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Successful use of three-dimensional conformal radiotherapy as adjuvant treatment for alveolar soft part sarcoma. A case report

Uso exitoso de la radioterapia conformada tridimensional como tratamiento adyuvante del sarcoma alveolar de partes blandas. Reporte de un caso

Running title: Radiotherapy in alveolar sarcoma

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Abstract

Introduction: Alveolar soft part sarcoma is a very rare and aggressive type of sarcoma. Although its histology and genetic characteristics have been identified, the benefits of adjuvant radiotherapy for its treatment are still being studied.

Case presentation: In November 2007, a 21-year-old woman presented with a primary tumor in the right thigh, with histological and immunohistochemical confirmation of an alveolar soft part sarcoma, which was totally resected in December 2007. Also, the large size of the mass suggested an unfavorable evolution. Two years after the first surgery, two metastatic tumors were detected in the right lung, which were completely resected separately. Two years later, the patient had two independent relapse events, five months apart: a mass in the right tight, and a metastatic tumor in the adrenal gland together with relapse in the tight. All tumors were successfully resected. In June 2014, after the last local relapse, adjuvant radiotherapy was started because of the risk of thigh amputation. At the end of treatment, the patient's general condition was good. Currently, at age 34, the patient is monitored through periodic evaluations, showing disease regression and stabilization.

Conclusions: Currently, it is known that radiation not only produces cytotoxic effects on the target region, but also induces an immune system-mediated systemic response with potential antimetastatic properties. The emerging radiobiological paradigms should be considered, particularly since they could explain some encouraging and unexpected results such as those described in this case.

Keywords: Alveolar Soft Part Sarcoma; Radiotherapy; Neoplasms (MeSH).

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Resumen

Introducción. El sarcoma alveolar de partes blandas es un raro y agresivo tipo de sarcoma. Aunque se han identificado sus características histológicas y genéticas, todavía se están estudiando los beneficios de la radioterapia adyuvante en su tratamiento.

Presentación del caso. En noviembre de 2007, una mujer de 21 años se presentó con un tumor primario en el muslo derecho, con confirmación histológica e inmunohistoquímica de sarcoma alveolar de partes blandas y que fue completamente removido en diciembre de 2007. La masa mostró un gran tamaño, sugiriendo una evolución desfavorable. Dos años después de la primera cirugía, se detectaron dos tumores metastásicos en el pulmón derecho, que también fueron removidos, de forma separada. Dos años después, la paciente tuvo dos relapsos, separados por cinco meses:

una masa en el muslo derecho, y un tumor metastásico en la glándula suprarrenal junto con una recaída en el muslo. Todos los tumores fueron extirpados con éxito. En junio de 2014, después de la última recaída local, el muslo estaba en riesgo de ser amputado, por lo que se decidió iniciar radioterapia adyuvante. Al final del tratamiento, la condición general de la paciente fue buena. Actualmente, ya con 34 años, es evaluada periódicamente, mostrando regresión y estabilización de la enfermedad.

Conclusiones. Actualmente, se sabe que la radiación no solo produce efectos citotóxicos en la región objetivo, sino que también induce una respuesta sistémica mediada por el sistema inmune, con propiedades potencialmente antimetastásicas. En este sentido, se sugiere considerar los paradigmas radiobiológicos emergentes, ya que estos podrían explicar algunos resultados alentadores e inesperados como los descritos en este caso.

Palabras clave*:* Sarcoma de parte blanda alveolar; Radioterapia; Neoplasias (DeCS).

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Introduction

Alveolar soft part sarcoma (ASPS) is a malignant soft tissue tumor of uncertain histogenesis, poor prognosis and a very low frequency among

the different types of soft tissue sarcomas (STSs) (1-3). It is a well-differentiated clinical and morphological entity characterized by a typical histological image, specific molecular alterations and a unique and distinctive clinical behavior (1, 4). Usually, ASPS occurs in the extremities, commonly in the thighs and buttocks of adolescents and young adults (2). Despite having a relatively indolent growth rate, up to 79% of patients suffering from ASPS develop a metastatic disease. Unlike other STSs, ASPS metastasizes not only in the usual places, but also in the brain (4). The histopathological differences among STSs subtypes may have an impact on optimal treatment. For instance, surgical resection with or without radiotherapy is the standard treatment for localized diseases, while chemotherapy is the mainstay for the management of advanced and metastatic situations (5-10). Although STSs are traditionally classified by the morphology and the type of tissue they resemble (11), understanding of tumor biology and sensitivity is continuously evolving, enabling better therapies. Surgery can improve ASPS prognosis even in cases of metastatic disease; on the other hand, traditional chemotherapeutic agents and radiation therapy have not yet been shown to be reliably capable of increasing the survival of patients with ASPS (11). The 5-year overall survival documented in the literature for patients younger than 25 years old is 83% (12).

Here the case of a patient with a rare pathology (ASPS) is reported, who had multiple episodes of relapse and metastases prior to adjuvant treatment with three-dimensional conformal radiation therapy (3DCRT), and who now remains disease-free. The 3DCRT technique includes imaging, accurate radiation dose calculation, computer-optimized treatment planning, and computer-controlled treatment delivery. Treatment plans

are individually designed and based on patient-specific 3D images. Using 3DCRT, higher doses of radiation can be delivered to cancer cells while significantly reducing the amount of radiation received by the surrounding healthy tissue. To date, the best therapeutic approach to ASPS is not clear. Given the particular evolution of the patient and considering the concepts emerging in current radiotherapy, it is appropriate to share this information and reflect on the management of these ASPS cases and the effectiveness of their potential treatments.

Case presentation

Patient information

In November 2007, an apparently healthy 21-year-old non-smoking woman taking no medication was admitted to the Instituto de Oncología Ángel H. Roffo, Buenos Aires, Argentina. The reason for consultation was an increase in volume of the right thigh, without pain or discomfort.

Clinical findings

The physical examination confirmed the presence of a lump. Regarding pathological history, the patient did not present a remarkable medical or family history. In this first medical appointment, a biopsy and a Magnetic resonance were prescribed.

Timeline, diagnostic assessment and therapeutic intervention

In December 2007, gross total resection of the primary tumor was executed. Macroscopically, it was brownish, firm and uniform, measuring 10 x 8 x 7 cm. Histologically, the tumor was composed of cells with a large nucleus, prominent nucleoli and clear cytoplasm, arranged in a predomi-

nantly solid and alveolar pattern. The resection limits were free of injury. Immunohistochemical staining revealed that the lesions were positive for vimentin, desmin, cytokeratin and cytoplasmic MYOD1, and negative for muscle-specific actin, S100 and MYF4 myogenin. Confirming the diagnosis of ASPS.

Two years after the first surgery, two metastatic tumors were detected in the right lung. Total resection of both tumors was performed separately. A sarcoma metastasis with alveolar pattern linked to its underlying pathology was observed. The resection limits were free of injury.

Two years after the second surgery, the patient had two independent events of relapse, five months apart. In both cases, gross total resection of the tumor was prescribed. In the first episode, an irregular brownish-white mass of 7 x 5 x 4 cm was observed at the level of the striated muscle of the right tight. The second event was presented to the Committee of Tumors of the Instituto de Oncología Ángel H. Roffo, because metastasis in the left adrenal gland together with local thigh relapse were observed. Brain magnetic resonance imaging (MRI), abdominal ultrasound and consultation with the infectious disease and endocrinology teams were indicated. The brain MRI was normal, but a solid, 3.5 cm nodular image was recognized on the right pectineus muscle. In the abdominal ultrasound, a heterogeneous 4.6-cm image was observed in the left adrenal gland. Plasma and urinary cortisol as well as adrenaline and noradrenaline were within the physiological range. Resection of the right thigh mass and laparoscopic adrenalectomy were performed. The margins of both resections were free of injury and the metastatic tumor was confirmed.

The following year, a focal area of enhancement of the right thigh was

identified by MRI. The patient was strictly followed-up until two years later, when an increase in size was observed and surgery was advised. Two focal lesions were seen by CT of lower limbs. No involvement of the adjacent cortical bone was detected. The proximal and smaller lesion was associated with the area where surgical traces and scarring changes were evident. The most distal lesion was associated with the thickening of the skin located in front of it. Both nodules were removed; from each resection, whitish lobed tumors measuring 2 x 1.5 x 1.5 and 5 x 3.5 x 3 cm were dissected. Both lesions were located in the plane of the subcutaneous cellular tissue and had non-infiltrative margins. The largest lesion extended to the muscular plane, compressing but not invading it. The limits of both resections were free of injury. The two thigh nodules that occurred during the last relapse caused a risk of amputation due to intimal injury with a nerve-vascular package. Therefore, the case was discussed by the Oncological-Surgical Forum of the Instituto de Oncología Ángel H. Roffo. The indication was to perform 3DCRT as adjuvant treatment with curative purposes on the thigh surgical bed.

In June 2014, the 28-year-old patient was received at the Radiotherapy Center in good general condition, but with a decrease of the muscular component in the right thigh as a consequence of previous surgery. The patient presented a complete surgical scarring and a hypertrophic scar due to thermal burns associated with a history of anesthesia, without clinical detectable disease at distance from this area. The virtual simulation was done, it was planned on tomography, having as reference the preoperative images MRI and CT. The limb was immobilized with a cushion, tattoos on the skin, longitudinal axis and laterals. The image was controlled with portal films in treatment equipment for the first 3 days.

The radiotherapy protocol consisted in irradiation from four fields. Figure 1A shows a 3D reconstruction of the right tight where the irradiated areas can be seen. The clinical target volume (CTV) was irradiated with a total dose of 46 Gy (ISO1), given at 2 Gy per day from two fields (Figure 1B). The other two fields correspond to two boosts. The irradiated regions are shown in Figure 1C, upper (ISO2) and lower (ISO3) (2Gy per day; total dose: 20Gy and 10Gy, respectively). The treatment plan could not avoid irradiating the scar caused by thermal burns. Consequently, ISO3 had to be suspended after one week of treatment because the patient presented grade two dermatitis in this area according to the RTOG toxicity criteria.

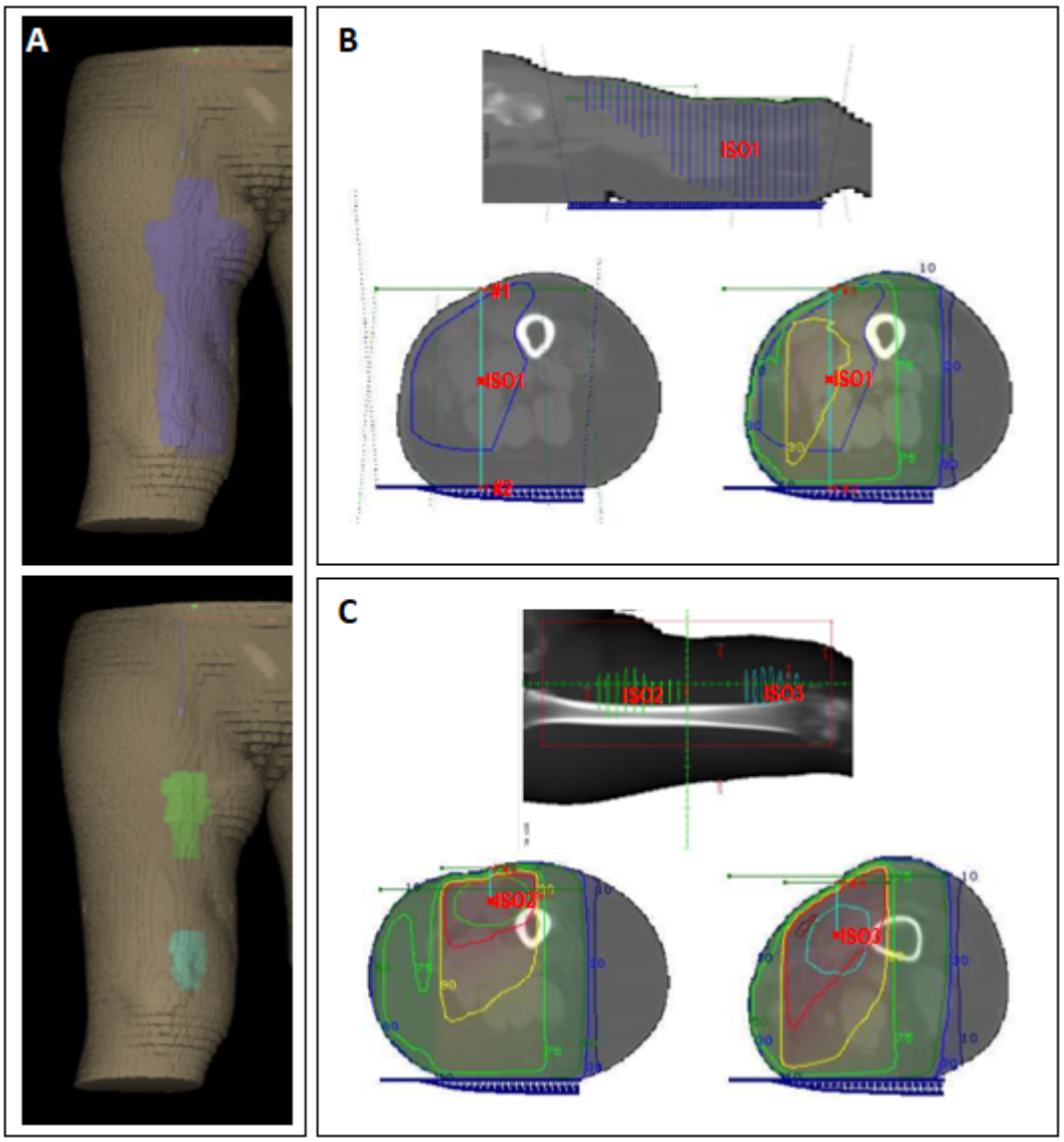

Figure 1. A. 3D reconstruction of the patient right thigh: clinical target volume (upper panel) and both boosts (lower panel). **B.** Clinical target volume. Upper panel: sagittal section of the thigh, showing the irradiated region and the accessory used in the irradiation treatment (wedge). Lower panel: axial section of the thigh. Left: irradiated region (blue), isocenter (red cross) and irradiation fields (#1 y #2). Right: irradiated region and isodose curves. **C.** Boosts. Upper panel: coronal section of the thigh showing the irradiated regions ISO2 and ISO3. Lower panel: axial section

of the thigh. Left: irradiated region in ISO2, isocenter (red cross) and isodose curves. Right: ISO3 and isodose curves (dark red: 105; red: 97; yellow: 90; green: 75; blue: 30; dark blue: 10). Source: own elaboration based on documents obtained during the study.

The estimated radiation dose for each ISO in the right thigh is shown in Figure 2. On the other hand, about 28% of the total volume of the femur (the risk organ), that is, the bone part close to the CTV, received the maximum dose of the treatment, the rest is preserved with less than 60% of the total dose. These data suggest that treatment plan was successful in avoiding damaging this organ. At the end of treatment, patient evolution was favorable in general terms, except for scar dermatitis. It is important to note that the patient did not receive any systemic treatment.

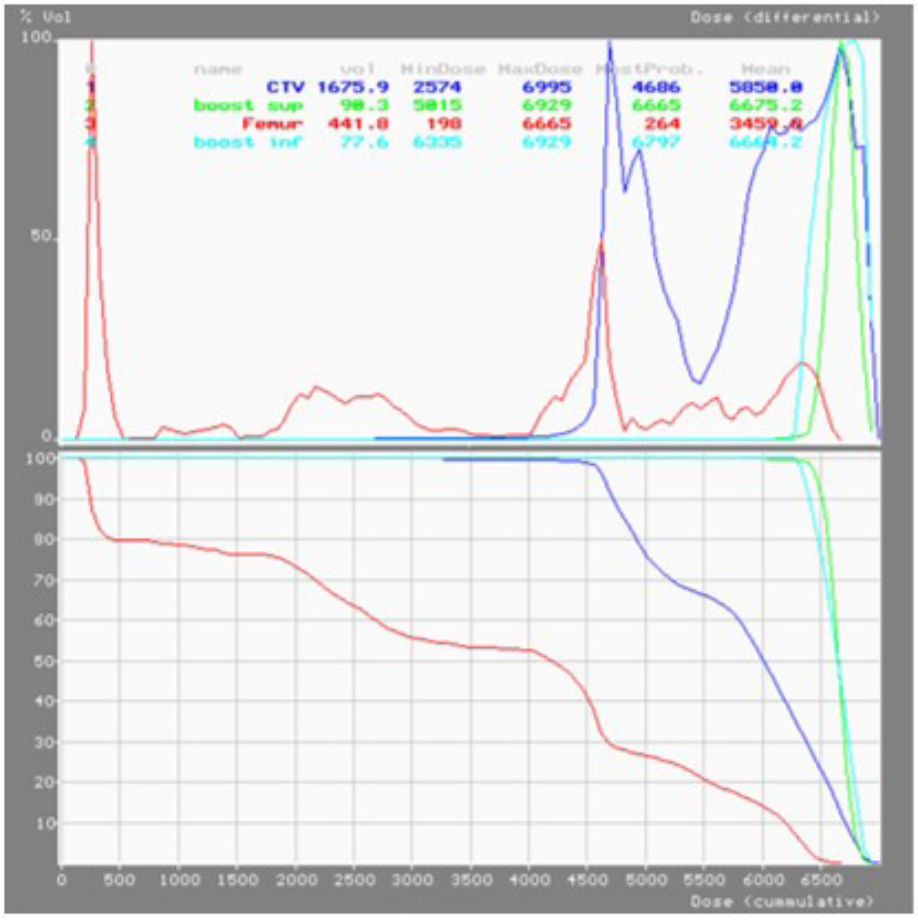

Figure 2. Histogram of radiation dose (X axis) versus tissue volume (Y axis). Upper panel: plot of the differential dose. Lower panel: plot of the accumulated dose (blue curves: CTV; green curves: upper boost; turquoise curves: lower boost; red curves: femur). Source: own elaboration based on documents obtained during the study

Follow-up and Outcomes

Currently, in September 2020, at age 34, the patient is followed-up through periodic evaluations by magnetic resonance in the thigh and knee and by tomography in the lung area. The patient does not receive any treatment and shows disease regression and stabilization without extension to other organs, completing the five-year disease-free survival.

Discussion

Alveolar soft tissue sarcoma is a rare disease that mainly affects female and young people. In young adults, it commonly occurs in the lower extremities and it usually presents as a large tumor mass established through a prolonged clinical history, similar to what happened with the patient of this case (2, 3, 13, 14). Although histological analysis is decisive for tumor characterization at ASPS diagnosis, CT and MRI allow to define the precise extent of the tumor, the areas of necrosis, hemorrhage, calcification and extension to the bone, intra- or extra-compartmental distribution, possible metastasis, and the relationship of vessels and neighboring nerves with the tumor (1, 11, 15).

In the present case, resection of the primary tumor morphologically showed a large size mass, larger than the average reported (9 cm), suggesting an unfavorable evolution (13, 14). Histopathological find-

ings showed tumor cells with conspicuous nuclei and clear cytoplasm, arranged in an alveolar pattern. The characteristic immunohistochemical markers of these sarcomas were also confirmed. It is important to emphasize that larger size and later stage indicate higher risk of metastasis and local recurrence. These tumors are very aggressive, and despite their slow development, or as a consequence of it, they can cause early distant metastasis (most often in the lung and brain) since they progress unnoticed and without discomfort, rarely with functional deterioration of the member on which they are located. These lesions can occur long after the initial resection, even if there is no local recurrence (2, 3, 13, 14). In the case presented here, following the normal progress of illness, two events of metastasis were observed with multiple local relapses, one in lung and the other in the suprarenal gland. All tumors were successfully excised.

The particular characteristics of this case are concerned with the results found after radiotherapy. Most reports suggest that quality resection of the primary tumor on its early stage is the mainstay of treatment,in the standard for the type of sarcoma, adjuvant RT is not indicated when negative margins are achieved, for the particular case it was referred to consultation given the multiple relapses . Conventional chemotherapeutic agents and radiotherapy have generally failed to improve patient survival (4, 11, 14). Even though its role is critically discussed, radiotherapy appears to reduce local recurrence, without influencing patient survival. For advanced cases with multiple metastases and recurrence, palliative treatment is preferred considering the poor prognosis (14). Although the case presented here shares the general characteristics discussed, a striking better efficiency of radiotherapy can be inferred, namely, disease control improved, neither metastases nor recurrences have been observed until

now, and five-year disease-free survival was completed.

Conventionally, radiotherapy has been considered as an integral component of oncological treatment. A conventional radiotherapy treatment consists of a total dose of 50-66 Gy delivered in 1.8 or 2 Gy per day, depending if the location allows it due to the tolerance of organs at risk. Being a locoregional therapy, it complements surgery and chemotherapy as local and systemic treatments, respectively. Radiotherapy is applied in at least 50% of patients, with curative intentions for localized cancers or isolated metastases and as a palliative treatment in patients with disseminated disease (16, 17). However, in recent years, salient evidence indicates that radiation not only produces cytotoxic effects on irradiated tumor cells, but also induces an immune-mediated systemic response, with potentially anti-metastatic properties (18, 19). This phenomenon is observed outside the irradiated zone and is known as abscopal effect. Currently, its elucidation constitutes an issue of central scientific attention. Thus, an "abscopal" effect occurs when localized radiation alters the body as a whole. The term encompasses a dichotomy, which mainly includes distant tumor regression from the irradiated area until the induction of genomic instability and cell death in normal tissues (20).

Conclusions

Beyond presenting a particular histology and a well-characterized genetic translocation, many questions about the pathogenesis and treatment of ASPS remain unanswered. Surgical removal of the primary tumor mass and metastases resulted in prolonged survival, while the benefit of adjuvant chemotherapy and/or radiotherapy has been questioned. Although more results based on stronger scientific evidence are needed,

taking into account the particular progress of the patient case, especially after 3DCRT, emergent radiobiological paradigms should be considered, since they sustain a holistic effect of radiotherapy and would eventually explain some of the encouraging and unexpected results reported here. In the light of the above mentioned, a better knowledge of the non-focused effects of radiation would help to resolve its relevance for optimal treatment and best clinical approach to ASPS.

Abbreviations

3DCRT: Three-dimensional conformal radiation therapy; CT: computed tomography; CTV: clinical target volume; MRI: magnetic resonance imaging; PET: positron emission tomography; STS: soft tissue sarcoma; RTOG: Radiation Therapy Oncology Group.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Consent was granted by the patient.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All collaborators made substantial contributions to the paper. AMG and EEO wrote the initial manuscript, analyzed and interpreted the patient data and edited the text and images. EPD was the radio-oncologist in charge and made the critical review. All authors read and approved the final manuscript

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