Abscopal effect induced by cryoablation in a 55-year-old patient with metastatic dedifferentiated liposarcoma: a case report

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Background: Metastatic dedifferentiated liposarcoma (DDLPS) is primarily managed with chemotherapy, yet with poor response rate. Locoregional therapies, such as radiotherapy and percutaneous cryoablation, can provide palliation for inoperable metastatic sarcomas. In rare instances, those ablative therapies can elicit an immune-mediated regression of untreated metastases in a process named the abscopal effect. With the growing use of immunotherapy, reports on the abscopal effect have become more frequent during the last decade.

Case Description: A 55-year-old patient with no prior medical history was diagnosed with a stage IV DDLPS. The patient was first treated with induction chemotherapy followed by *en bloc* resection and adjuvant radiotherapy. After two local relapses treated with chemotherapy, the patient developed a systemic disease progression. While progressing on immunochemotherapy, the patient underwent palliative percutaneous cryoablation. Three months after the procedure, the ^{18}fluorodeoxyglucose positron emission tomography/computed tomography (^{18}FDG PET/CT) showed regression of the distant metastasis alongside the regression of the cryoablated tumor, suggesting an abscopal effect.

Conclusions: The occurrence of the abscopal effect after progressive disease suggests that cryoablation triggered a systemic immune response, highlighting the potential of this treatment combination. However, it remains a rare phenomenon, and further research and clinical trials are required to determine optimal treatment sequencing.

Keywords: Case report; abscopal effect; metastatic liposarcoma; percutaneous cryoablation; immunotherapy

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Introduction

Definitive management of dedifferentiated liposarcoma (DDLPS) includes primary resection with or without perioperative radiotherapy and/or chemotherapy. However, treatment options for metastatic disease are limited and outcome is poor. Local therapies such as radiotherapy and percutaneous cryoablation are alternative approaches for tumor control in the treatment of metastatic soft tissue sarcoma (STS) (1,2). These locoregional therapies have been reported to elicit a systemic anti-tumor immune response, a phenomenon referred to as the abscopal effect in other tumors including sarcomas.

The abscopal effect, originally described by Mole in 1953, refers to the partial or complete regression of a tumor at a location distant from the site of local treatment (3). Although it is traditionally regarded as a phenomenon induced by radiotherapy, reports of cryoablation-induced abscopal effects have increased over the last decade in parallel to the introduction of immunotherapy (4-7). Cryoablation is a technique originating from the 19th century, using extreme cold locally for tissue destruction. Modern cryoablation uses cryoprobes to deliver inert argon gas to produce freezing effect and damage tissues (8). In recent years, cryoablation has become an area of intense study and its popularity has increased since the establishment of more efficient live imaging techniques to guide the cryoprobes and monitor freezing (9,10). Yet, studies on the use of cryoablation for the treatment of STS are still scarce (11).

This case report aims to highlight the rare occurrence of the abscopal effect in a metastatic DDLPS patient after palliative percutaneous cryoablation and immunotherapy.

Highlight box

Key findings

- An abscopal effect was triggered by cryoablation in a metastatic dedifferentiated liposarcoma treated with concomitant anti-PD1.

What is known and what is new?

- Abscopal effect is the ability of local ablative therapy to induce systemic anti-tumor effect.
- Cryoablation-induced abscopal effect is a rare observation.
- Treatment combination with immune checkpoint inhibitors may enhance the occurrence of cryoablation-related abscopal effects.

What is the implication, and what should change now?

- Clinical trials are necessary to investigate the suitable combination and sequencing of treatments.

We present this case in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1868/rc).

Case presentation

Diagnosis and initial treatment

A 55-year-old patient with no prior medical history presented to our hospital in July 2016 with a three-month history of left lower limb pain. An abdominal computed tomography (CT)-scan revealed a 35-cm retroperitoneal mass suspicious for liposarcoma. CT-guided core needle biopsy was performed. Anatomopathologic and immunohistochemistry analyses demonstrated a DDLPS with MDM2 amplification. A second left paraaortic 3 cm mass, localized between the aorta and the pericardium, was confirmed to be a regional metastasis. The diagnosis of stage IV DDLPS, according to the Dutch/Memorial Sloan-Kettering Cancer Center classification, was confirmed.

The patient was treated with a 14-day continuous infusional ifosfamide regimen (1,000 mg/m^2/day) for 13 cycles. In September 2017, an exploratory laparotomy and *en bloc* resection of the tumor were performed. This was followed by an adjuvant radiotherapy at a total dose of 59.4 Gy in 33 fractions of 1.8 Gy at the level of the operative site and in left para-aortic area with a simultaneous boost in a dose of 66 Gy in 33 fractions of 2 Gy in the tumor bed (*Figure 1*).

Disease progression and lines of treatment

Between January 2018 and February 2019, the patient presented twice with local disease progression, treated with eribulin and doxorubicin-olaratumab regimens. In February 2019, the patient developed systemic progression with a supra-diaphragmatic extension of the disease. A rechallenge with the 14-day continuous infusional ifosfamide regimen was introduced with stable disease for up to 9 months (*Figure 2*).

Due to progression and lack of available clinical protocol, we opted for the addition of anti-programmed cell death protein 1 (PD1) nivolumab with continuation of same chemotherapy in February 2020. Our decision was supported by the presence of tumor-infiltrating lymphocytes in the initial pathology report. In June 2020, ^{18}fluorodeoxyglucose positron emission tomography/computed tomography (^{18}FDG PET/CT) showed partial metabolic response (*Figure 2*). In March 2021, after 17 cycles of immunochemotherapy, the follow-up imaging

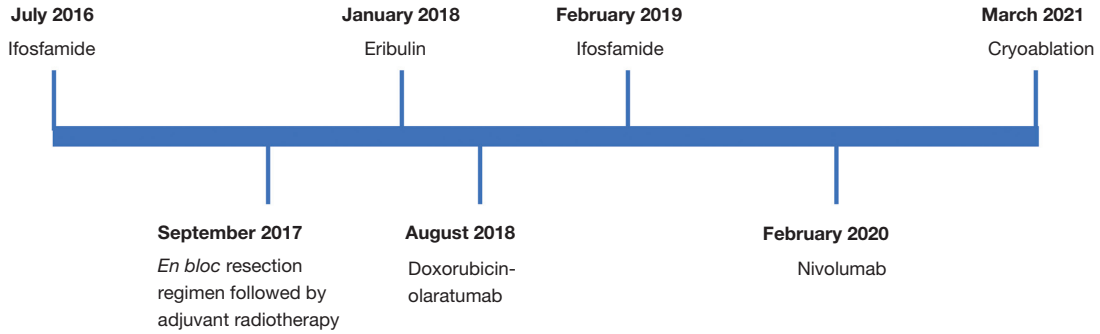

Figure 1 Treatment timeline.

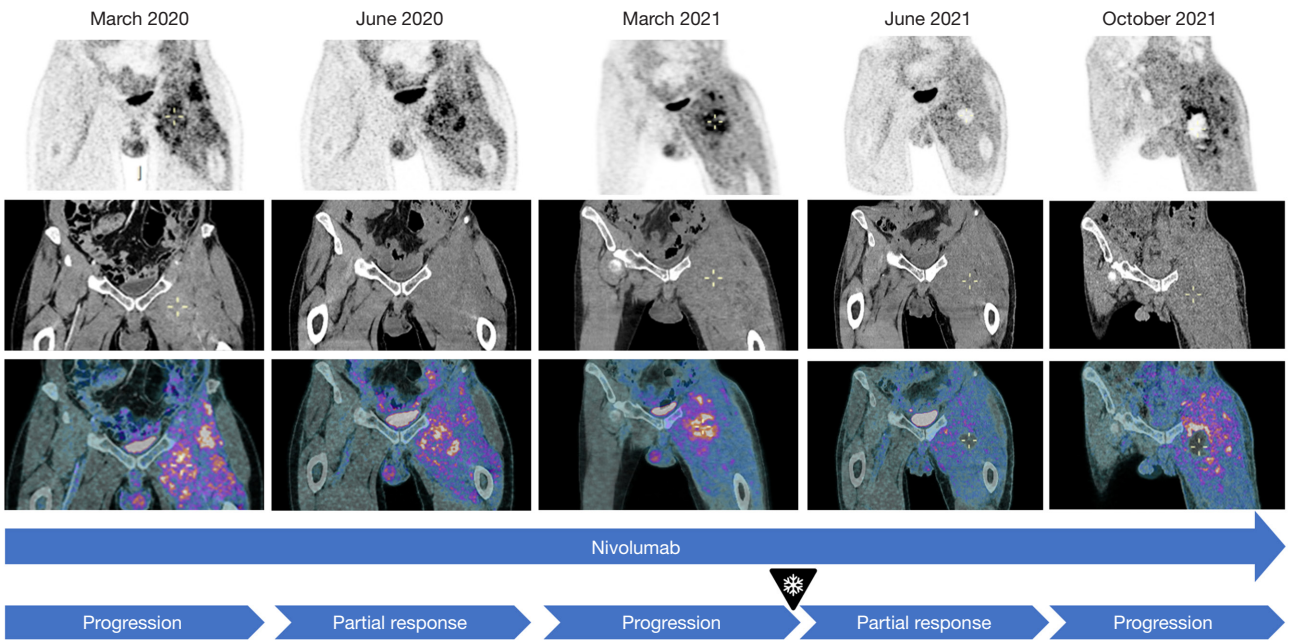

Figure 2 Treatment timeline and tumor response ^{18}FDG PET/CT images showing evolution of left thigh involvement before/during immunotherapy and before/post cryoablation. ^{18}FDG PET/CT, ^{18}fluorodeoxyglucose positron emission tomography/computed tomography.

showed progression of a pelvic lesion and emergence of a new paraaortic lesion (*Figure 2*).

Cryoablation and outcome

While pursuing ifosfamide and nivolumab, percutaneous cryoablation of the most vascularized portion of the pelvic mass was performed. Three ICE EDGE CX and three ICE Rod needles were placed in the left thigh tumoral mass under CT and ultrasound control (*Figure 3A*). A first cryoablation cycle was performed with cooling for ten minutes, passive reheating for eight minutes, then active reheating for one minute. A second cryoablation was performed after ensuring no secondary needle displacement and good coverage of the lesion by the cryotherapy ice (*Figure 3B,3C*).

Three months after cryoablation, the ^{18}FDG PET/CT revealed regression of the paraaortic mass in addition to the metabolic regression of the majority of hypermetabolic foci within the pelvic tumor (*Figures 2,4*). The response of the untreated paraaortic lesion suggests an abscopal phenomenon. Unfortunately, in October 2021, the patient presented with systemic disease progression. A new line of treatment with trabectedin was started but, due to rapid

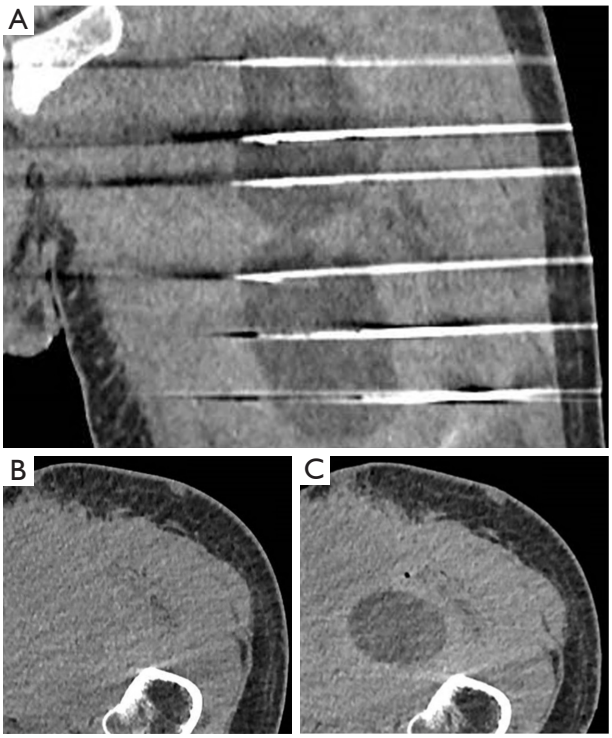

Figure 3 CT-scan images showing cryoablation procedure. Placement of 6 needles into the left thigh lesion (A). The tumor before (B) and after (C) cryoablation showing the formation of the ice ball. CT, computed tomography.

worsening of clinical status, the patient was admitted to the palliative care unit.

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made, but oral consent was obtained in accordance with local recommendations and the article has been sufficiently anonymized to cause no harm to the patient or his or her family.

Discussion

Management of DDLPS

DDLPS is one of the most common histologic subtypes of STS in adults. Despite advances in the understanding of sarcoma biology and development of novel therapies, the outcome of metastatic DDLPS remains poor. The management of metastatic disease mainly relies on systemic chemotherapy; however, objective response rate is around 20% (12-14). Promising response rates to immune checkpoint inhibitors (ICIs) in metastatic STS were reported in early readouts of the SARC028 and ALLIANCE A091401 trials (15,16). However, the results of subsequent series have not been able to reproduce those promising early results. Given the limited efficacy of systemic therapies, surgery and local ablative approaches are recommended strategies for tumor control in the treatment of metastatic STS (1). The retrospective METASARC study reported that over 80% of patients alive 5 years after diagnosis had received locoregional treatment of metastatic lesions, including surgery, radiation, or radiofrequency ablation (17).

Cryoablation and the abscopal effect

The abscopal effect was first described over 50 years ago and refers to the regression of distant metastatic lesions following radiation therapy of a primary lesion (3). This phenomenon is believed to be due to the release of tumor-specific antigens into the patient's circulation and the development of a systemic anti-tumor immune response (4). Compared to other local therapy modalities, cryoablation triggers higher immunogenicity which can be observed by significantly increased levels of IL-1, IL-6, NF-κB, and TNF-α (18-20). Percutaneous cryoablation is a procedure that uses liquified gas that cool as they expand, such as argon, to create extremely low temperature at the end of the cryoprobe. The repetition of freeze-thaw cycles primarily results in cellular death by necrosis (21,22). This results in the release of intracellular contents and activation of the innate immune system (23). It is hypothesized that freezing prevents tumor antigens denaturation, allowing the immune system to initiate a tumor-specific response (6). The first observation of abscopal effect following cryoablation was reported in 1970 in metastatic prostate cancer patients (24). However, this phenomenon is rarely observed, the release of antigens being insufficient to overcome the tumor immune escape mechanism.

Cryoablation and immunotherapy

The use of ICIs could allow the immune system to recognize these new cryoablation-induced circulating antigens prompting a robust systemic immune response (*Figure 5*). While data regarding this combination is still

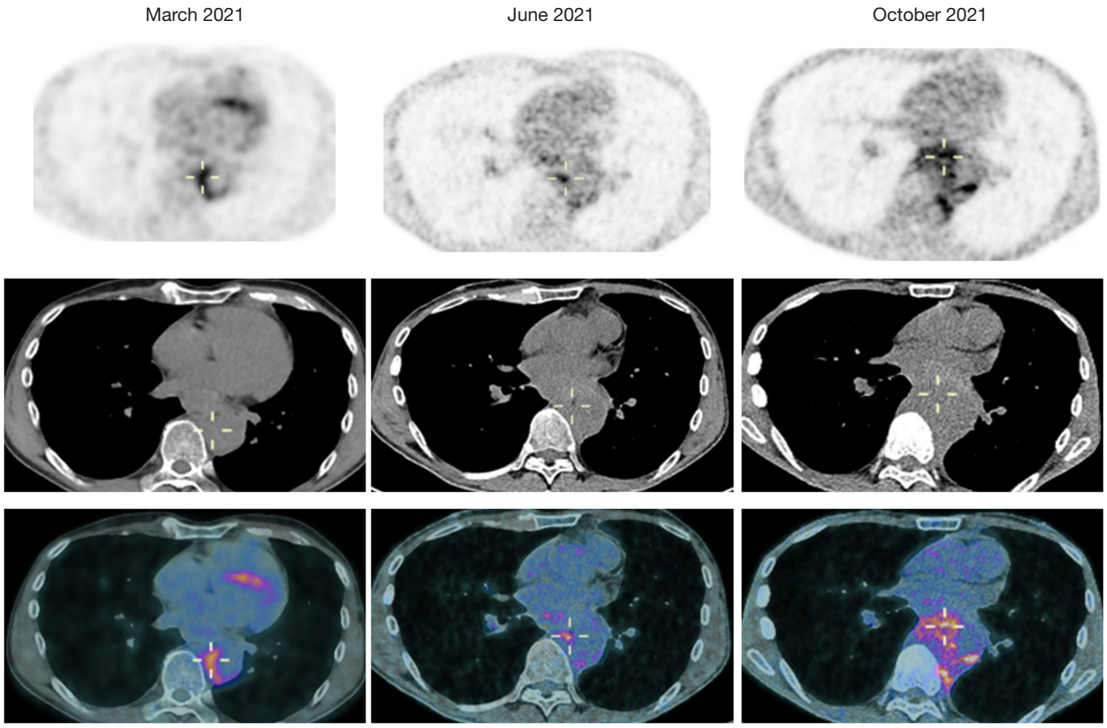

Figure 4 [18]FDG PET/CT images showing partial response at distance from the cryoablation site. [18]FDG PET/CT, [18]fluorodeoxyglucose positron emission tomography/computed tomography.

limited, increased survival in patients who underwent cryoablation and immunotherapy compared with those who received cryoablation or immunotherapy alone was demonstrated in several pilot studies and small series (25-31). One aspect of this combinational therapy that requires to be addressed is determining the appropriate regimen of cryoablation and immunotherapy. This decision should be based on the tumor's immune status. This involves distinguishing between "hot" tumors, characterized by high mutational burden and immune cell infiltration, and "cold" tumor. To minimize treatment toxicities, a promising alternative approach is the administration of intratumoral immunotherapy (32). Several clinical trials are currently studying the combination of cryoablation and immunotherapy in various metastatic cancers (*Table 1*).

The feasibility and safety of combining cryotherapy with immunotherapy in patients with advanced STS was demonstrated in a retrospective study (33). Out of the 16 patients, seven had a clinical benefit of the cryoablation procedure, including one complete response, one partial response, and five stable diseases. A recent phase II trial investigated the hypothesis that the addition of cryoablation would increase the response rate to immunotherapy by promoting a proinflammatory tumor microenvironment and cause an abscopal effect (34). In this study, 30 patients with STS were treated with a combination of ipilimumab, nivolumab and cryoablation. However, the combination of cryotherapy and ICI did not increase the response rate to immunotherapy with only one patient demonstrating a partial response.

Perspectives on the described case

Following multiple lines of treatment, our patient presented disease progression after one year of immunochemotherapy. While continuing with the systemic treatment, palliative percutaneous cryoablation was performed on the pelvic mass. The patient developed unexpected response in a distant untreated lesion. We believe that the observed response is an abscopal effect as it occurred after progression to several cycles of immunochemotherapy, suggesting that the cryoablation triggered a systemic immune response. Unfortunately, the response was not sustained. While the pathological analysis of the primary tumor showed the presence of tumor-infiltrating lymphocytes, less than one percent of tumor cells expressed

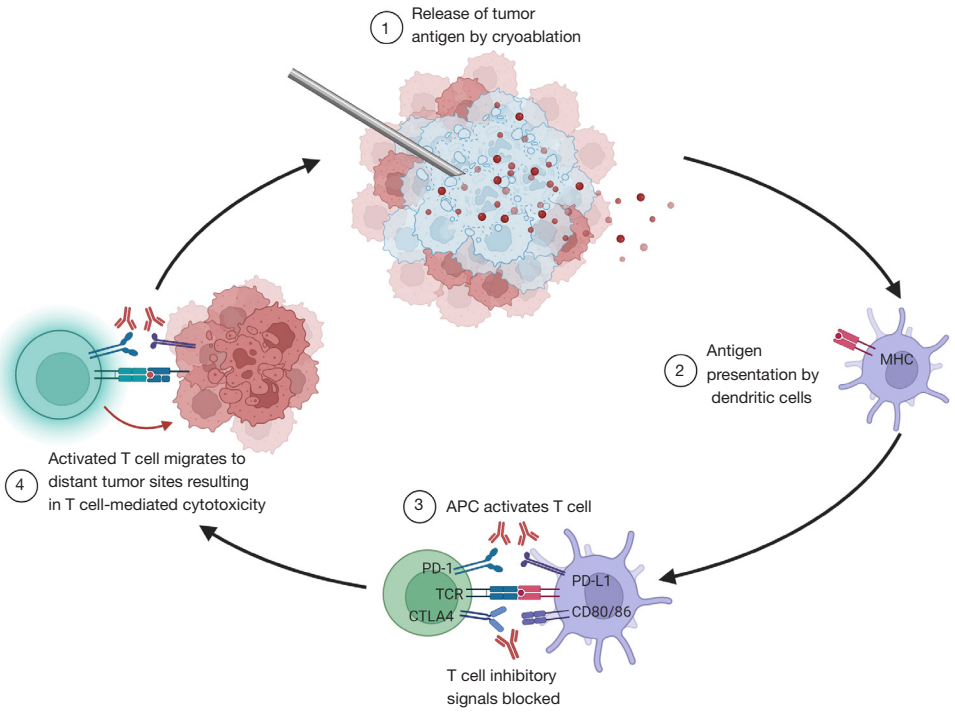

Figure 5 Cryoablation induces tumor cell necrosis and release of tumor antigens, which are taken by dendritic cells. Dendritic cells present tumor antigens to naive T-cell leading to their activation and differentiation into effector T-cells which migrate to the tumor sites. Introduction of checkpoint inhibitors allow the effector T-cells to kill tumor cells, leading to the regression of metastases. MHC, major histocompatibility complex; APC, antigen presenting cell; TCR, T cell receptor.

Table 1 Ongoing trials testing the combination of cryoablation with ICIs

Title	Treatment combination	Phase	NCT number
A Pilot Study of Combined Immune Checkpoint Inhibition in Combination with Ablative Therapies in Subjects with Hepatocellular Carcinoma (HCC) or Biliary Tract Carcinomas (BTC)	Durvalumab + tremelimumab + CA/TACE/RFA	II	NCT02821754
A Study of Pre-Operative Treatment with Cryoablation and Immune Therapy in Early Stage Breast Cancer	Ipilimumab + nivolumab + CA	NA	NCT02833233
Tremelimumab with or Without Cryoablation in Treating Patients with Metastatic Kidney Cancer	Tremelimumab + CA	I	NCT02626130
Pembrolizumab and Cryosurgery in Treating Patients with Newly Diagnosed, Oligo-metastatic Prostate Cancer	Pembrolizumab + CA	NA	NCT02489357
Peri-Operative Immune Checkpoint Inhibition and Cryoablation in Women With Triple-negative Breast Cancer	Pembrolizumab or ipilimumab and nivolumab + CA	II	NCT03546686
Cryoablation+Ipilimumab+Nivolumab in Melanoma	Ipilimumab + nivolumab + CA	II	NCT05779423
Cryoablation in Combination (or Not) with Pembrolizumab and Pemetrexed-carboplatin in 1st-line Treatment for Patients with Metastatic Lung Adenocarcinoma (CRYOMUNE)	Pembrolizumab + CHT + CA	III	NCT04339218
Cryoablation Combined with Camrelizumab and Apatinib in Advanced Hepatocellular Carcinoma (C-couple)	Camrelizumab + apatinib + CA	II	NCT04724226

ICIs, immune checkpoint inhibitors; CA, cryoablation; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; NA, not applicable; CHT, chemotherapy.

PD-L1 and the tumor mutational burden was low. In such a case, cryo-immunotherapy might not be sufficient to generate a sustained anti-tumor effect. Strategies combining cryoablation with new therapeutic options such as adoptive cell therapy or vaccine could elicit a profound abscopal response in less immunogenic tumor (35).

While our observation is intriguing, it has significant limitations being a single-patient report and lacking pathological confirmation for the metastatic lesion and tissue samples indicating a positive immunological effect.

Conclusions

Abscopal effect may be observed in metastatic DDLPS treated with concomitant anti-PD1 and cryoablation. However, this is a rare event and the optimal treatment sequencing, target lesion selection for cryoablation, and immunotherapy type and dose remain to be determined. To implement this treatment combination in our routine clinical practice, additional preclinical studies and prospective clinical trials are necessary.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-23-1868/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1868/coif). R.D. reports payment or honoraria via institution by Society of Interventional Oncology, Boston Scientific, Guerbet and BTG. A.D. reports payment or honoraria via the institution by Genentech/Roche, Pharmamar, Traconpharma, AstraZeneca, Boston Scientific and Bristol-Myers Squibb. 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 national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made, but oral consent was obtained in accordance with local recommendations and the article has been sufficiently anonymized to cause no harm to the patient or his or her family.

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