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## **Late solitary bone metastasis of a primary pulmonary synovial sarcoma with SYT-SSX1 translocation type: case report with a long follow-up**

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## Late solitary bone metastasis of a primary pulmonary synovial sarcoma with SYT-SSX1 translocation type: case report with a long follow-up

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**Abstract** Primary synovial sarcoma outside its classical presentation in para-articular soft tissue of young patients is rare but regularly reported. One of the rarest primary locations is the lung. We describe a 73-year-old female patient who presented with a solitary malignant bone tumor 8 years after the resection of a lung neoplasm. The bone tumor was classified as an osteosarcoma and the lung tumor as an atypical carcinoid tumor at their first respective diagnostic work-ups. The resection of the affected humerus with allograft and endoprosthesis implantation followed. Reevaluation of the tumor samples at the time of the local recurrence of the bone tumor 6 years following the initial symptoms of the bone tumor lead to the reclassification of both specimens as synovial sarcomas. Both neoplasms contained the SYT-SSX1 type of the diagnostic translocation t(X;18) as detected by the reverse-transcription polymerase chain reaction analysis. The patient died 14 years after the resection of the primary synovial sarcoma of the lung and 6 years following the occurrence of the bone metastasis. This prolonged clinical course is uncommon for the SYT-SSX1 translocation, which, in other locations, is usually associated with an unfavorable prognosis.

**Keywords** Synovial sarcoma · Lung tumor · Bone metastasis · Gene translocation

### Introduction

Synovial sarcomas, which account for approximately 10% of all malignant soft-tissue tumors, arise most commonly in the para-articular tissues in adolescents and young adults [13, 25]. It has become increasingly apparent, however, that synovial sarcomas may arise in a wide variety of other sites, including head and neck, mediastinum, heart, kidney, prostate, esophagus and vulva, and that they also occur in elderly patients [6]. There are four different morphological subtypes of synovial sarcoma: biphasic, monophasic spindle cell type, monophasic glandular type and poorly differentiated. While the histological diagnosis of a classical biphasic subtype is usually not difficult, the other types may be confounded with many other entities, especially when presenting in an unusual clinical context. The identification of the specific cytogenetic alteration in form of a balanced translocation t(X;18) with fusion product between SYT and SSX genes allows reliable diagnosis and/or confirmation of the diagnosis of a synovial sarcoma [13]. The correct diagnosis leads to the institution of the proper treatment and the estimation of prognostic factors. Although at present, surgery is still the mainstay of the treatment of synovial sarcomas and although there are no specific adjuvant methods (except for the notion of better response to some chemotherapy regimes), the situation may change in the future. The results of molecular studies on the oncogenic mechanism of the SYT-SSX fusion product [10, 11, 20] and on the expression profiles of synovial sarcomas [1, 21] may possibly allow the development of tumor-specific medications with the best candidate targeted at present being epidermal growth factor receptor.

Spindle cell tumors of the lung fall into several prognostically and pathogenetically different categories, such as sarcomatous carcinomas, malignant mesotheliomas and sarcomas. Primary sarcomas of the lung are exceedingly rare and constitute about 0.1% of malignant lung tumors.

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Reports of primary synovial sarcomas of the lung and pleura began to appear with increasing frequency in recent years due to the potent diagnostic tools in the form of immunohistochemistry and molecular genetics [5, 12, 18].

We present an unusual case of a late solitary bone metastasis—at first erroneously diagnosed as an osteosarcoma—occurring 8 years after a resection of a primary pulmonary synovial sarcoma—at first erroneously diagnosed as an atypical carcinoid tumor—with confirmatory molecular analysis of the SYT-SSX translocation. Thanks to this examination, both tumors proved to represent manifestations of the same disease (monophasic synovial sarcoma), despite differing diagnoses in the preceding biopsies.

## Case report

A 73-year-old female patient presented in September 1995 with slowly progressive pain in her right shoulder and weight loss. Within few weeks, the intensity of the pain increased and was also present at night. Standard radiographs obtained in December 1996 demonstrated an extensive aggressive, osteolytic lesion in the proximal humerus (Fig. 1A). Scintigraphically, no other bone lesions were found. An incisional biopsy of the tumor was performed in January 1996. The histological diagnosis was consistent with small cell osteosarcoma. The thorough staging procedure revealed no other tumor manifestations, specifically no pulmonary or bone metastases. The patient rejected an amputation, and the transarticular resection of the proximal humerus with implantation of an allograft and endoprosthesis was performed in January 1996 without direct complications. The postoperative follow-up was uneventful, with satisfying healing and no metastases radiologically.

In March 1998, 2 years later, standard radiographs and computed tomography of the chest demonstrated small pulmonary nodules compatible with metastatic spread. The

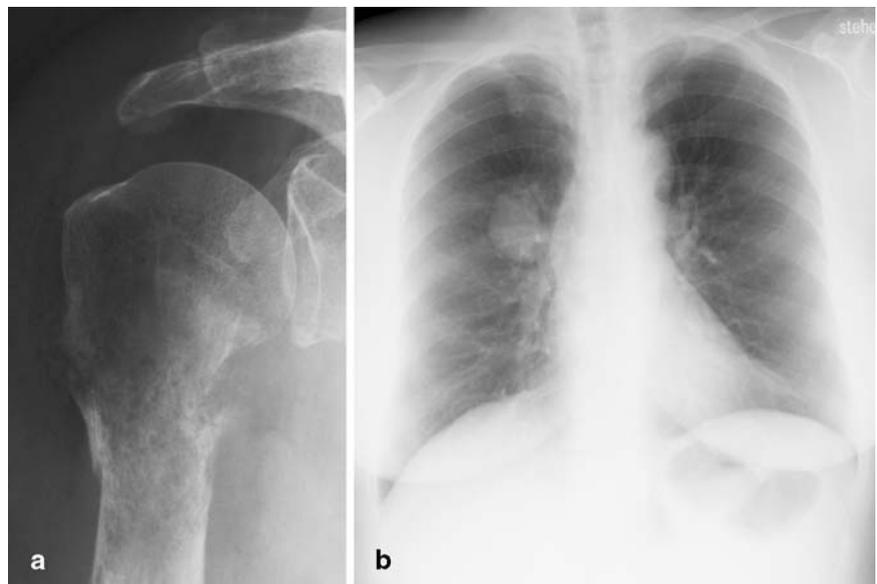
patient declined further diagnostic and therapeutic procedures, and radiological follow-up showed slow progression of the pulmonary findings. Local recurrence of the tumor in the right humerus in August 2000, 4 years after the resection of the proximal humerus, proved unresponsive to radiation therapy. An accelerated growth as well as development of exulcerated tumor necrosis prompted palliative resection in December 2001. The patient died within 1 week of postoperative cardiac complications, 14 years following the resection of the pulmonary primary tumor. The patient was a housewife, and her medical history was otherwise uneventful, except for a remote history of a cholecystectomy, high blood pressure and slight aortic valve stenosis. No autopsy was performed.

At review, the tumor tissue resected in December 2001 as well as the previous histological specimens from this location were strongly suggestive of a monophasic spindle cell synovial sarcoma. The careful study of the patient file revealed the history of an operation of a lung tumor 8 years prior to the current onset of symptoms in the right shoulder (Fig. 1B) with the histological diagnosis of an atypical carcinoid tumor. At the time of the lung resection, no other tumor manifestations were found clinically and radiologically. The slides and paraffin blocks of this tumor could be recovered from another institution. The comparison of the morphology, immunohistochemical properties and the status of the t(X;18) proved identical tumor cell types morphologically and immunohistochemically with the same SYT-SSX1 translocation specific for synovial sarcoma.

## Materials and methods

Clinical information was obtained from the files of the medical facilities where the patient had been treated. The study was performed in accordance with the guidelines of the local ethics commission. Histological material from the lung and bone tumors was fixed in buffered 4% formalin

**Fig. 1** **A** Extensive osteolytic tumor in the metaphysis of the proximal right humerus (standard radiograph). **B** Proximally located lung tumor resected 8 years prior to the presentation of the bone lesion (standard radiograph)



and embedded in paraffin according to standard procedures. Sections (1–2  $\mu\text{m}$ ) were cut for conventional histology and immunohistochemistry. The following antibodies were used: pan-cytokeratin (1:250; Biomedicals AG, Augst, Switzerland), early membrane antigen (EMA, 1:20; Dako, Glostrup, Denmark), S100 (1:3000; Dako), CD34 (1:50; Serotec Ltd., Oxford, UK), synaptophysin (1:30; Dako), chromogranin (1:50; Dako), alpha-smooth-muscle actin (SMA) (1:20,000; Sigma, St. Louis, USA), desmin (1:20; Dako). Immunohistochemistry was performed on deparaffinized sections using the Ventana NexES automated staining system with diaminobenzidine as substrate. For antigen retrieval, slides were either enzymatically predigested or heated in citrate buffer for 3 min using a pressure cooker. Slides were counterstained with hemalaun. The quality of the reactions was controlled on tissue slides with known reaction patterns stained in parallel with the examined probes.

#### Reverse-transcription polymerase chain reaction

RNA extraction and reverse-transcription polymerase chain reaction (RT-PCR) analysis were performed as previously described [14]. For subtyping SYT-SSX fusion transcripts, 3  $\mu\text{l}$  of each PCR product was enzymatically hydrolyzed at 65°C for 1 h with 5 units of the restriction enzyme *TaqI* (Roche Diagnostics) in a final volume of 10  $\mu\text{l}$ . The digestion patterns of the PCR products were analyzed on 2% agarose gels and visualized using ethidium bromide staining. The size of digested products were 65 bp and 32 bp for the SYT-SSX1 fusion gene transcripts, but remained at 97 bp for SYT-SSX2.

Subtyping was determined in parallel by single-strand conformation polymorphism (SSCP) analysis. Aliquots of 5  $\mu\text{l}$  of PCR products were mixed with 5  $\mu\text{l}$  of denaturing buffer (0.1 M NaOH and 2 mM ethylenediaminetetraacetate), heated at 50°C for 10 min. After addition of 1  $\mu\text{l}$  of formamide dye, the samples were immediately loaded

onto a 40% mutation detection enhancement (MDE) gel (FMC BioProducts, Rockland, Maine USA) and electrophoresed in 0.5 $\times$ Tris–borate–EDTA (TBE) buffer at 20°C and 300 V (20 V/cm) for 5 h. The gels were stained with a SYBR Gold gel stain (Molecular Probes, Eugene, OR, USA) diluted 1:10,000 in 1 $\times$ TBE buffer and visualized under ultraviolet light using a charge-coupled device camera.

## Results

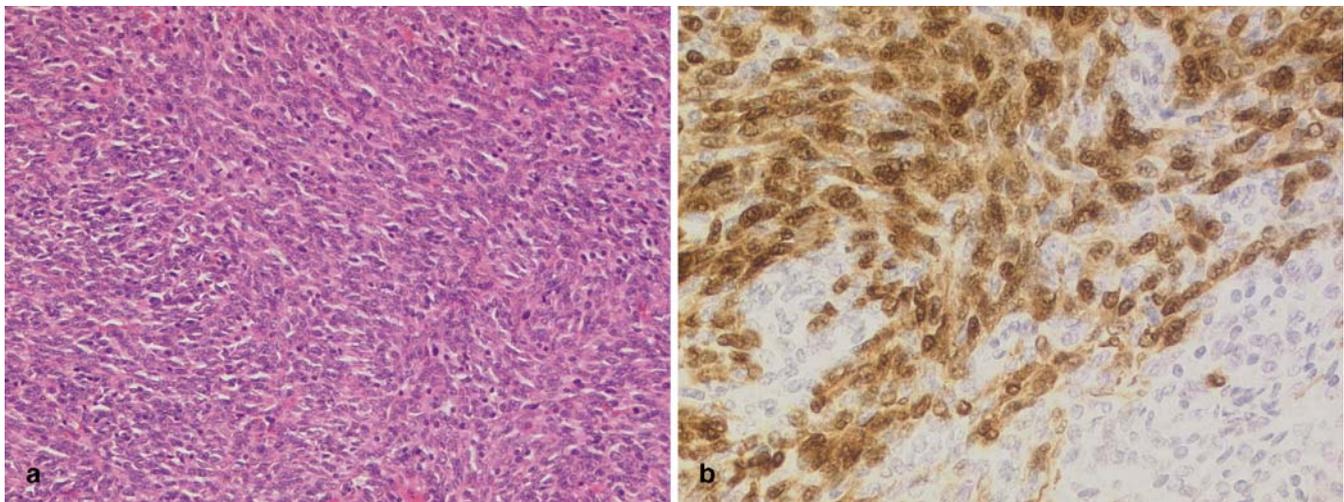
### Pathological findings

#### *Lung tumor (1987)*

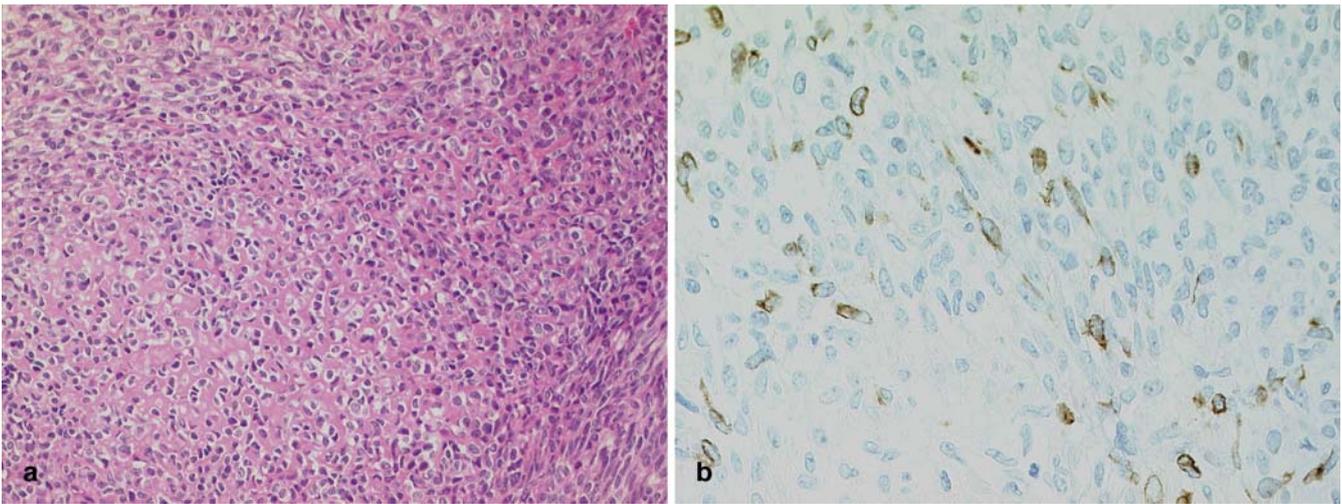
The resected right upper lobe contained a 3-cm whitish, well-circumscribed tumor mass in the vicinity of a proximal segmental bronchus without infiltration of the mucosa. Microscopically, the tumor consisted of plump, oval and spindle cells densely packed, partially infiltrating the outer bronchial wall (Fig. 2A). Focally, a trabecular pattern was found. The mitotic activity was 12 mitoses per 10 high power fields. No necrosis or lymph-node metastases were found.

#### *Bone tumor (1996 and 2001)*

The incisional biopsy contained hypercellular tumor tissue consisting of closely packed plump spindle and oval cells with scant cytoplasm, indistinct cell borders, arranged in irregularly intersecting fascicles or in a haphazard fashion. There were some variably ramifying and gaping, thin-walled vascular channels with a hemangiopericytoma-like appearance. Small foci of ossification (Fig. 3A) were present. Mitotic figures were easily found. The resected proximal humerus contained a large tumor mass with a longitudinal diameter of 8 cm, destroying the cortical bone



**Fig. 2** Lung tumor. **A** Plump, relative monomorph spindle cells (hematoxylin and eosin  $\times 10$ ). **B** Intracytoplasmatic and nuclear expression of S100 protein ( $\times 20$ )

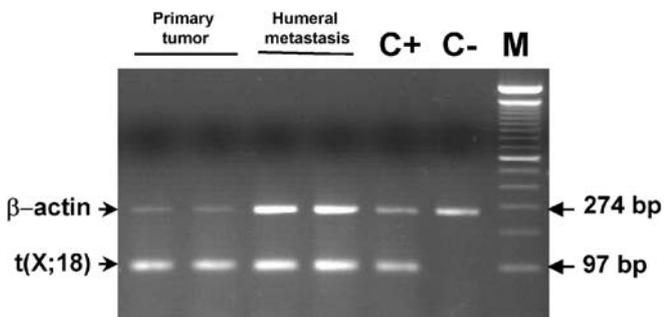


**Fig. 3** Humerus tumor. **A** Spindle and oval tumor cells with focal osteoid production (hematoxylin and eosin  $\times 200$ ). **B** Expressin of cytokeratin by individual tumor cells ( $\times 400$ )

and minimally infiltrating the adjacent soft tissue. The tumor tissue was similar to the biopsy material, but areas with matrix hyalinization and slender spindle cells were more prominent. No tumor necrosis except for the biopsy site was noted. The recurrent tumor following radiotherapy was partially necrotic, showing high mitotic activity and somewhat stronger pleomorphism.

#### Immunohistochemistry

The lung tumor was negative for cytokeratin, EMA, synaptophysin, chromogranin and showed focal positivity for S100 (Fig. 2B). Contrary to the biopsy and resection material of the bone tumor, the recurrence showed focal positivity for cytokeratin and EMA. Focal positivity for S100 was present in all bone tumor specimen (Fig. 3B). Other markers remained negative.



**Fig. 4** Detection of the t(X;18) (SYT-SSX) translocation in the primary lung tumor (lanes 1 and 2), in the humeral metastasis (lanes 3 and 4), using reverse-transcription polymerase chain reaction (PCR). For each sample, two PCR amplifications were performed in parallel, both containing the primer set necessary for the amplification of SYT-SSX fusion gene transcripts and a set of primers for the ubiquitously expressed  $\beta$ -actin gene transcripts (positive control). A biphasic synovial sarcoma was used as a positive control (lane 5) for the t(X;18) detection. Negative control consisted of t(X;18)-negative desmoid tumor. Lane 7 pGEM DNA size markers (Promega Madison, WI)

#### RT-PCR for SYT-SSX translocation

SYT-SSX fusion transcripts were detected in both primary lung tumor and humeral metastasis. Subtyping using SSCP showed that both were of SYT-SSX1 type (Fig. 4).

#### Discussion

The definition of synovial sarcoma has strikingly changed since its initial description in the beginning of the 20th century. Due to its commonly para-articular location, the tumor was initially falsely considered to originate from the synovial lining of joints. The most recent definition of synovial sarcoma includes the occurrence of a specific genetic abnormality [13]. After observation of the translocation between chromosome X and 18 in synovial sarcomas in 1986 [11], the fusion products of SYT-SSX with its variants -SSX1, -SSX2 and -SSX4 were described, depending on the SSX gene involved. The oncogenic potential of this gene is currently a subject of many studies [1, 10, 20, 21, 25]. The abnormalities mentioned above are specific to synovial sarcoma and are found in more than 95% of this tumor type with isolated reports on related cytogenetic abnormalities [23]. There are, at present, no convincing reports of its occurrence in other tumor types [4, 8, 14]. Thanks to the progress in molecular techniques, the detection of the fusion product is currently possible on standard pathological paraffin-embedded archive material [2, 4]. According to several reports, synovial sarcomas in unusual locations or in unusual clinical contexts have been previously diagnosed under various names, such as “classical” soft tissue fibrosarcoma for cases of monophasic fibrous synovial sarcoma [25] or embryonal sarcoma of the kidney for renal monophasic synovial sarcomas [3]. In our patient, the difficulty in classifying the lung neoplasia resulted in the diagnosis of an atypical carcinoid tumor.

We present a case where a synovial sarcoma was not considered as a diagnostic possibility either during the primary presentation in the lung or during the work-up of the solitary bone metastasis 8 years later. The examination of the local recurrence of the bone metastasis with review of all the slides and the molecular analysis of the SYT-SSX fusion product allowed the diagnosis of a primary lung synovial sarcoma. This tumor type is very rare, as the primary in the lung. Only about 50–60 cases (most of them monophasic spindle cell type and only two of the biphasic type) have been recorded in the English-language literature [5, 12, 16, 18, 22, 24]. This probably underestimates the prevalence of the disease, due to the diagnostic difficulties in differentiating among various spindle cell tumors of the lung. Many entities must be considered, namely sarcomatous carcinoma, malignant mesothelioma, spindle cell thymoma invading the lung, metastatic melanoma or—in women—metastatic malignant mixed Müllerian tumor and, of particular importance, metastatic sarcoma. Other primary sarcoma types also occurring in the lung must be taken into account, such as leiomyosarcoma, malignant peripheral nerve sheath tumor, solitary fibrous tumor, fibrosarcoma and mesenchymal chondrosarcoma. The eventual diagnosis of a spindle cell tumor of the lung depends in many cases on the results of the immunohistochemical reactions and—if the synovial sarcoma is a morphological consideration—on the molecular analysis.

Due to the small number of the described synovial sarcomas of the lung, the course of the disease is not yet fully known. There are only few reports with specific reference to the SYT-SSX translocation type [5, 16, 22, 24]. Patients with the SYT-SSX2 translocation, generally considered to have a relatively favorable outcome [17, 19], fared poorly and died within months. Most patients (including the patient described in the current study) with the SYT-SSX1 fusion product demonstrated a prolonged disease course with survival of up to 14 years, but a few died as early as at 12 months [16, 22, 24].

Synovial sarcoma in elderly patients is uncommon. Less than 10% of synovial sarcomas occur in patients over 60 years. Chan et al. [6] analyzed 32 patients older than 60 years with synovial sarcoma. They concluded that the tumors in this age group occur more often in unusual locations and have more often poorly differentiated morphology. Four of their cases were primaries of the lung, with none being metastatic at 36–48 months of follow-up.

The possibility of a primary bone synovial sarcoma presenting metachronously as lung tumor may theoretically be considered in our patient. However, the long time lag between both tumor presentations as well as the lacking clinical skeletal symptoms at the time of the lung resection make this possibility unlikely. Synovial sarcoma metastasizes predominantly hematogenously, most commonly to the lung (90–100% of the patients with metastases), followed by lymph nodes (<10%) and, in rare cases, by bone marrow [25]. At least two cases of a primary pulmonary sarcoma have been reported as metastatic to bone [16, 22]. A primary synovial sarcoma of bone is practically unknown. Hiraga [15] describes a radius tumor with mor-

phological properties of a synovial sarcoma and the t(X;18) translocation, but there is no mention of the past medical history of the patient, and the possibility of a late metastasis (as in our case) is not excluded. The tendency of the synovial sarcoma for late metastases is well known and is mirrored in marked differences between short- and long-term survival [25]. The case of Cohen [7] probably represents a classical presentation of a synovial sarcoma in the para-articular soft tissue of the knee of a 22-year-old man with secondary infiltration of the tibia. Because no radiological or pathological documentation is included, the topography of the tumor cannot be definitively estimated.

The necessity of molecular testing in every case of a synovial sarcoma has been discussed in the recent paper of Coindre [9]. The authors conclude that this examination is not required in every case. Diagnosing synovial sarcoma in its classical biphasic form and/or classical clinical presentation does not cause any difficulty. It is, however, more problematic in its more common, monophasic spindle cell variant or poorly differentiated type. Because, in many cases, the immunohistochemistry is not sufficient, the option of molecular testing represents a helpful alternative.

In conclusion, the presented case demonstrates that for the proper understanding of the natural course of some of the rare mesenchymal tumors, very long follow-ups must be taken into account. The possibility of molecular testing for the presence and type of the t(X;18) translocation is valuable in the differential diagnosis of spindle cell malignant tumors and allows precise classification of some of them. Its role for the prognosis of the primary pulmonary synovial sarcoma remains to be established.

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