NOWOTWORY Journal of Oncology • 2006 • volume 56
Number 3 • 270–274

Spindle cell carcinoma of the esophagus

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Introduction. Spindle cell carcinoma of the esophagus is a rare malignancy with obscure and controversial histogenesis. These tumors constitute approximately 1%-2% of all esophageal neoplasms, with approx. 200 cases documented in literature. This is the first report concerning this unusual, both carcinomatous and sarcomatous malignant tumour, published in Poland. The aim of this paper is to clarify the histogenesis and the present clinical, morphological and immunohistochemical characteristics of spindle cell carcinoma of the esophagus.
Materials and methods. We present the cases of two patients with esophageal tumors. including endoscopic, histological and immunohistochemical results.
Results. Histologically, in case I, the tumour consisted of two components, malignant spindle cells with no specific differentiation and islands of well-differentiated squamous carcinoma. A gradual transition between the sarcomatous and carcinomatous elements was found. Regional lymph nodes were metastatically involved and demonstrated both carcinoma and spindle cell components. In case II, the sarcomatous component resembled malignant fibrous histiocytoma intermingled with poorly differentiated squamous carcinoma. Regional lymph nodes were uninvolved. The spindle cells of the tumors were positive for vimentin and negative for cytokeratin. The squamous carcinoma cells were immunoreactive for cytokeratin and negative for vimentin. The tumor cells in the transitional zone between the carcinomatous and sarcomatous elements were positive for vimentin and cytokeratin. The nodal metastases in case I were positive for vimentin in the spindle cell component and positive for cytokeratin in the carcinoma component.
Conclusion. In terms of the histogenesis of carcinosarcoma of the esophagus, there has been a controversy over whether the sarcomatous component consists of malignant non-epithelial cells or of a morphological variation of carcinoma cells. The histological and immunohistochemical findings of these two neoplasms and ultrastructural, DNA flow-cytometry and molecular findings presented in other studies suggest that the spindle cells component of these tumors is epithelial in orgin.

Key words: carcinosarcoma, spindle cell carcinoma, pseudosarcomatous carcinoma, pseudosarcoma

Introduction

The tumour referred to as carcinosarcoma of the esophagus is currently called spindle cell (squamous) carcinoma in accordance with most recent World Health Organization (WHO) classification [1].

Spindle cell carcinoma of the esophagus is a malignant tumor consisting of both carcinomatous and sarcomatous components. These tumors constitute approximately 1%-2% of all esophageal neoplasms. In the world literature around 200 cases have been documented, most of them by Japanese authors [2-12].

More than 17 different terms have been applied to this intriguing neoplasm. It has been described under the names of carcinosarcoma, pseudosarcoma, so-called carcinosarcoma, so-called pseudosarcoma, metaplastic carcinoma, carcinoma with sarcomatoid change, polypoid carcinoma, pseudosarcomatous carcinoma, spindle cell carcinoma, true carcinosarcoma. There is evidence that tumors described under different names were morphologically and clinically the same entity [13-14]. The confusing terminology bases on the uncertainty of the histogenesis of this tumor or, to be exact, on its spindle cell component. Three theories have been discussed in the literature. Explanations of the origin of this component include (1) reactive mesenchymal response to carcinoma, (2) metaplastic spindle cell carcinoma, (3) sarcoma mixed with carcinoma (collision tumor). Recent immunohistochemical, ultrastructural, DNA flow-cytometry and genetic studies support the metaplastic hypothesis.

In this paper we present two cases of spindle cell carcinoma of the esophagus – the first to be reported in Polish literature, discuss the histogenesis of the neoplasm and review world literature.

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Case Reports

Clinical History

Case I

A 60-year old man was admitted to our hospital in July 2002 with a history of dysphagia and weight loss. Esophagoscopy showed a polypoid tumor, 35 cm from the incisors. Biopsy was performed revealing poorly differentiated squamous cell carcinoma. There was no CT evidence of enlarged mediastinal lymph nodesand subtotal esophagectomy with regional lymphadenectomy was performed. In the postoperational course a subdiaphragmal abscess was drained surgically. CT examination performed 4 months later showed enlarged mediastinal and abdominal lymph nodes. The patient died 2 months later.

Case II

A 55-year old man consulted his family doctor due to progressive dysphagia and slight weight loss. Endoscopic examination showed a polypoid tumor in the mid- and lower third of the esophagus, 38 cm from the incisors. The patient was referred to the M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw in August 2001. CT examination showed enlarged lymph nodes in the mediastinum and subtotal esophagectomy with lymphadenectomy was performed. The post-operative course was uneventful. 21 months after surgery hepatic and retroperitoneal lymph node metastases were detected in the course of diagnostic imaging. The patient died 3 months later.

Pathological Findings

The resected specimens were fixed in 10% formalin and paraffin embedded sections were hematoxylin-eosine stained. The immunohistochemical reactions were performed with antibodies to: cytokeratin CKAE1/AE3, vimentin, TP53, MIB1, chromogranin, synaptophisin (DAKO).

Grossly, both tumors were polypoid (type1) 6 cm and 2.5 cm in diameter, respectively. The cut surface was gray and, in case I, we also detected extensive necrosis and haemorrhage. Microscopically, the tumors showed an infiltrating malignant neoplasm with biphasic pattern including areas of carcinoma, as well as areas of spindle cells with malignant appearance. In case I poorly differentiated squamous cell carcinoma infiltrated deeply into the adventitia and also serosa of the cardia. At the upper part of the tumor there was a sarcomatous component, with a lot of bizarre, multinucleated cells, resembling malignant fibrous histiocytoma [Figure 1]. Intraepithelial carcinoma was found focally on the surface of the tumor [Figure 2]. In case II, the sarcomatous component consisted of sheets of malignant spindle cells with no specific differentiation discerned in the upper-central part of the tumor. The invasive carcinomatous component at the base of the tumor was poorly differentiated, with small nests of glandular differentiation consisting of small, rounded, monomorphic cells [Figure 3]. The squamous cell carcinoma invaded the muscle layer, but not the adventitia. A transitional zone between the sarcomatous and carcinomatous components was observed [Figure 4].

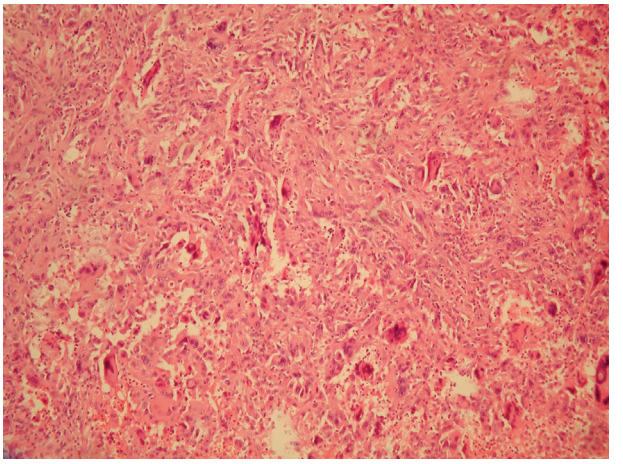

Figure 1. H&E. Case I – Sarcomatous component resembling MFH

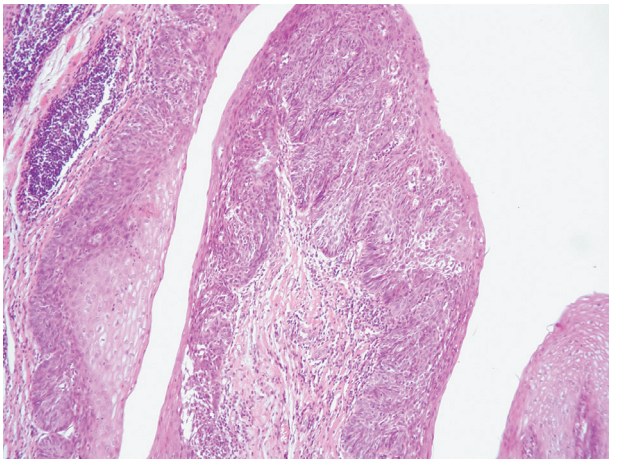

Figure 2. H&E. Case I – Squamous cell carcinoma in situ

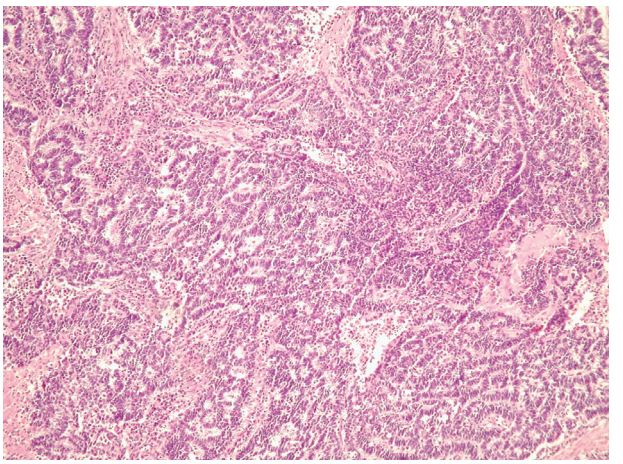

Figure 3. H&E. Case II – Glandular differentiation in the epithelial component

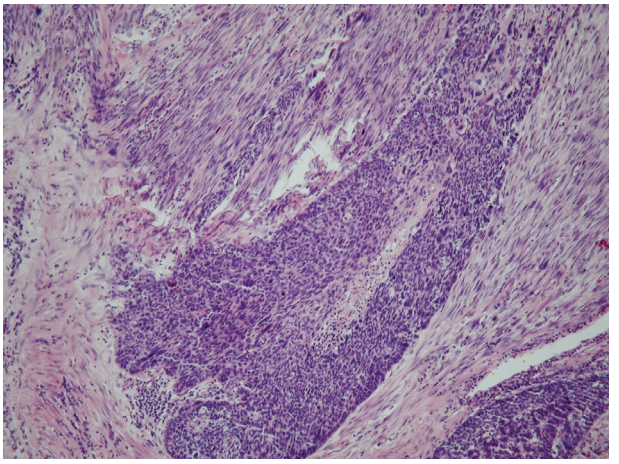

Figure 4. H&E. Transitional area between carcinomatous and spindle cell components

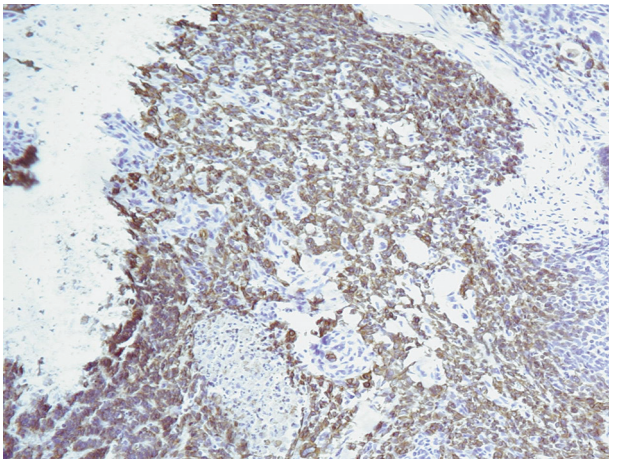

Figure 5. Immunohistochemical positive reaction for keratin in both carcinoma cell and spindle cell areas

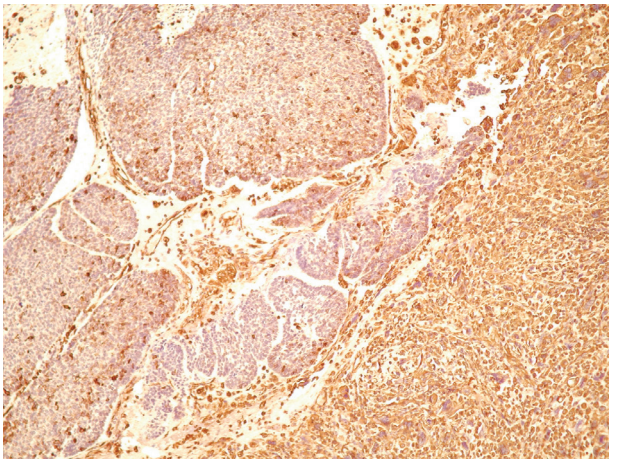

Figure 6. Immunohistochemical positive reaction for vimentin in canceromatous and spindle cell components

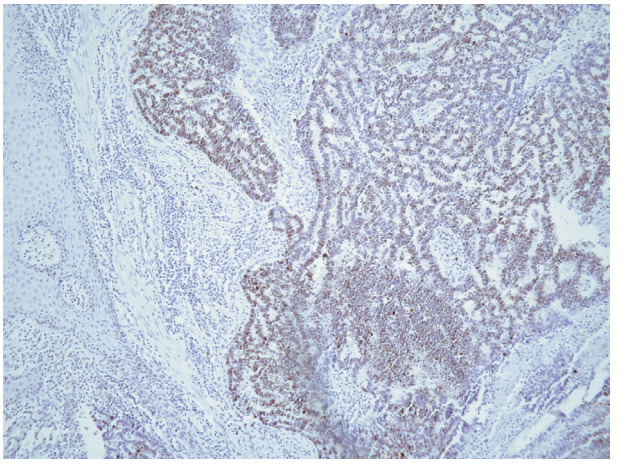

Figure 7. MIB1 – immunohistochemical positive reaction in the most of carcinomatous cells

Metastases of both components were found in regional lymph nodes.

Immunohistochemically, positive strong staining for cytokeratin was detected in both tumors within the carcinomatous component and within most spindle cells [Figure 5]. The sarcomatous components and some carcinomatous cells were positive for vimentin [Figure 6]. In the transitional zone some cells showed positive staining for both cytokeratin and vimentin. The similar strong positive pattern of p53 protein expression was found within the two tumor cells types. MIB1 positive cells were more frequent within the squamous cell carcinoma, as compared to the sarcomatous area [Figure 7]. In case II, the adenocarcinoma cells showed strong cytokeratin antigen expression but did not expressed neuroendocrine markers.

Discussion

Carcinosarcoma of the esophagus is a rare malignant tumor most common in men above fifty. Grossly, it is characterized as a polypoid mass in the mid- or lower third of the esophagus with infiltration usually limited to the esophageal wall. Earlier studies [15-16] have indicated better prognosis of carcinosarcoma possibly related to the polypoid nature and high resectability of this tumor. Iyomasa [17] has shown that there was no significant difference in 5-year survival rates between carcinoma and carcinosarcoma and the latter could be treated in the same way as ordinary squamous cell carcinoma. Histologically, in a majority of the reported cases of esophageal carcinosarcoma the epithelial component is squamous carcinoma, although some cases have contained adenocarcinoma [18-19]. The sarcomatous component usually consists of undifferentiated spindle cells, but occasionally it contains pleomorphic, bizarre cells resembling malignant fibrous histiocytoma [2, 4, 11]. In many cases there is a transitional zone between the carcinomatous and the sarcomatous components [5-9].

It was, in fact, Virchow who first applied the name *carinosarcoma* to this rare tumor in 1864 [20]. In 1919 Meyer presented his hypothesis as to the origin of the tumor and proposed the concept of collision tumor, combination or composition tumor [21]. Stout, in 1949,

described the first surgically resected pedunculated esophageal carcinosarcoma [15].

Carcinosarcoma is a very controversial tumor, not only because of its nomenclature, but more importantly, because of the origin of the spindle cell component. Various theories have been described in the earliest papers – attempts to explain the sarcomatous component. The first hypothesis of the origin of spindle cells was directly related to the tumors described by Lane (1957) [16], who had presented similar polypoid tumors in other localizations – mouth, fauces and larynx and called them pseudosarcoma. The term meant that sarcomatous-looking tissue is not neoplastic and does not metastasize, but rather it is an atypical, reactive mesenchymal response to the carcinoma. This theory has been laid asides because the malignant nature of the mesenchymal element has been clearly indicated by the presence of its deep invasion of the esophageal wall and its possible metastasizing. From a morphologic standpoint it has been stated by some authors that in *pseudosarcoma*, the carcinomatous and sarcomatous-looking element was juxtaposed to the intimate intermingling of both the epithelial and the mesenchymal elements seen in carcinosarcoma. In 1973 Ming [22] emphasized the difficulty of differentiating pseudosarcoma and carcinosarcoma according to the proposed morphologic criteria and he preferred to regard all these tumours as carcinosarcomas. Matsusaka (1976) [2] described 3 cases of similar tumors of the esophagus and compared the cases reported as pseudosarcoma with those reported as carcinosarcoma finding no substantial differences in their clinicopathologic features. It meant that pseudosarcoma and carcinosarcoma are the same entities and the carcinomatous component is associated with both spindle cell transformation and with reactive or desmoplastic change of stroma. A second theory suggested that the spindle cells were metaplastic epithelial cells which had assumed mesenchymal characteristics. Electron microscopic and immunohistochemical studies have suggested that the spindle cells may be epithelial in origin. Electron microscopic examinations performed by Lichtinger (1970) and Shields (1972) [23] have shown the presence of keratohyline, tonofilaments, desmosoms and premelanosomes in the sarcomatous component of pseudosarcomas. Earlier, some authors have asserted the probable transformation or spindle cell metaplasia of carcinoma cells (Krompecher 1900 [24], Martin and Steward 1935 [25], Saphir and Vass 1938 [26]). Besides, negative keratin staining in the spindle cells may not exclude the possibility of epithelial derivation. Gal (1987) [27] has suggested that the important variable in determining the origin of the cells is the level of keratin production by the neoplastic spindle cells; minimal keratin production may not be detected by current immunohistochemical methods. Finally, the cross-linking of keratin antibodies by formalin fixation may result in false negative staining while the positive staining for vimentin in spindle cells does not remain in conflict with the metaplastic hypothesis. Although vimentin was initially believed to be restricted to mesenchymal cells, later studies have demonstrated that it may be found in a large number of epithelial tumors. Therefore, the vimentin-positive and keratin-negative cells would represent metaplastic epithelial cells that have lost the ability to synthesize keratin. The immunohistochemical and ultrastructural studies reported by other authors suggestthe epithelial origin of the spindle cell component (Battifora 1976 [28], Takubo 1982 [29], Kuhajda 1983 [30], Hanada 1984 [3], Ooi 1986 [4], Ellis 1987) [31]. This is akin to the so-called divergence (monoclonal) hypothesis of carcinosarcoma genesis, which suggests that a single totipotential steam cell differentiates along separate epithelial and mesenchymal lines. The third theory includes the tumors representing collision tumors from independent malignant clones. This convergence (multipotential) hypothesis suggests that two, or more, stem cells give rise to the different lines of differentiation. This hypothesis referred to tumors called true carcinosarcoma which we have described further in this paper.

Further studies on the histogenesis of carcinosarcoma are based on genetic (clonality) and DNA flow-cytometric analysis. Lauwers (1998) [32] and Natsugoe (1999) [9] have shown that the sarcomatoid component was aneuploid, while, in contrast, the carcinomatous component was diploid. Lauwers concluded that in esophageal spindle cell carcinoma the sarcoma-like phenotype differs biologically in two ways from the carcinomatous: (1) it has higher TPI, and (2) it has higher aneuploidy with a greater dispersion of the DNA content. These findings explain the predominance of the sarcoma – like component over the carcinomatous component. Kashiwabara (2001) [11] and Handra-Luca (2001) [33] have analyzed p53 protein expression and shown that a similar pattern in the two tumors cell types of the spindle cell carcinoma suggests their common origin. Further molecular analysis performed by Kashiwabara has revealed that two components had the same somatic mutation in the p53 gene, thus suggesting a monoclonal origin of this biphasic tumor. In the most recent study Matsumoto (2004) [12] has analyzed the allelic status with 25 microsatellite markers on chromosomal arms 3p, 5p, 6q, 8p, 9p, 13q, 17p and 18q. In all 6 cases he found multiple and homogenous allelic losses in both components, strongly supporting the concept of monoclonal origin of the neoplasm.

There remain a few reported cases in which the sarcomatous component has shown undisputed specific mesenchymal differentiation, thus verifying the designation of true carcinosarcoma. In these collision tumors the sarcomatous component has shown specific differentiation towards rhabdomyosarcoma, leiomyosarcoma, osteosarcoma, chondrosarcoma or malignant fibrous histiocytoma. Iwaya (1997) [6] described an esophageal tumor, in which the clonal differences between its carcinomatous and sarcomatous components were genetically and immunohistochemically demonstrated. Losses of heterozygosity (LOH) at D6S265 and D17S929 were detected only in the carcinomatous

component, whereas LOH at D9S176 was confirmed only in the sarcomatous element. These differences suggest that the tumor composed of squamous cell carcinoma and leiomyosarcoma originated separately from epithelial and mesenchymal precursors. However, the transitional zone was observed between the carcinomatous and sarcomatous elements and this tumor was initially diagnosed as the so-called carcinosarcoma according to the criteria of the Japanese Society for Esophageal Disease. Numerous other papers have presented cases defined as carcinosarcoma with definite differentiation towards rhabdomyosarcoma/osteosarcoma in the transitional area and, in some of them, praecancerous epithelial changes. Wang (1992) [5] has concluded that sarcomatous components with specific differentiation may also be involved in the metaplasia of carcinoma in its wide sense or in the disdifferentiation from carcinoma to sarcoma.

We agree with the report of Hanada (1984) [3], that the validity of rigid separation between the so-called carcinosarcoma and true carcinosarcoma is questionable. Genetic analysis remains an increasingly useful tool for the study of the clonality and the clarification of the histogenesis of these rare tumors is still a matter for investigations.

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Paper received: 6 December 2005
Accepted: 1 March 2006