

Early Metastatic Recurrence to the Brain in  
Tibial AdamantinomaFacundo Alberti<sup>1\*</sup>, Alberto Moreno<sup>1</sup> and Rafael Sanchez<sup>2</sup><sup>1</sup>Department of Clinical Oncology, Reina Sofía University Hospital, Cordoba, Spain<sup>2</sup>Department of Histopathology, Reina Sofía University Hospital, Cordoba, Spain

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## Abstract

Long bone adamantinoma is a very rare malignant tumor of epithelial origin. In most cases it affects unilateral tibia and fibula, and the definitive treatment is surgical. Distant recurrence is unusual and its systemic treatment has heterogeneous results. We are reporting an unusual case of brain recurrence of tibial adamantinoma and the poor results with systemic treatment.

## Introduction

Adamantinoma is a rare tumor that encompasses less than 1% of all primary bone tumors [1]. We describe the first case in Europe of brain metastasis secondary to an adamantinoma.

## Case report

A fifty-year-old woman with no past medical history arrived at the Traumatology service, due to an appearance of a tumor with pain in the left tibia in the last two months. It began with local pain after a minor tibial trauma with an increase in the intensity, and later an appearance of a tumor of a 2cm diameter of rapid growth.

She did not use any usual pharmacological treatment, and she was an ex-smoker for a year, with an increasing consumption of 15paq / year.

The clinical examination revealed a fixed tumor of a hard consistency, 6 cm in diameter on the left anterior tibia, without skin alterations, bone-dependent, with pain on palpation and not bleeding to the touch. The patient tolerated gait with pain and had no clinical signs of tibial fracture. The vascular and ganglionic exploration of the limb had no alterations. The rest of the physical examination had no significant findings. In the left-sided single radiograph, there was an area of central diaphyseal ovoid osteolysis with well-defined borders (Figure 1).

## Investigations

The CT scan of the left leg was performed showing an osteolytic lesion in the anterior cortical of the middle of the tibial shaft surrounded by a peripheral sclerosis zone with suspicion of osteoid osteoma (Figures 2 and 3). The left leg MRI study was completed in which the cortical osteolytic lesion was significantly increased concerning the previous test, as well as a substantial thinning and insufflation of the outer margin of the cortical, with extensive bone edema in the adjacent periosteum, and great heterogeneous enhancement with contrast. No soft tissue component was evident (Figures 4 and 5).

Due to the previous findings, a biopsy was performed, with anatomopathological results: adamantinoma of long bones.

The extension study was conducted with a CT of the thorax / abdomen / pelvis and mammography, with no metastasis.

## Differential Diagnosis

- Osteoid osteoma
- Ossifying Fibroma
- Intracortical fibrous dysplasia
- Osteblastoma
- Osteosarcoma
- Adamantinoma
- Metastasis of squamous cell carcinoma
- Subacute osteomyelitis



Figure 1: Radiograph of left leg.



Figure 2: Computer Tomography(CT)of both legs (front image).

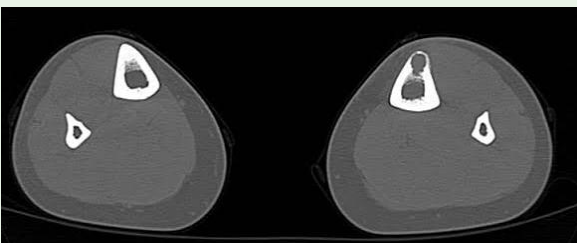


Figure 3: CT of both legs (axial image).

**Treatment**

After evaluation by the multidisciplinary team, surgical excision with marginal resection of the left tibia and wide margins of the tumoral lesion with bone allograft was done.

In the anatomopathological analysis of the surgical specimen, the diagnosis of adamantinoma of long bones was confirmed, without cortical repercussion, and without affectation of the resected

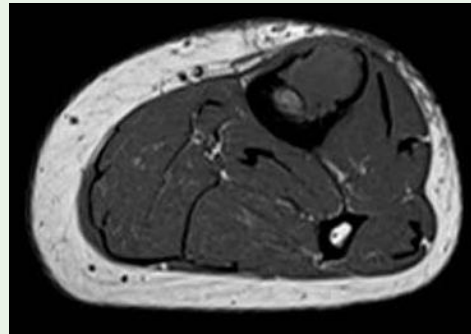


Figure 4: MR of left leg (axial image).

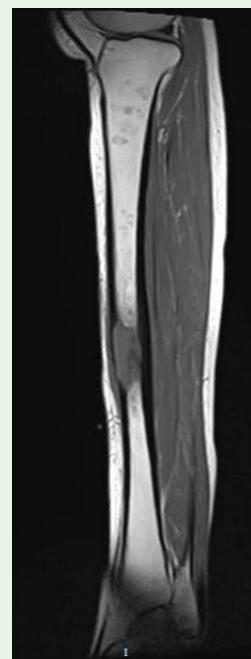


Figure 5: Magnetic Resonance (MR) of left leg (sagittal image).

margins. Histopathologically the tumor had a mixed fibrous-osseous and epithelial component, with the immunohistochemical positivity of pan-CK AE1 / AE3, EMA, vimentin, p63, laminin, galectin 3 and EGFR in the epithelial component. Mitotic activity was three mitotic figures per 10 high-power fields.

**Outcome and follow-up**

One month after primary tumor intervention, the patient debuted with generalized epileptic seizures. Cranial CT was done without evidence of alterations. In the presence of recurrent crises, cerebral MRI showed multiple hypercaptive lesions, with homogeneous ring-shaped enhancement, cortical- subcortical localization in both cerebral hemispheres, in both cerebellar, protuberance, and meningeal hemispheres (Figures 5-8).

CT thorax / abdomen / pelvis were performed, as well as a clinical and radiographic study of the left leg without evidence of tumoral disease. There were no alterations in the tumor markers, and the bacterial, viral and fungal serological tests were negative.

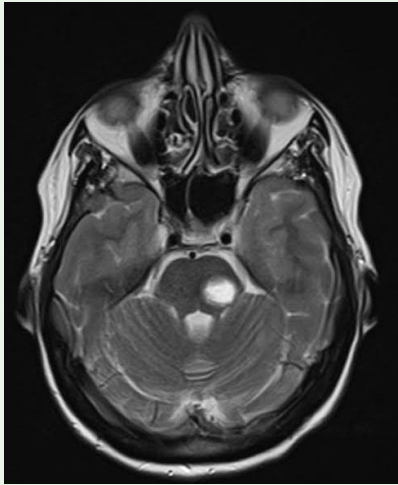


Figure 6: MR of cranium, T2 sequence (axial image).

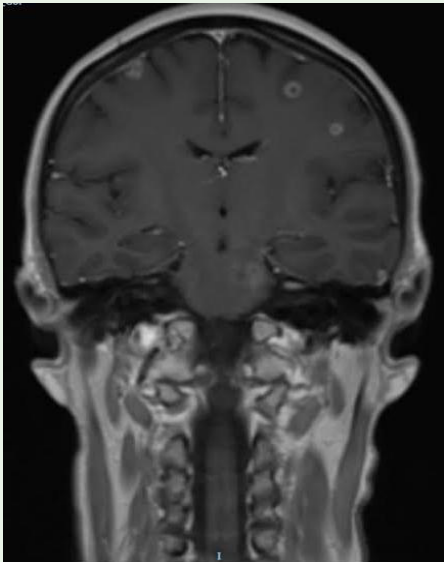


Figure 7: MR of cranium, T1 sequence (coronal image).

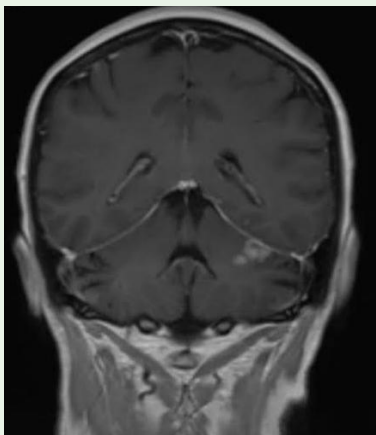


Figure 8: MR of cranium (coronal image).

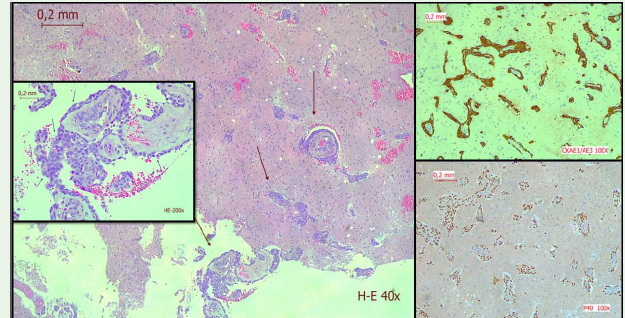


Figure 9: He-40X: Brain tissue infiltrated by neoplasia composed of basaloid cells that are arranged in nests and braids with peripheral palisade reminiscent of basal cell carcinoma. H3-200X: Higher detail of basaloid neoplastic cells forming a nest and palisade on fibrous stroma. CKAE1 / CKAE3 100X: Membrane immunostaining in neoplastic cells for pancytokeratin. P40-100X: Nuclear immunostaining of neoplastic cells for p40.

Given the absence of certainty diagnosis, a neurosurgical biopsy was performed on one of the left frontal lesions, where the metastasis of adamantinoma was confirmed. The morphological and immunohistochemical description was the same as the previous tibial lesion (Figure 9).

Secondary to metastatic affectation, the patient presented right upper body paresthesia and loss of strength in cubital and sacrum right territories.

With the diagnosis of metastatic adamantinoma, chemotherapy treatment with undifferentiated bone sarcomas with cisplatin/ adriamycin was initiated.

Three cycles of treatment were given with worsening of the neurological manifestations. Radiographs of the tibia were performed without relapse data and cranial MRI of response control, showing the progression of multiple hyper-capturing lesions of cortical-subcortical localization in both cerebellar, and protuberance hemispheres, with little perilesional edema. Also had generalized dural enhancement compatible with meningeal progression.

Based on these results, a new line of treatment with pazopanib was initiated. After two cycles of treatment, in the absence of clinical benefit and persistent functional impairment, there was decided to discontinue antitumor treatment, with maintenance of palliative treatment.

Eight months after the initial diagnosis, the patient died.

**Discussion**

Long bone adamantinoma is a very rare malignant tumor of epithelial origin, with an estimated incidence of 0.1-0.3% of the primitive bone tumors [2]. The range of presentation is between 25 and 35 years of age, more frequently in men than in women [3].

It is a tumor of tibial origin in up to 85% of cases, with an ipsilateral involvement of the fibula and other main limb bones in 15% of patients [4].

The most frequent initial presentation is a subacute picture of tibial swelling with or without local pain. The history of minor trauma in this

area has been described in 60% of the cases [5]. In the histopathology, the tumor consists of an epithelial component that can present in several types and proportions on a fibrotic stroma or of osteofibrosis [6,7]. Four classic histological patterns have been described: basaloid, tubular, squamous and fusiform, basaloid and tubular patterns being the most frequent. Due to its epithelial nature and its histological variability, adamantinoma may resemble metastatic lesions, being the shortage of mitotic figures, age, and clinical history the discriminatory factors arising from neoplastic lesions from another location. In the same way, the realization of immunohistochemical techniques allows the detection of cytokeratins, which function as an epithelial marker [8-10].

The radiographic features of this lesion range from an eccentric cortical tumor to the presence of intramedullary lytic semiology with multilobulated appearance and areas of sclerosis.

Magnetic resonance imaging is the radiographic technique that allows better characterization of the lesions. Usually, a lesion with low signal intensity on T1 and high in T2 that can extend to the adjacent soft tissues is evidenced [11].

The role of PET / CT in the evaluation of adamantinoma is unclear, with cases where 18F-FDG PET / CT has been shown to be useful in staging tumour and response assessment.

Surgery with tumor block resection with wide surgical margins and subsequent reconstruction is the treatment of choice for localized disease [12].

To date, adjuvant chemotherapy or radiation therapy has not been shown to improve patient survival [13].

Adamantinoma is considered resistant to chemotherapy and radiotherapy, therefore, once the metastatic disease begins, the prognosis is poor.

Although clinical benefit has been described with combinations of platinum, ifosfamide, doxorubicin, etoposide or paclitaxel, the responses are usually short with an early progression [14].

Due to the immunohistochemical expression of the adamantinoma of EGFR, VEGFR, and PDGFR-beta, cases have been reported in which the use of a VEGFR inhibitor, such as sunitinib or pazopanib, has achieved clinically significant responses or stabilizations [15].

In our case, we present a 50-year-old woman with no constitutional symptoms, nor in other organs or systems that made the suspicion of another neoplasia suspicious, as well as semiology that would lead to an infectious process.

Although lytic lesion on plain radiography and CT can predict the probable histological origin, as well as the behavior of the lesion under study, it was the MRI that best established the intra / extraosseous relationship as well as the most probable diagnoses.

Given the aggressive radiological behavior, rapid growth and suspicion of a malignant tumor, a biopsy was performed to confirm the diagnosis of adamantinoma, since it is a low-grade tumor and shares radiological characteristics with other entities that can only be differentiated with Histological analysis.

The evaluation of extension in the rest of the organism in this

type of neoplasia is not standardized given the low frequency of this entity, as well as the exceptionality in the synchronous affectation of other bones.

Hence, in the extension study, a CT scan of the thorax/abdomen / pelvis was performed, which resulted without alterations. Since the patient did not present at the initial findings, neurological manifestations and the synchronous cerebral dissemination of adamantinoma had not been described, no imaging study of the central nervous system was done.

Because the histological appearance of adamantinoma may morphologically be similar from osteofibrous dysplasia to metastasis of squamous cell carcinoma, it is essential to rule out the presence of a primary squamous neoplastic lesion at another site to exclude metastatic origin.

With the histological diagnosis in the adamantinoma biopsy, we proceeded to the radical surgical treatment, where it was evident the absence of margins and extra-compartmental growth, so taking into account these factors of relapse, the risk of recurrence was low.

Due to the lack of studies that support radiotherapy or antineoplastic adjuvant treatment in this pathology, clinical-radiological surveillance was established after the intervention to rule out a recurrent/metastatic disease.

In this case, the presence of focal neurological deficit at the month of oncologic surgery and the subsequent radiological study lead to the diagnosis of supra / infratentorial intracerebral Space Occupying Lesions (SOL).

Due to the exceptional cerebral dissemination of adamantinoma and the need to rule out that the brain LOEs were due to another neoplasm or even an infectious process, the brain biopsy was done.

Once the adamantinoma's metastatic brain involvement was confirmed, a new radiological extension study was performed without any evidence of nodular or pulmonary metastases, which are the most frequent sites of dissemination of this type of neoplasm.

Due to the absence of prospective data for the chemotherapeutic treatment of metastatic adamantinoma, treatment regimens for undifferentiated sarcoma were used, with no evidence of response.

The use of a tyrosine kinase inhibitor, pazopanib, also did not achieve the clinical benefit demonstrated in other cases.

The intrinsic characteristics of the metastatic disease in the Central Nervous System (CNS), such as the blood-brain barrier or pharmacokinetics in that area, may be responsible for the lack of effectiveness.

Tumor progression in the CNS leads to rapid deterioration of our patient as well as to death within a short period since diagnosis.

Our case is not only exceptional because of the sub acute local behavior in a neoplasia characterized by low growth rates, but the histologically confirmed cerebral metastatic presentation the first described to date gives a new profile on the potential for dissemination of adamantinoma.

Extension studies in the nervous system at diagnosis and during follow-up could be considered taking into account this described behavior.



The aggressive evolution and the poor response to chemotherapeutic / molecular treatment, as opposed to extra-CNS metastatic disease, oblige us to look for other molecular targets to treat this type of patients.

For this, pathophysiological studies are necessary to indicate which cellular signaling pathways are subsidiaries of effective systemic treatment for this disease.

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