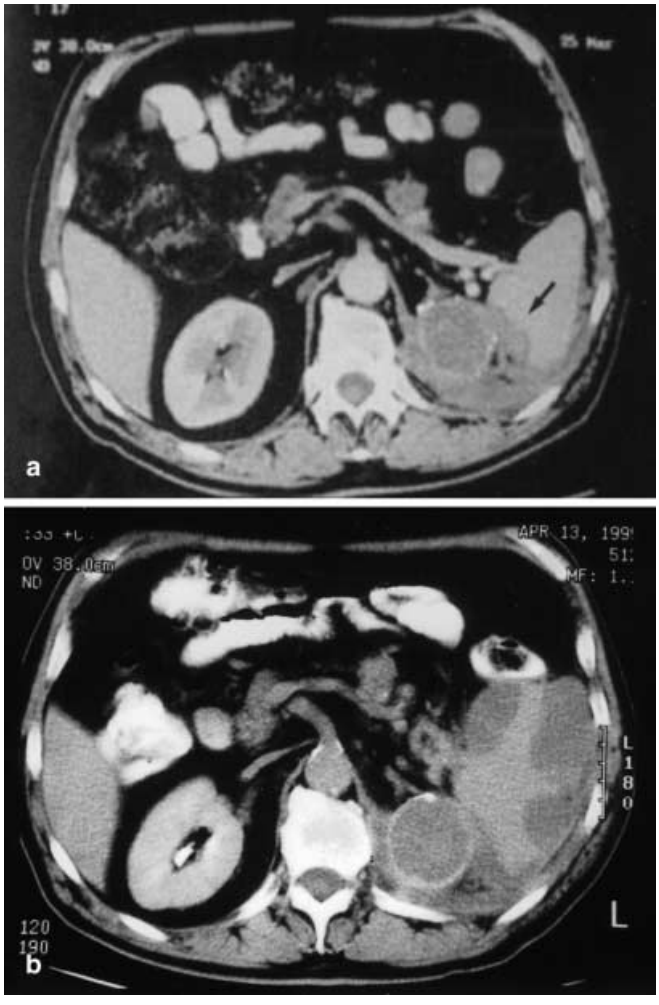


Fig. 1 **a** Computed tomography (CT) scan of the lumbar region. At the site of left nephrectomy, a rounded nodule is seen abutting the spleen (*arrow*). **b** CT scan lumbar region 3 weeks later. The spleen is surrounded by an irregular, hypodense process

K. Cokelaere (✉) · R. Sciot
Department of Pathology, University Hospital Gasthuisberg, St. Raphael Ziekenhuis, Minderbroederstraat 12, B-3000 Leuven, Belgium
e-mail: Kristof.Cokelaere@uz.kuleuven.ac.be
Tel.: +32-16336622

J. Vanvuchelen · P. Michielsen
Department of Pathology, Hospital St. Jan, Brugge, Belgium

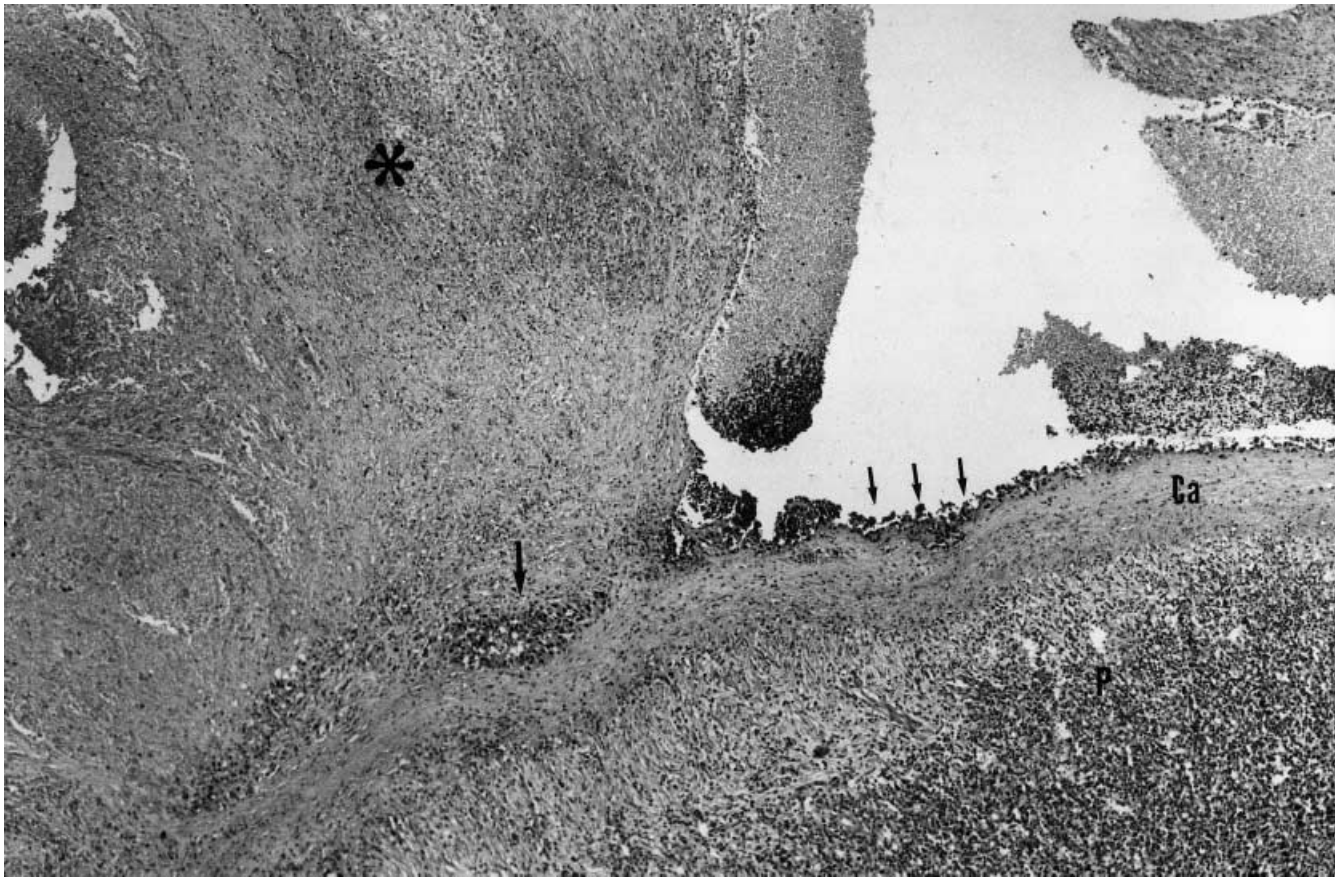
Fig. 2 Fragment of the spleen, surrounded by fibrofatty tissue. Note the capsular indentation (*large arrow*). There is early invasion of the splenic parenchyma (*small arrow*)

plasm and the close topographical association to a retained gauze sponge reemphasize the relevance of solid-state carcinogenesis in the development of sarcomas.

Clinical history

A 67-year-old male patient was admitted to the hospital with a 1-month history of pain in the left hypochondrium. There was no history of recent trauma. The patient reported having had a left-sided nephrectomy 38 years earlier, for localized renal tuberculosis. A rounded nodule present at the site of nephrectomy, abutting the lower pole of the spleen, was observed using computed tomography (CT). This nodule showed no contrast enhancement. A conspicuous peripheral calcified rim was present (Fig. 1a). A diagnosis of an encapsulated hematoma with peripheral calcification was made. Contrast enhancement was noted at the lower pole of the spleen, adjacent to the above-mentioned nodule. This was interpreted as a small subcapsular hematoma. There was no evidence of retroperitoneal lymphadenopathy. A CT scan performed 3 weeks later showed the same rounded nodule with peripheral calcification. The spleen was surrounded by a contrast-enhancing process, with multiple hypodense areas (Fig. 1b). In view of the rapid progression of this process, urgent laparatomy was performed, with removal of the spleen and adjacent nodule. This nodule proved to be a gauze sponge, largely intact but fragile, being partly surrounded by a dense fibrotic capsule. The spleen was embedded in fibrohemorrhagic tissue that extended into the gastrosplenic ligament. After initial recovery and transfer to another hospital, the patient died suddenly, only 10 days after surgery.

Fig. 3 Scanning magnification. The splenic capsule (*Ca*) and parenchyma (*P*) are easily discernable. An inflammatory process is present (*asterisk*) surrounding the spleen, intermingled with areas of a high-grade neoplasm (*large arrow*). The splenic capsule is lined by atypical, epithelioid cells (*small arrows*)



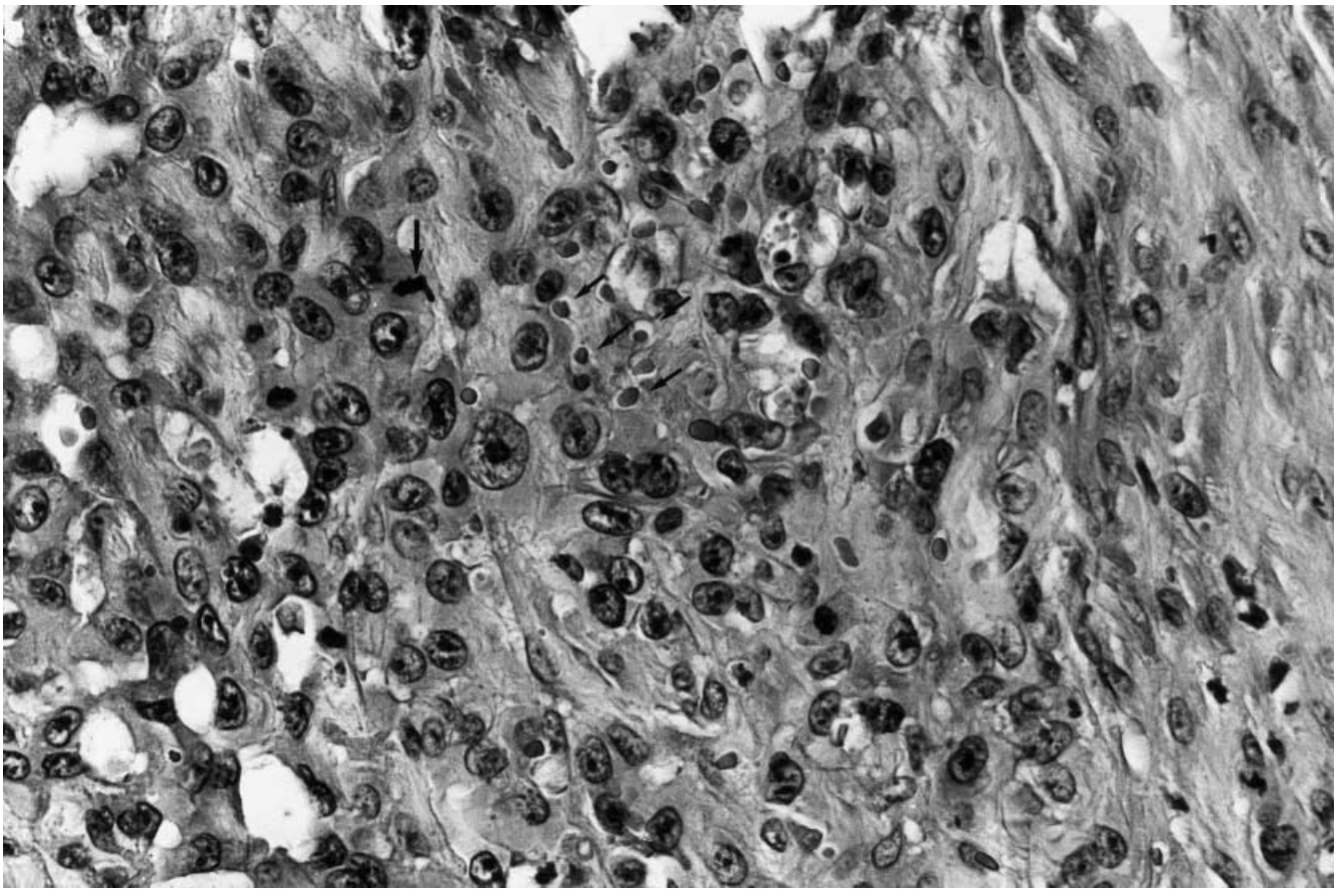


Fig. 4 Sheath-like growth pattern of tumor, with epithelioid cells displaying high-grade nuclear atypia. Atypical mitoses are present (*large arrow*). Note multiple intracytoplasmic lumina, with single red blood cells (*small arrows*)

Macroscopic findings

The gauze sponge, measuring 5×4×4 cm, was embedded in fibrous tissue and clotted blood. The spleen with surrounding tissue measured 12×10×4 cm, for a total weight of 360 g. There was encasement of the spleen by partly hemorrhagic fibro-fatty tissue. A local indentation of the splenic capsule was also involved by the necrotic tissue (Fig. 2).

Light microscopic findings

Microscopically, the perisplenic tissue consisted of fat, cellular fibrous tissue, and areas with fibrin deposition, numerous neutrophilic granulocytes, lymphocytes, and foamy histiocytes. A single layer of epithelioid cells covered most of the splenic capsule, displaying a large amount of eosinophilic cytoplasm, large round to oval nuclei, a vesicular chromatin pattern, and a prominent nucleolus (Fig. 3, 5a). There was pseudostratification of tumor cells, with tufts and micropapillary projections. A high-grade neoplasm was easily identified, spreading along the splenic capsule, extending into the gastrosplenic ligament. Careful sectioning revealed only a single focus of microinvasion of the splenic parenchyma (Fig. 2). The tumor consisted of freely anastomosing vascular channels lined by atypical endothelial cells (Fig. 5b). A significant portion of the neoplasm displayed a sheet-like growth pattern, with barely discernable vascular channels. Multiple intracytoplasmic lumina were present, some of which contained single red blood cells (Fig. 4). Some acellular collagenous tissue, with scattered foci of hemosiderin-laden macrophages, calcifications, and cholesterol clefts, was present at the lower pole of the spleen, forming a fibrous capsule partly surrounding the gauze sponge. Sections of this sponge revealed birefringent fibers, with interspersed acellular, necrotic tissue. No foreign body giant cells were seen.

Immunohistochemistry

Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue, utilizing the avidin–biotin complex method, with a panel of immunohistochemical markers comprising cytokeratin (1:50; Immunotech; France), epithelial membrane antigen (1:100; EMA; Dako; Glostrup, Denmark), vimentin (1:40; Dako), factor VIII related antigen (FVIIIRag; 1:30; Dako), CD31 (1:50; Dako), and CD34 (My10; 1:10; Becton Dickson; San Jose, Calif.). The tumor cells

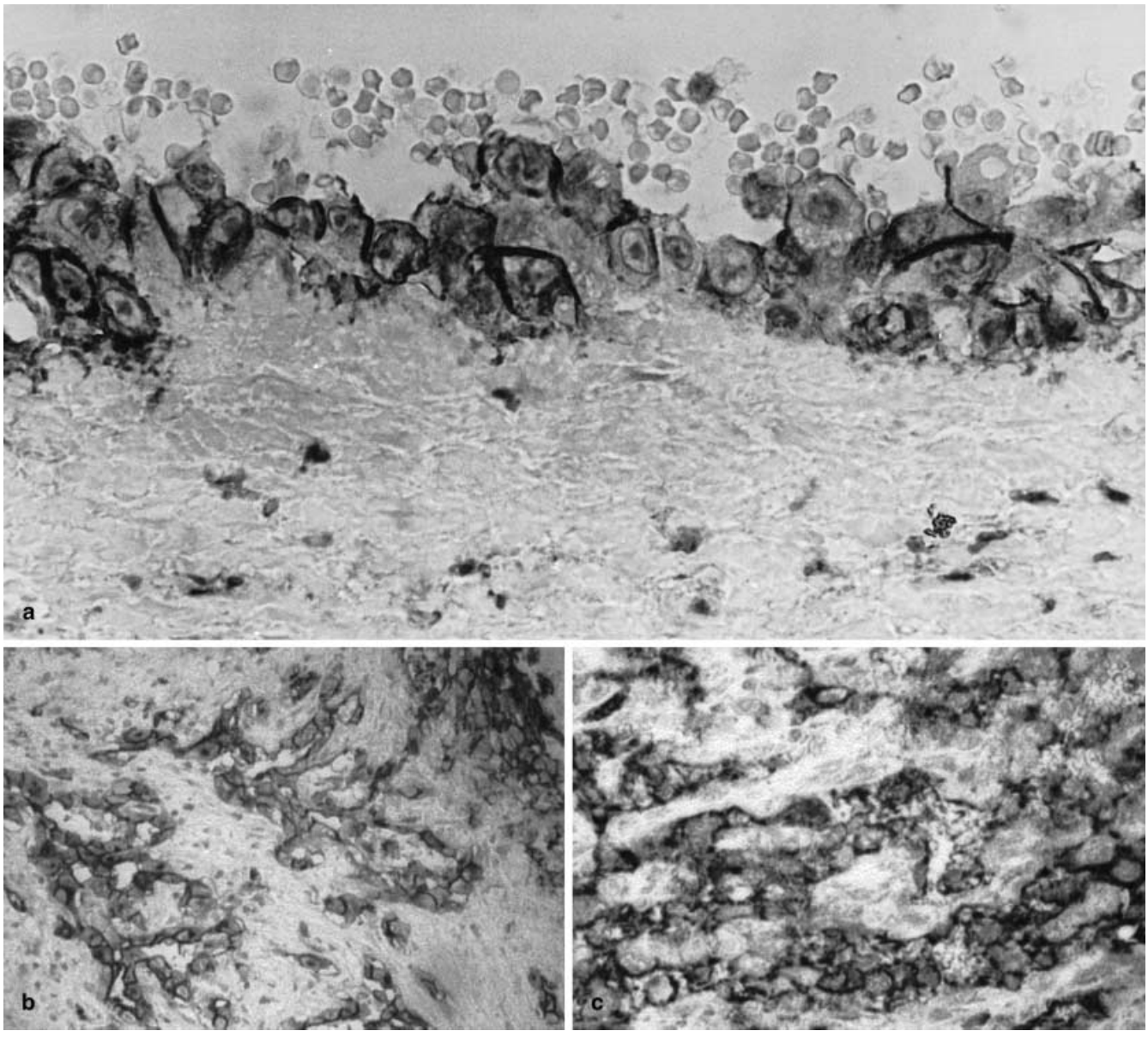


Fig. 5 **a** CD31 stain, highlighting the endothelial nature of the atypical epithelioid cells lining the splenic capsule. These cells lacked cytokeratin or epithelial membrane antigen positivity (detail of Fig. 3). **b** CD31 stain illustrating freely anastomosing vascular channels lined by atypical endothelial cells. **c** Factor VIII-related antigen stain, showing strong cytoplasmic positivity

showed strong cytoplasmic staining for both factor VIII-Rag and vimentin and were strongly positive for CD31 (Fig. 5b, c). All other markers were negative. The bizarre epithelioid cells lining the splenic capsule displayed the same staining pattern (Fig. 5a).

Discussion

The concept of solid-state carcinogenesis can, in addition to ultraviolet and ionizing radiation, burns, and physical trauma, be included among the so-called physical causes of cancer [22]. The tumorigenic capacity of ultraviolet and ionizing radiation has been well recognized for a long time [32]. There have been several reports of sarcomas developing in scar tissue from burns [8, 27]. Experimental animal studies, dating back to the 1940s, suggested that implanted inert foreign material could have a similar tumorigenic potential. The first observations came from experiments with cellophane sheets implanted in rats, inducing fibrosarcomas [28]. Further studies with all kinds of plastic sheets and a variety of other inert substances confirmed these initial findings and delineated several critical properties of this proposed mechanism of carcinogenesis [2, 5, 29]. Larger, smooth-surfaced implants appear more tumorigenic than smaller, fragmented, or perforated ones. The carcinogenic effect can persist, even after removal of the implant. There is a variable latent period, which ranged from

Table 1 Foreign body-associated angiosarcomas. *DOD* dead of disease

	Reference	Age (years)/gender	Site	Foreign body	Latency (year)	Outcome
1	Ott et al. [31]	?	Lumbar vertebra	Shrapnel	12	?
2	Dube et al. [10]	84/Male	Bone (tibia)	Steel plate	26	DOD 4 months
3	Wallnofer et al. [37]	59/Male	Aorta	Plastic graft	3	?
4	Fehrenbacher et al. [11]	79/Male	Aorta	Dacron graft	12	DOD 7 months
5	Hayman et al. [13]	84/Male	Chest wall	Shrapnel	63	DOD 2 years
6	Moncure et al. [26]	?	Aorta	Dacron graft	63	?
7	Jennings et al. [15]	79/Male	Thigh	Bullet	54	DOD 3 months
8	Jennings et al. [15]	70/Female	Peritoneum	Sponge	20	DOD 2 months
9	Jennings et al. [15]	64/Female	Bone (tibia)	Bone wax	20	DOD 11 months
10	Beer et al. [15]	28/Male	Soft tissue (knee)	Bone graft[a]	9	?
11	Ben-Izhak et al. [3]	70/Female	Colon	Sponge	25	DOD 2 months
12	Weiss et al. [38]	?	Aorta	Dacron graft	?	?
13	Schneider et al. [33]	?/Male	Leg	Shrapnel	46	DOD 6 weeks
14	Ben-Izhak et al. [4]	71/Male	Iliac artery	Dacron graft	8	DOD 6 months
15	Meis-Kindblom et al. [25]	?	Iliac artery	Dacron graft	?	?
16	Meis-Kindblom et al. [25]	?	Popliteal bypass	Dacron graft	?	?
17	Current case	67/Male	Splenic capsule	Sponge	38	DOD 2 weeks

[a]Autologous bone graft

7 months to 30 months in previous rat experiments [29]. Some authors stress the importance of fibrous encapsulation of the chemically inert implant, following the initial granulation tissue response [15]. Free radicals generated by reactive foreign body macrophages during the acute stage of the foreign body reaction could damage the DNA of surrounding stem cells, creating clonal preneoplastic cells [7, 23]. It is hypothesized that an abnormal clone of mesenchymal stem cells is allowed to proliferate in the relatively quiescent microenvironment provided by the fibrous capsule, not hampered by the potent chemical mediators and active phagocytosis accompanying the more active chronic inflammation seen in response to less inert substances [7, 15].

Further data from animal models seem to support this hypothesis [17, 18, 36]. There is a significant increase in the incidence of tumors if sarcomatous cells are subcutaneously transplanted to mice as a suspension into the capsules around previously implanted foreign material, relative to transplantation into normal tissue [36]. There appears to be a substantial reduction in tumor formation on subcutaneously implanted porous polyethylene pieces after surface modification with collagen immobilization through covalent binding [17].

While the formation of a fibrous capsule surrounding an inert foreign body might be a critical event in this particular form of tumorigenesis, it is apparent from the literature that a more active, chronic inflammatory process, such as chronic tuberculous pyothorax, long-standing venous ulcer, or recurrent rectal ulcer, can lapse into a so-called 'granulation tissue sarcoma' [1, 9, 21]. Experimental studies with transgenic mice expressing the v-jun gene show uncontrollable granulation tissue formation and sarcomatous transformation in wound healing, providing a molecular basis for this mind-boggling phenomenon [34].

Whatever the mechanism, several case reports and limited series attest to the fact that this inert foreign body tumorigenesis is indeed operative in humans as well [5, 6]. Sixteen cases of foreign body-associated angiosarcoma have been described, arising at different sites and in relation to many different substances (Table 1). We believe that the clinical, radiological, and gross features of the tumor described herein add to the validity of the concept of a solid-state mechanism of carcinogenesis. Two consecutive CT scans, taken with a 3-week interval, create an intriguing “dynamic” impression of tumor progression, with spreading of the tumor along the splenic capsule. Judging from the initial CT scan, this angiosarcoma apparently originated at the lower pole of the spleen in close topographical association with the gauze sponge.

Since most of the foreign body-associated angiosarcomas have been claimed to develop from the capsule surrounding the implant [3, 15], this same reasoning could be followed in the tumor under consideration, with secondary involvement of the splenic capsule by a neoplastic process originating in the fibrous tissue surrounding the gauze sponge.

In summary, we report on an epithelioid angiosarcoma involving the splenic capsule, thereby mimicking mesothelioma. The close topographical association with a gauze sponge retained for many years strongly points to a solid-state mechanism of histogenesis, given the rarity of malignant vascular tumors of the serosal membranes. This case report reemphasizes the importance of histological examination of all foreign body-related tissue upon removal.

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