

# Pleural synovial sarcoma patient treated with combined chemotherapy and Endostar, plus sunitinib maintenance therapy: A case report and review of the literature

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**Abstract.** Synovial sarcoma is a rare, highly malignant soft-tissue tumor that occurs primarily in the extremities. At present, there is no effective clinical treatment for this condition. The present study reports the case of a 49-year-old male who was diagnosed with pleural synovial sarcoma and treated with recombinant human endostatin (Endostar) combined with chemotherapy for a total of six cycles, followed by sunitinib maintenance therapy. To the best of our knowledge, this is the first reported use of sunitinib for maintenance therapy in pleural synovial sarcoma. The patient survived for 25 months after the recurrence of the disease following surgery. The results indicate that this combination therapy was effective in the treatment of pleural synovial sarcoma. The present study also briefly reviews the literature on pleural synovial sarcoma, and the features and treatments for this rare case are discussed.

## Introduction

Synovial sarcoma is a malignant tumor that accounts for 10% of all soft-tissue tumors (1). In total, <3 cases per million individuals are diagnosed each year. The disease can occur at any age, but is more common in teenagers and young adults. Despite its name, synovial sarcoma does not develop in the synovial tissues of the joints. The disease mostly presents in the extremities, particularly the periarticular regions.

However, synovial sarcoma is also found in the head and neck, mediastinum, heart, esophagus, lungs, abdominal wall, mesentery, forearms, thighs, and muscle and fascia of the waist and back (1-5). In 1996, Gaertner *et al* reported the first case of synovial sarcoma in the literature (3). The diagnosis of synovial sarcoma is difficult due to its rarity and the fact that its clinical and histological characteristics are similar to other spindle cell pleural tumors. Histopathology and/or immunohistochemistry investigations are essential to diagnose synovial sarcoma; the diagnosis in the present study was based on immunohistochemistry, but cytogenetics can be used to detect chromosomal translocations specific to synovial sarcoma, which aids in the confirmation of the diagnosis (2). Cytogenetic studies are useful for differential diagnosis. Chromosomal translocation (chromosome X or 18) is observed in >90% of synovial sarcomas and may be detected by the FISH method (fluorescence in-situ hybridization) w5x (2). In spite of its high sensitivity, the FISH method is not obligatory for the diagnosis, and it is indicated in cases of histological and immunohistochemical overlapping.

The main poor prognostic factors are complete resection, a tumor size >5 cm, the male gender, a high-grade tumor and an age of >20 years. The patient in the present study did not undergo a complete resection due to the presence of a giant tumor. These factors are likely reasons for the disease progressing in a relatively short period of time.

## Case report

A 49-year-old male was admitted on October 5 2010, to the Harbin Thoracic Hospital due to left-sided chest pain that had persisted for 1 month. Computed tomography (CT) chest scans showed bilateral pleural effusion. Between October 2010 and August 2011, the patient was treated with anti-inflammatory therapy 7 times for a duration of 2 weeks (penicillin, 4.5 mg, twice a day intravenous drops; quinolones, 100 ml, once per day intravenous drops) and underwent pleural drainage surgery, which caused a subsequent partial remission. The patient underwent an evacuation of a hematoma on April 28, 2011, as CT showed a huge low-density mass in the left pleural space (Fig. 1A-C). The histopathological specimen showed (left pleural) fibrous wall

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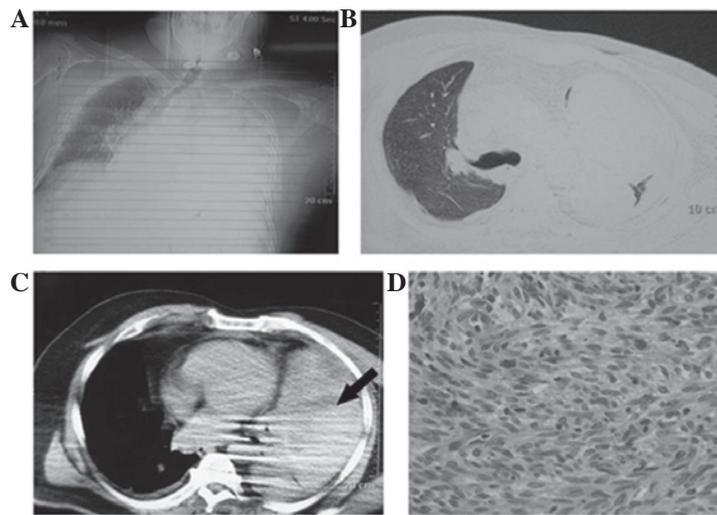


Figure 1. Pre-operative computed tomography showing (A) left lung atelectasis, (B) a patchy shadow in the lower lobe of the right lung and (C) an irregular soft-tissue shadow in the left side of the chest. (D) Specimen showing synovial sarcoma composed of spindle cells (H&E staining; magnification, x400).

tissue, with hemorrhage, necrosis, collagen degeneration and a diffuse spindle cell proliferative zone. Following morphological and immunohistochemical analysis, the patient was diagnosed with synovial sarcoma. The tumor cells exhibited immunohistochemical positivity for vimentin, epithelial membrane antigen and calponin, but negativity for S-100 and cluster of differentiation 34 (Fig. 1D). The patient's pain was relieved after the surgery and the follow-up chest CT showed that the mass was significantly reduced in size (Fig. 2A). The patient went home after the surgery on May 17, 2011, without further treatment.

After 2 months, a follow-up chest CT scan showed local recurrence (Fig. 2B). Between July 15, 2011, and September 23, 2011, the patient received four cycles of chemotherapy consisting of 7.5 mg/m<sup>2</sup> Endostar intravenous guttae (ivgtt) on days 1-14 and 1.0 g/m<sup>2</sup> ifosfamide ivgtt on days 1-6. During the treatment, the imaging evaluation was of a partial response (Fig. 2C). The main adverse effects of the treatment were grade IV nausea, vomiting and dizziness.

Between November 14, 2011, and February 2, 2012, due to chest pain and disease progression on chest CT (Fig. 2D), the patient was administered 3 cycles of chemotherapy (250 mg/m<sup>2</sup> pemetrexed ivgtt on days 1-8 and 7.5 mg/m<sup>2</sup> Endostar ivgtt on days 1-14). The subsequent therapeutic evaluation was of stable disease (Fig. 2E). On February 2, 2012, the patient began to receive sunitinib (375 mg/m<sup>2</sup>) as maintenance therapy. On July 23, 2013, the patient succumbed to respiratory and circulatory failure due to tumor progression.

## Discussion

In the present study, sunitinib was administered to the patient following combined treatment with chemotherapy and Endostar. To the best of our knowledge, this is the first reported use of sunitinib for maintenance therapy in pleural synovial sarcoma and it achieved a good curative effect. An imaging examination showed that the tumor size was significantly reduced and the patient's survival time was 25 months when the tumor recurred after surgery. The main adverse effects during treatment were hypertension and neutropenia.

Although the treatment was effective, the patient's quality of life was poor. From March 2012 onwards, the patient was unable to function independently due to chest pain. The sarcoma had a brittle texture, and as a result any careless action may have led to tumor rupture and severe pain. The experience of bleeding greatly affected the psychology of the patient, who became afraid and depressed due to the pain and had to use a Fentanyl transdermal system for a prolonged period of time, with a maximum dose of 134.4 mg. In April 2013, the patient accepted a nerve block and nerve ablation, but the procedures did not produce the desired therapeutic effect.

The incidence of pleural synovial sarcoma has been shown to be increasing and the most common therapy is a surgical resection (6,7), followed by chemotherapy. In general, synovial sarcomas are chemosensitive to ifosfamide and doxorubicin, but there is no established gold standard for the treatment of pleural synovial sarcoma. The rarity of synovial sarcoma means that there is no consensus on the role of chemotherapy in preventing metastases and improving survival.

However, antiangiogenic therapy in general shows promise for the treatment of malignancy, tumor invasion and metastasis of a number of different types of cancer. O'Reilly *et al* first identified endostatin in hemangioendothelioma cells as an antiangiogenic molecule (8). The targets of endostatin are the newly formed capillary endothelial cells, which are intimately associated with tumors (9). Endostar (YH-16) is a novel recombinant human endostatin, which has a broad spectrum of antiangiogenic activity; its mechanism of action is to stimulate the migration of endothelial cells by inhibiting the formation of blood vessels and tumor neovascularization, thus blocking the nutrient supply of the tumor, inhibiting tumor proliferation and metastasis. Endostar also exhibits anti-xenograft activity against human tumor cells (SPC2A4 lung cancer, SGC7901 gastric cancer, HeLa cervical cancer, and SMMC27721 and Bel7402 hepatoma cells). Endostar has also shown antitumor activity *in vitro* in a murine tumor model of broad-spectrum cancers (such as S180 sarcoma and H22 hepatocellular carcinoma cells).

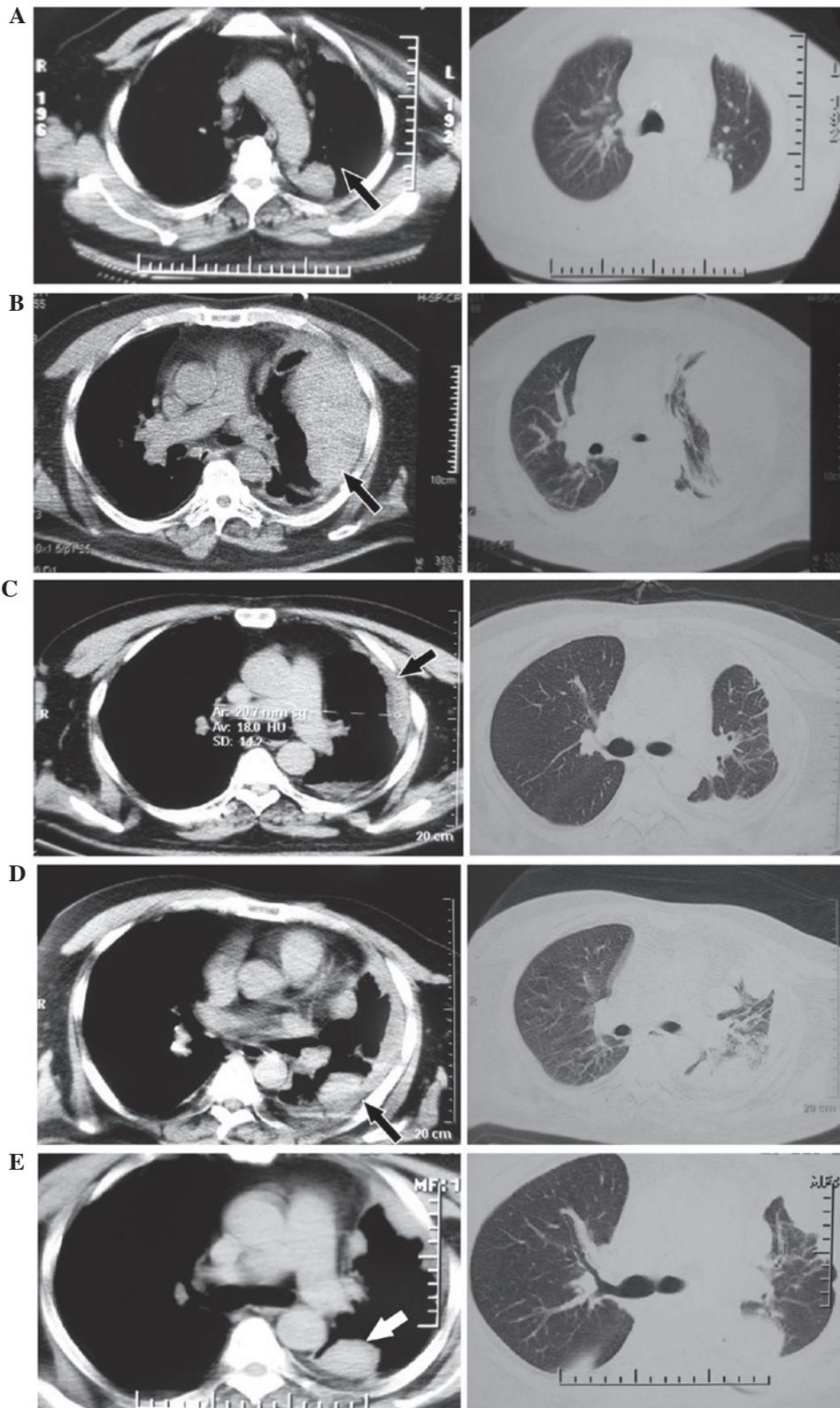


Figure 2. Chest (computed tomography) CT at the different stages of treatment. (A) Post-operative CT showing a significant reduction in the tumor mass. (B) Left pleural effusion, bilateral pleural thickening calcification, left huge pleural tumor formation. (C) After 4 cycles of Endostar + ifosfamide, the imaging evaluation was a partial response; left pleural fluid. (D) High-density shadows in the left mediastinum and pleural inner circular lesions characteristic of bilateral pulmonary infection (December 23, 2011). (E) The therapeutic evaluation after several cycles of Endostar + pemetrexed was of stable disease. Arrows indicate pleural tumor.

Sunitinib is an orally active tyrosine kinase inhibitor (TKI) that affects various signaling cascades involved in antiangiogenesis and tumor proliferation, including vascular endothelial

growth factors and platelet-derived growth factors. The drug is used in the first-line therapy of clear cell renal carcinoma and imatinib-resistant gastrointestinal stromal tumors, and

is also used to treat numerous other types of solid tumors, including breast, lung, prostatic and colorectal cancer (10-13). For example, the efficacy of the TKIs imatinib (Gleevec) and sunitinib (Sutent) in patients with advanced gastrointestinal stromal tumors (GISTs) has been demonstrated by observations in the clinic, a disease for which there were previously no highly effective treatment options for metastatic disease. There is a paucity of data in the literature regarding the role of sunitinib in synovial sarcoma, therefore the present study investigated its efficacy in synovial sarcoma. One previous report was located in the literature about a patient with synovial sarcoma, who also had a non-GIST and stable disease following 16 weeks of therapy with sunitinib (14).

In conclusion, it is worth considering using Endostar and targeted therapy following chemotherapy to optimize the treatment of pleural synovial sarcoma. Sunitinib can be used in pleural synovial sarcomas as maintenance therapy. The optimal dose and treatment time with Endostar and sunitinib remains to be established in clinical trials with more patients. Sunitinib is a useful practical adjuvant for the management of pleural synovial sarcomas.

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