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Prognostic factors in solitary fibrous tumors of the pleura

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ABSTRACT

Background: Solitary fibrous tumors of the pleura (SFTP) are rare neoplasms originating from submesothelial mesenchymal cells with fibroblastic differentiation. The clinical behavior of SFTPs is mostly benign; however, up to 20% of patients develop local recurrence and/or distant metastasis. Although different risk-stratification models have been described, definitive criteria to predict a malignant clinical course of SFTP are still lacking.

Methods: In a retrospective analysis at a single-institution, 25 patients with histologically proven SFTP were identified. Clinicopathologic and survival data were collected and pathologic sections reviewed. Different markers and risk-stratification models were correlated with disease- and overall-free survival by Kaplan–Meier analysis.

Results: Of 25 SFTP, 8 tumors (32%) were classified as malignant according to the World Health Organization criteria. Three patients (12%) developed recurrence. Cohort median follow-up was 28 mo, and median overall survival was 160 mo. Comparison of proliferation markers showed higher mitosis count per high-power field and *MIB*-1 labeling index (*MIB*) in malignant compared with nonmalignant SFTP. *MIB* was identified as a predictor for disease-free survival. Applying the previously reported classifications to categorize SFTP according to the probability to show malignant behavior, significant differences in disease-free survival were also present in our cohort.

Conclusions: In the present analysis of rare SFTP, previously proposed staging systems were applicable for prediction of disease-free survival. Independently of treatment, *MIB* was the only sole predictive marker. A prospective multi-institutional database could be helpful in establishing detailed predictive criteria in patients diagnosed with SFTP.

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1. Introduction

Solitary fibrous tumors of the pleura (SFTP) are relatively rare neoplasms originating from submesothelial mesenchymal cells with a fibroblastic differentiation [1,2]. SFTPs are equally diagnosed in both genders, and patients of all ages are affected with a peak in the sixth and seventh decade. Clinical presentation is rather unspecific, and tumors are often detected incidentally. Large tumors can present with paraneoplastic phenomena such as digital clubbing in up to 20% of patients [3,4]. Solitary fibrous tumors are mostly localized in the thoracic cavity but tumors with similar histomorphologic features have been described in many other localizations [5–8]. The main histopathologic features are hemangiopericytomatous branching vessels, a patternless architecture, and a variable amount of hyalinized stroma and cellularity. Myxoid change is common. Likewise, immunohistochemistry-based studies revealed an expression profile of certain markers (CD34 80%, CD99 70%, and B-cell lymphoma-2 [BCL-2] 30%) in the vast majority of SFTP [9]. Our present knowledge of the clinical course is mainly based on monocentric retrospective data with low-patient numbers. Approximately 1000 cases of SFTPs have been described in the literature [10–15]. The biological behavior of SFTs is mostly benign; however, about 15%–20% show malignant behavior with recurrence and distant metastasis [3,16]. Traditionally, it has been a challenge for the treating physician to predict the clinical course of SFTP, and there are no definitive prognostic criteria. Different risk-stratification models for SFTP have been proposed, and the most commonly applied and adopted in the World Health Organization (WHO) Classification for Pathology and Genetics of Tumors of the Lung, Pleura, Thymus, and Heart are the criteria by England *et al.*, who suggested specific pathologic features, such as high mitotic activity, high cellularity, necrosis, hemorrhage, and pleomorphism to determine whether an SFT is to be defined as malignant [3,4,17]. De Perrot *et al.* [18] used morphologic and histologic features to categorize SFTPs into five stages. Another risk-stratification model based on a scoring system was recently proposed by Tapias *et al.* [13], in which points are given for certain histologic and morphologic features to determine the risk for recurrence of disease.

In an attempt to further describe the clinical patterns of the rare SFTPs, we retrospectively reviewed 25 cases of SFTP in our institution, analyzed their clinicopathologic features, collected survival data, and correlated data with existing classification systems.

2. Materials and methods

Between January 2002 and January 2014, 27 patients with proven SFTP were treated at the Department of Thoracic Surgery of the University of Freiburg. Twenty-five patients were included in the study, two refused to participate. Patient charts were reviewed, and clinical data including age, sex, clinical presentation, tumor location, tumor size, radiologic features, surgical procedure, and extent of surgery were collected.

All pathologic slides were reviewed by a single pulmonary pathologist (A.C.) for the presence of pleomorphism, nuclear atypia, hypercellularity, necrosis or hemorrhage, and the count of mitosis per 10 high-power fields (HPFs). Immunohistochemical staining was also carried out under standardized conditions (Fig. 1). For histologic analysis, all tissues were fixed in buffered formalin and routinely processed to paraffin. For the immunohistochemistry, 2-μm-thick, paraffin-embedded tissue sections were mounted on coated glass slides, dewaxed, and rehydrated in xylol and graded alcohol. Heat-induced antigen retrieval was performed with citrate buffer (pH 6.0) at 105°C using a pressure cooker for 5 min for Ki-67 and for 2 min for CD34, BCL2, and vimentin. Samples were incubated for 30 min with the primary antibodies (monoclonal mouse anti–human BCL-2, 1:500 dilution, clone 124; Dako, monoclonal mouse anti–human CD34, 1:400 dilution, clone QBEnd 10; Dako, monoclonal mouse anti–human *MIB*-1 labeling index (*MIB*-1), 1:2000 dilution, clone *MIB*-1; Dako, and monoclonal mouse anti–human vimentin, 1:500 dilution, clone Vim 3B4; Dako). Visualization was done by alkaline phosphatase (REAL K5005, Dako, Hamburg, Germany). All staining procedures were performed on the Dako autostainer platform. For the scoring, protein expression was considered positive if specific cytoplasmic staining was detected for BCL-2, CD34, and vimentin and specific nuclear positivity was seen in case of *MIB*-1. Considering BCL-2, CD34, and vimentin, staining was evaluated semiquantitatively with 0 and/or "negative", if no expression was observed; 1 and/or "weak staining", if less than 30% of SFT cells were positive, 2 and/or "moderate staining", if 30%–60% of SFT cells were positive; and 3 and/or "strong staining", if more than 60% of SFT cells were positive.

For evaluation of the proliferation index measured by *MIB*-1, 100 tumor cells were counted five times. For statistical analysis, the mean value was applied. Pathologic slides were unavailable in two cases in which the data were acquired from the pathologic report.

Survival data were acquired from the clinical cancer registry of the Comprehensive Cancer Center Freiburg. Seven patients were not listed in the database and were contacted directly. Written informed consent was obtained from the latter.

The study was approved by our local ethics committee and registered in the German Registry for Clinical Trials (DRKS-ID: DRKS00006151).

Data were recorded in a database designed in Microsoft Office Excel (Microsoft, Redmond, WA), and GraphPad Prism 6.03 (GraphPad Software Inc, La Jolla, CA) was used for statistical analysis. The D'Agostino–Pearson omnibus normality test was performed. Normally distributed values were compared using the Student *t*-test. If the D'Agostino–Pearson omnibus normality test failed, the Mann–Whitney test was used. The log-rank test was used to perform univariate analysis. Results were considered significant if the *P* value was <0.05. Overall survival was defined by the time interval from surgery to death by any cause. Disease-free survival was defined as the time interval from surgery to tumor recurrence or death by any cause. Tumors were defined as malignant using the current WHO criteria based on the publication by England *et al.* [17].