Case Report

Spontaneous remission of a pulmonary sclerosing epithelioid fibrosarcoma: a case report of a possible abscopal effect

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Background: Spontaneous remission (SR) is defined as the complete or partial disappearance of a diagnosed malignant disease in the absence of known active medical treatment. The role of the immune system is thought to be important, but has not yet been elucidated. On this matter, there are studies that suggest that the abscopal effect (AE), which is defined as the remission of untreated lesions beyond the irradiated area, may be explained by the activation of a systemic immune response against the tumor. Sclerosing epithelioid fibrosarcoma (SEF) is a rare variant of soft tissue sarcoma that is characterized by a slow evolution, with local recurrences and late metastases. The treatment is based on surgery, leaving a minimal role to chemotherapy (ChT) and radiotherapy (RT) for metastatic unresectable disease, and no cases of SR have been reported in the literature so far.

Case Description: We present the case of a patient with a lung metastatic recurrence of SEF, diagnosed and treated with surgery 8 years before. After progression to pazopanib and other ChT drugs, because of the chest pain associated with a pleural mass invading the second costal arch, the patient received antalgic local RT treatment. Months later, and without any further treatment, a partial remission of all the tumoral lesions was presented, and she is alive 25 years after the first diagnosis.

Conclusions: As far as reported in the literature, this is the first case of SR in SEF. Among the possible causes of this SR, we think that the most plausible is that palliative treatment with RT of the pleural mass induced an AE, leading to a reduction of all tumoral lesions, even those outside the irradiated region.

Keywords: Sclerosing epithelioid fibrosarcoma (SEF); spontaneous remission (SR); abscopal effect (AE); case report

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Introduction

Spontaneous remission (SR) is defined as the complete or partial, temporary or permanent disappearance of a diagnosed malignant disease in the absence of medical treatment or therapy that does not adequately explain the resulting regression (1). Few cases of SR involving sarcomas have been reported, and none of these are of a sclerosing epithelioid fibrosarcoma (SEF), which is already an extremely rare subtype of sarcoma, and it is considered an orphan disease with not known effective options of systemic treatments (2).

We present the case of a patient who progressed to surgery, chemotherapy (ChT) and treatment with pazopanib. At last, she received palliative radiotherapy (RT) and, after an initial increase in the tumor's size, presented partial remission both in radiated and non-irradiated fields without receiving any specific treatment. We present this case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2276/rc).

Case presentation

This is the case of a 58-year-old woman who in January 2008, had an excision surgery of a 7-cm pleural mass that had been discovered during the perioperative assessment for anal fistula surgery. The initial diagnosis was a low-grade fibrotic pleural neoplasm. After surgery, the patient was followed by periodical chest computed tomography (CT).

A second surgery was performed in April 2012 for a pulmonary nodule of 9 mm in the lingula, with a pathological report of a fusocelular proliferation suggesting solitary fibrous tumor/hemangiopericytoma.

A third surgical intervention was performed in July 2016. A total of 7 pulmonary nodules (2 in the posterior segment of the left inferior lobe, 2 in the lateral segment of the left inferior lobe, 2 others of the sixth segment of the left inferior lobe, and one more in the pulmonary fissure) were resected. At this time, the positron emission tomography-CT (PET-CT) also showed affectation of the lymphatic nodules of the mediastinum (prevascular) that were biopsied during the same procedure. The final pathologic report informed of a low-grade fusocelular and epithelioid sarcoma, with diffuse positive immunostaining for MUC4 was detected (*Figure 1A-1C*). Vimentin and BCL-2 (focal) were also positive, and it was negative for other markers (CD34, STAT6, EMA, cytokeratin AE1/AE3, S100, CD31, CD99, SMA and desmin). Index proliferation was made with Ki67, ranging from 12% in the most proliferative areas to 2% in the sclerosing areas. FUS gene rearrangements were evaluated by fluorescence in situ hybridization (FISH) in our center with a negative result (*Figure 1D*) and confirmed by next-generation sequencing (NGS) in another reference hospital, where no FUS or EWRS1 fusions were detected. The diagnosis was consistent with SEF.

In a later chest CT, persistent disease was present in both lungs (more than 7 nodules), and added lymphatic nodes (para-aortic) were affected as well, finally after slow disease progression systemic treatment was initiated.

Between March and June 2017, she received six cycles of doxorubicin with stabilization of tumoral lesions. Then she started with pazopanib at an initial dose of 800 mg/day, which was later reduced to 600 mg/day due to diarrhea and palmo-plantar syndrome, persisting the stabilization of all the lesions.

The patient continued systemic treatment with pazopanib, until the gradual progression of the pulmonary lesions. Four months later, a second line with gemcitabine and dacarbazine was tried, receiving a total of nine cycles between October 2020 and February 2021 with no remarkable side effects. After new pulmonary progression, re-treatment with pazopanib was tried in an attempt to at least slow the progression of the disease. After searching and not finding any possible therapeutic target with NGS, we finally stopped pazopanib in January 2022.

Due to increasing pain in the right hemi-thorax and the lack of any other targeted therapy, the patient received RT in that area, a total of 5 sessions of 4 Gy (total dose of 20 Gy) was given in February of 2022.

Pain was controlled after RT. As the patient was clinically stable and asymptomatic, she was followed up with CT controls and no further ChT treatment. In the following images, the evolution of the main tumoral mass is shown (*Figure 2*). At first, one month after RT, it increased in size to be followed by a reduction of the mass (9 months after).

Highlight box

Key findings

- This is the first case reported in the literature of spontaneous remission in sclerosing epithelioid fibrosarcoma, and due to the observed abscopal effect, it leads to the question on what is the role of immune system in the pathogenesis of this malignancy.

What is known and what is new?

- Abscopal effect and spontaneous remission is an uncommon immunomodulated phenomenon in malignant tumors, and it is especially rare in sarcomas.
- Our case report is, as far as we know, the first case of spontaneous remission of an advanced sclerosing epithelioid fibrosarcoma, revealing a possible immunological mechanism that until now no one has described in this ultra-rare entity.

What is the implication, and what should change now?

- There have to be more studies about the role of the immune system in sclerosing epithelioid fibrosarcoma and other rare sarcomas, because with the development of different and newer immunotherapy molecules, these rare tumors are being left aside.

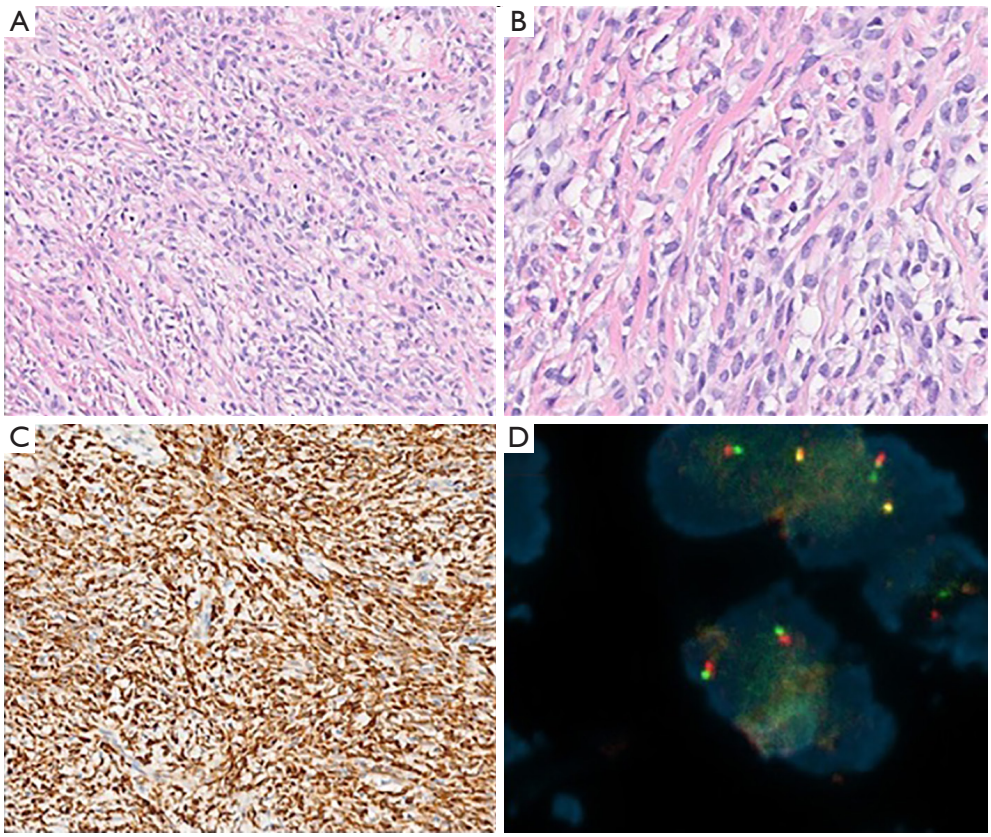

Figure 1 Histology and immunohistochemistry images from the tumor. (A) Proliferation of epithelioid monotonous population of mesenchymal cells with slight atypia and no evident mitotic activity. H&E 200×. (B) More magnification shows thick collagen bundles among tumor cells which are arranged in cords. H&E 400×. (C) Immunostaining diffusely positive for MUC4. 200×. (D) FISH probe for FUS gene. No translocation was identified (both signals are present and together). FISH, fluorescence in situ hybridization.

This reduction was observed in all the metastatic lesions, even in those that were not irradiated.

The patient does not mention any relevant infection recently or prior to the reduction of the lesions, although she mentions receiving a fourth dose of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination in May 2021.

A timeline scheme is shown in *Figure 3* to summarize the clinical evolution of this case.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Soft tissue sarcomas (STS) are a heterogeneous and complex group of mesenchymal tumors with low incidence. SEF is a very uncommon and aggressive subtype of fibroblastic differentiation that is characterized by a high tendency to relapse and metastasize, mainly pulmonary and pleural, in about 50% of cases (2). With a poor outcome despite its misleading low-aggressive histological appearance (3).

SEF is characterized by a proliferation of epithelioid cells arranged in nets or cords within a prominent collagen matrix and shows MUC4 immunoreactivity in 80% of cases (4). Staining for epithelial membrane antigen (EMA) can also be positive (ranging from 27% to 88%) and negative for cytokeratin AE1/AE3, CD34 and S100. It is frequent the presence of an EWSR1-CREB3L1 fusion, but rare cases with alternative fusions have also been

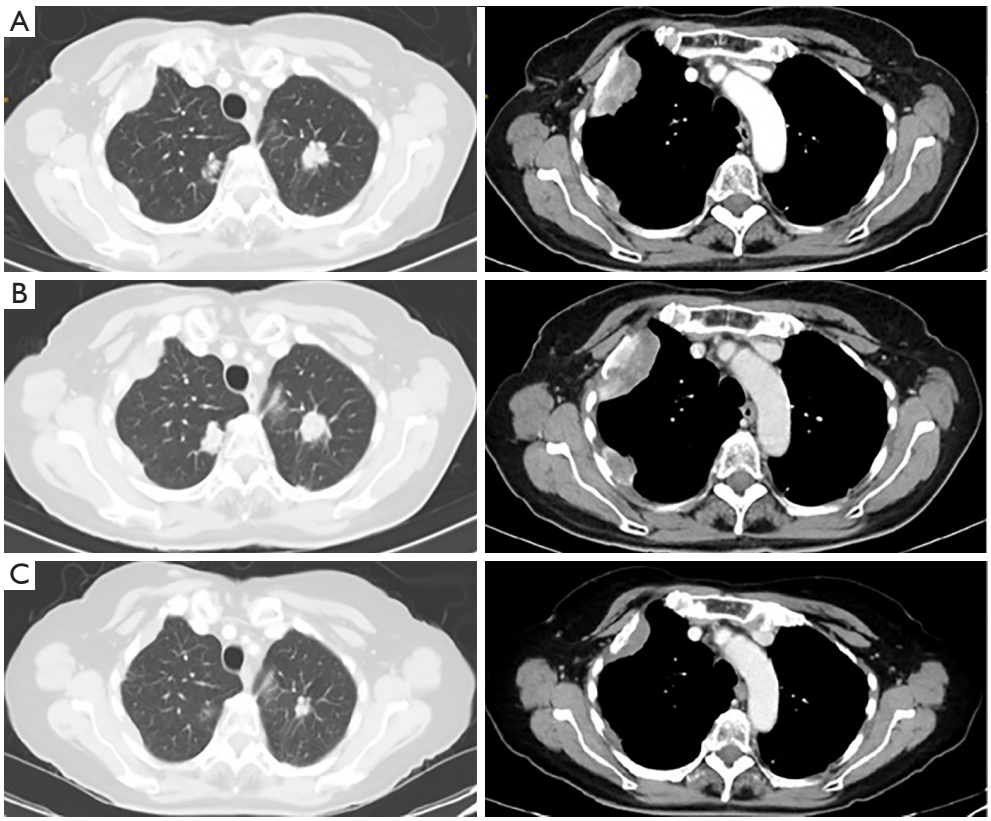

Figure 2 Radiological evolution of the lesions. (A) CT of 01/10/2021: 3 main nodules before RT (16 mm in the right pulmonary apex, 20 mm in the left pulmonary apex, and 5 cm × 2.2 cm 2nd costal arch invading pleural mass). (B) CT of 03/21/2022: evolution of tumoral lesions one month after RT (21 mm in the right pulmonary apex, 23 mm in the left pulmonary apex, and 5.7 cm × 2.5 cm 2nd costal arch invading pleural mass). (C) CT of 11/23/2022: evolution of tumoral lesions nine months after RT (15 mm in the right pulmonary apex, not measurable in the left pulmonary apex, and 13 mm 2nd costal arch invading pleural mass). CT, computed tomography; RT, radiotherapy.

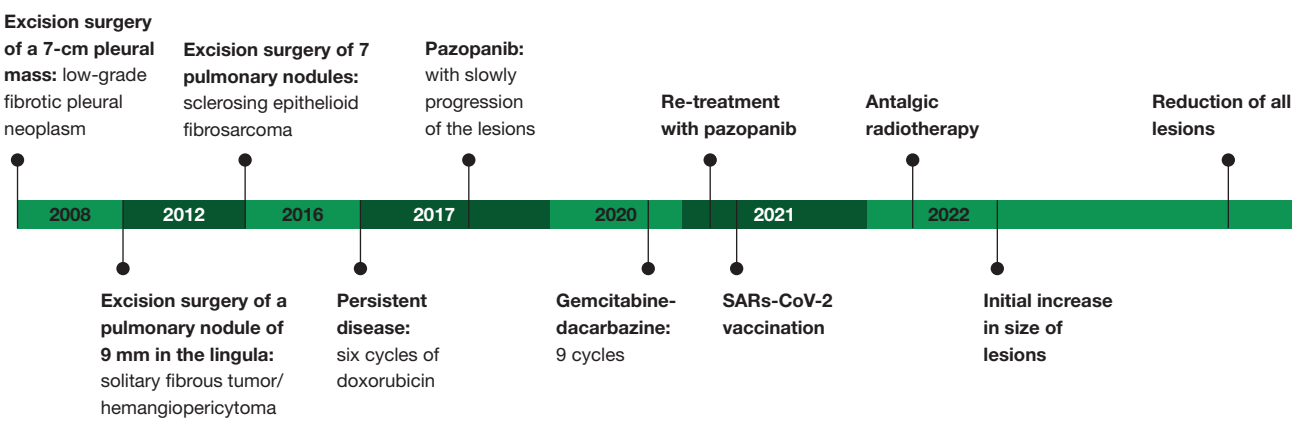

Figure 3 Timeline scheme showing previous surgeries and treatments received through the years.

reported, such as EWSR1-CREB3L2 and FUS-CREB3L2 transcripts (5,6).

Treatment is based on surgery, which must be as wide as possible. The efficacy of adjuvant therapy in the control of SEF is not yet demonstrated. ChT is used in cases of recurrence based on a combination of several molecules (1). Various agents, including single-agent doxorubicin, combinations of doxorubicin and ifosfamide, gemcitabine and docetaxel, and trabectedin have been tried, with mixed results. Immunotherapy (IO) for programmed death-ligand 1 (PD-L1) expressing tumors has also been tried, with significant regression rates (7). Pazopanib is a new treatment option for patients with metastatic non-adipocytic soft-tissue sarcoma after previous ChT (8).

Some authors support RT treatment, it has been reported in adjuvant context and without enough evidence to support its routine use, with high rates of recurrence. It is usually not considered in metastatic disease, leading to ChT being the main form of treatment (9,10).

SR is defined as the complete or partial, temporary or permanent disappearance of a diagnosed malignant disease in the absence of medical treatment or therapy that does not adequately explain the resulting regression (9).

A few cases have been reported of SR in STS; the most common is myeloid cutaneous sarcoma (with only 3 cases reported in the literature) and is associated with leukemia. About SEF, there have been no cases reported until now. In the few cases of SR in STS, authors support the role of the patient's immune system, due to the observed incidence of infections prior to SR that lead to high levels of diverse serum cytokeratins (11). In our patient, there were no infectious diseases that could lead to this specific explanation, but the SARs CoV-2 vaccination. There are few case reports about lymphoma remissions after bacterial or virus infections, including recently the SARs-CoV-2 infection, suggesting that the infection can trigger the immune system against the tumor cell. Although there is none associated with vaccination, there are no cases reported yet (12,13).

Another possibility could be an induced abscopal effect (AE). The AE is a systemic immune response mediated by the effects of radiation on the immune system and describes tumor regression even outside the irradiated region. It has been observed in a number of cancer types. RT can increase the immunogenicity of a tumor and therefore could be used to improve IO effectiveness, or vice versa (14). To stimulate AE, it is necessary to stimulate the recruitment and activation of antitumor cells, including CTLs and NK cells. It seems that the conventional RT dose of 1.8–2 Gy is not sufficient for immunogenic responses. Preclinical trials show that a dose of 8–12 Gy is more effective in inducing antitumor immunity compared to lower doses such as 15 or 20 Gy per fraction, which may even reduce AE, damaging tumor vascularity and reducing immune cells' infiltration. Studies combining IO with RT have been initiated utilizing anti-PD-1 or anti-CTLA4 drugs (15,16).

It is of interest to elucidate the role of the immune system in the treatment of different cancer types. To try to elucidate this, some inflammatory markers have been studied, including STS. In a study by Erdogan *et al.*, an early decrease of C-reactive protein (CRP), serum neutrophils and neutrophil-lymphocyte ratio (NLR) was significantly associated with tumor response in patients with STS (and renal cell carcinoma) treated with pazopanib (17). As well, patients with high NLR and other inflammatory indices, showed worse survival than patients with lower values, in a study conducted by Fausti *et al.* (18).

Immune checkpoint inhibitors (ICIs) have been studied in multiple cancer types, including STS. The low frequency of these tumors makes clinical trials difficult to achieve, and they tend to include subtypes even when they may have different aggressiveness and clinical evolution; therefore, conflicting results are usually obtained (19). About SEF, Doshi *et al.* presented two cases of patients with SEF treated with ICI, where both presented clinical benefit (one of them showed significant remission to nivolumab and ipilimumab combination and the other one to nivolumab monotherapy) (20).

Conclusions

As far as we know, this is the first reported case of SE in a SEF. Among all possible explanations, we think that the most reliable is that palliative treatment with RT of the pleural mass in this patient may have induced AE, leading to regression of SEF. Possibly in this case, as demonstrated in preclinical trials, RT led to immune system activation within the micro-tumoral environment. The dose used per fraction in this case, although not being the ideal dose for inducing AE, is compatible with this explanation. The role of SARs CoV-2 vaccination is unknown in this patient, as all cases reported until now in the literature are about patients with symptomatic infections and not just vaccination. Since SEF is an orphan disease with no clear treatment options, this case adds relevant information about clinical behavior, and illustrates the potential role of IO.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2276/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2276/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2276/coif). J.M.T. is currently serving as an unpaid editorial board member of *Translational Cancer Research* from June 2023 to May 2025. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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