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Multi-Metastatic Extra-Skeletal Myxoid Chondrosarcoma: A Case Report and Review of the Literature

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Abstract **Case Report**

Extraskeletal Myxoid chondrosarcoma (EMC) is a rare and aggressive soft tissue malignancy with a high risk of metastasis because it is radio-chemoresistant. The aim of this study is to describe the clinical evolution of this tumor after the detection of distant metastases and to schematize its metastatic evolution. This is a 26-year-old man, followed for more than 9 years in our institution for EMC of the right leg with synchronous pulmonary metastases, documented by medical imaging. Pathological analysis confirmed the diagnosis and the patient underwent surgical treatment (amputation) followed by adjuvant chemotherapy and follow-up revealed multiple metastases. The present case showed that EMC has the potential for a more invasive transition during its prolonged clinical course, which may lead to a poor prognosis. In addition, this work recommends that we consult a specialist in the event of the slightest swelling, however trivial, whatever the site, in order to clarify its histological nature thus avoiding unfortunate progression.

Keywords: Chondrosarcoma, myxoid, metastasis, surgery.

INTRODUCTION

Extraskeletal myxoid chondrosarcoma (EMC) is a rare malignant soft tissue tumor characterized by uniform spindle-shaped cells arranged in a reticular growth pattern within abundant myxoid stroma [1, 2]. Histologically, the tumor is classified as a tumor of uncertain differentiation due to its lack of cartilaginous differentiation, although it was originally thought to be a variant of chondrosarcoma [3], and it is distinguished from other sarcomas by its unique histology and characteristic chromosomal translocation, typically t (9; 22) (q22;q12.2) [4].

EMC has an incidence of 1 cas per 10 million [1-6], represents less than 3% of soft tissue sarcomas [7], and usually occurs in adults with a median age of 50 years and a male to female ratio of 2: 1 [8].

The tumor has a slow growth curve, but it has a high risk of metastasis. Recent studies have revealed that EMC is a more aggressive malignancy due to the high rate of local recurrence and distant metastases even after radical resection [6-10], with 10-year survival rates ranging from 65 to 78% [8].

Several clinical trials have not yielded the expected results: mixed responses to different therapies [8-11], and stability of the disease for 6 months in only 25% of patients [8].

The aim of this study was therefore to analyze the metastatic evolution of this disease over the long term in order to plan surveillance and provide clinical data for subsequent studies.

CASE REPORT

In October 2014, a 17-year-old young man, with no particular pathological history, consulted for a swelling in his right leg that had been developing for 4 years and had gradually increased in size until suppuration.

On admission examination, it is an oval, suppurated and necrotic mass with a blood bladder, of hard consistency, adhering to the deep plane and measuring 10x15cm in diameter, in the lower third of the leg. Histopathological study after biopsy revealed a tumor proliferation strongly suggestive of malignancy which should first rule out a low-grade sarcomatous origin in the first instance; supplemented in March 2015

by an immunohistochemical study, reporting a morphological and immunohistochemical appearance primarily suggestive of an extraskeletal myxoid chondrosarcoma and by an extension assessment, a CT-TAP revealing secondary pulmonary nodules, some of which are calcified.

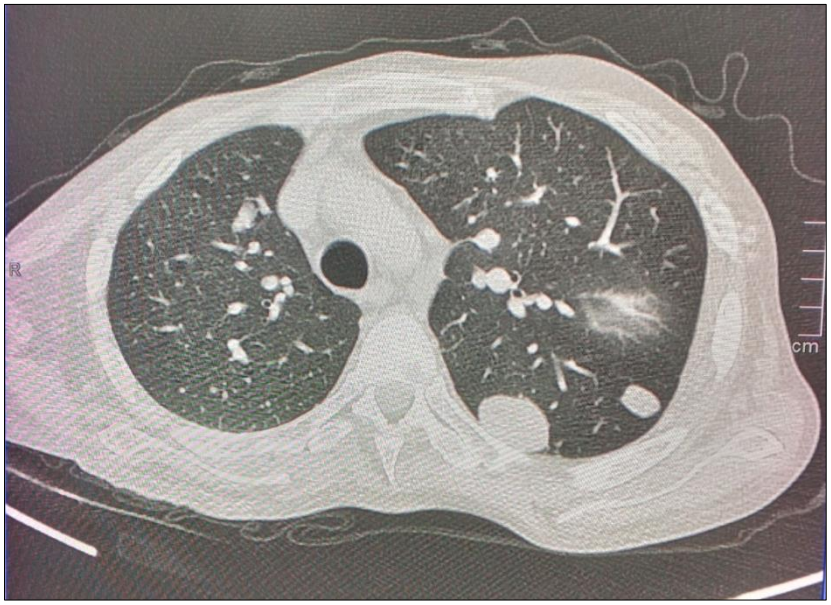

Figure 1: CT image of CT-TAP revealing pulmonary metastasis

An amputation of the right leg was scheduled and carried out in March 2015. Then, the patient underwent adjuvant chemotherapy consisting of 5 courses of VAC-IE, the last course of which dates from December 2015 and whose evaluations after 3 courses by a CT-TAP in September 2015 and after 5 courses by a chest CT from January 2016 reported stability of pulmonary nodules.

The bone scan in October 2015 showed no secondary bone lesions. An immunohistochemical study on biopsy of pulmonary nodules from February 2016 showed a morphological and immunohistochemical appearance compatible with a high-grade sarcoma.

Given the persistence of the pulmonary nodules after 5 courses of VAC-IE, the patient was placed on the CIE protocol and received 3 courses, the last of which was in May 2016. The CT-TAP evaluation of June 2016 also reported stability of pulmonary nodules of secondary origin.

In the 3rd line, the patient received 3 courses of Docetacel-Gemcitabine, the last course of which was in November 2016. Evaluation by chest CT of the same November 2016 also reported stability of the pulmonary nodules.

The decision to continue with this protocol was stymied by the unavailability of Docetaxel in the hospital. The patient received 4 courses of Gemcitabine monotherapy, the last of which was in March 2017 and whose evaluation by chest CT in March 2017 revealed an increase in the volume of certain nodules with the appearance of new nodular lesions increasing from 9 nodules to 15.

After the availability of Docetaxel and the unavailability of Gemcitabine, he received 6 courses of Docetaxel monotherapy, the last one in August 2017. After 3 courses, the CT scan in June 2017 showed stability of the pulmonary nodules. While that of August 2017 after the 6 courses revealed an increase in the size of almost all pulmonary nodular lesions with the appearance of hepatic nodules.

Afterwards, the patient was placed in palliative care.

Once again, the CT-TAP of April 2018 and May 2019 reported stability of the pulmonary nodules while that of June 2020 revealed the increase in the size of the pulmonary nodules, according to the RECIST criteria: 73% increase in the sum of target lesions in favour of disease progression

To manage certain emergencies and ensure proper medical follow-up, the patient was hospitalized on several occasions:

- In November 2020, due to respiratory distress: The thoracic angioscan performed during this hospitalization showed a thrombus of the LA of probably tumor origin, extended to the right lower pulmonary vein.

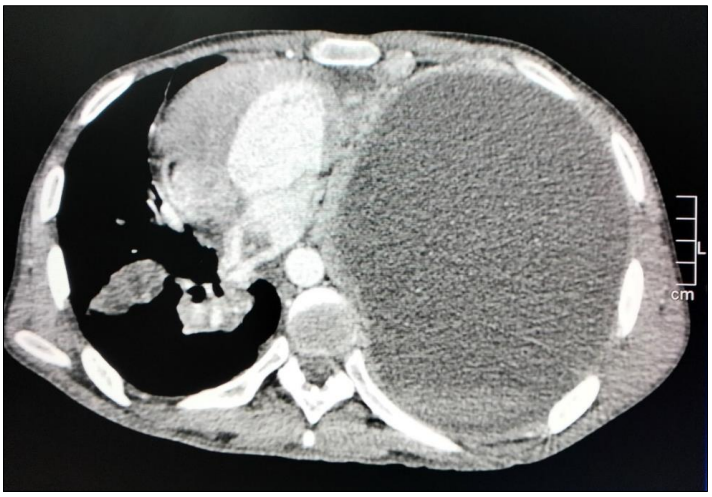

Figure 2: Thoracic angioscan showing thrombus in the right inferior pulmonary vein

- In February 2021, for disturbances of consciousness: cerebral CT revealed a capsulo - lenticular ischemic stroke.
- In October 2021, due to pulmonary distress once again: The emergency thoracic angioscan revealed an increase in size and number of pulmonary nodules, a right pulmonary embolism of tumor origin and a thrombus of the LA still extended to the right lower pulmonary vein

In early 2022, swelling of the frontal scalp motivated him to consult. Two brain CT scans were performed in May 2022 and April 2023 showing a well-limited, oval nodular lesion, measuring 21.8 x 13.3 mm in diameter in the right frontal scalp and respecting the bone.

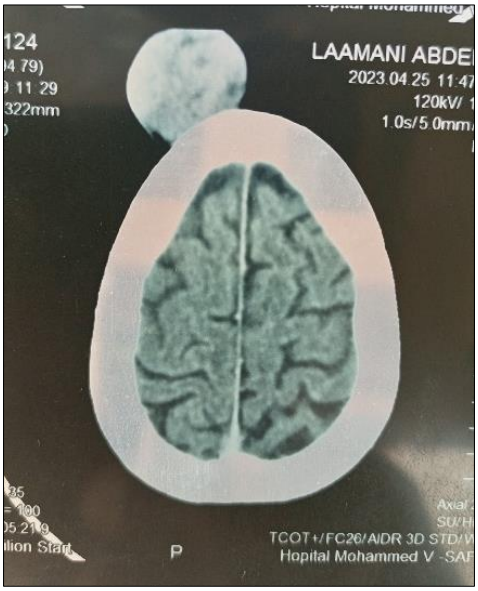

Figure 3: Scan image showing frontal swelling

A series of Hospitalizations continued:

- In June 2022, for respiratory distress: A right distal pulmonary embolism associated with a tumor thrombus of the LA measuring 18 x 35 mm in diameter and a left pleural effusion of most likely secondary origin were revealed by the thoracic angiogram in June 2022.
- In August of the same year, he was admitted to hospital for abdominal pain. Abdominal ultrasound showed two lesions: one on the left adrenal and the other on the right kidney.

The onset of dyspnea, during this hospitalization, necessitated a transthoracic ultrasound which showed a mass completely blocking the cardiac cavities and a chest CT which revealed an encysted and compressive left pleural collection associated with pulmonary masses, nodules and micronodules and supradiaphragmatic ADP of secondary origin.

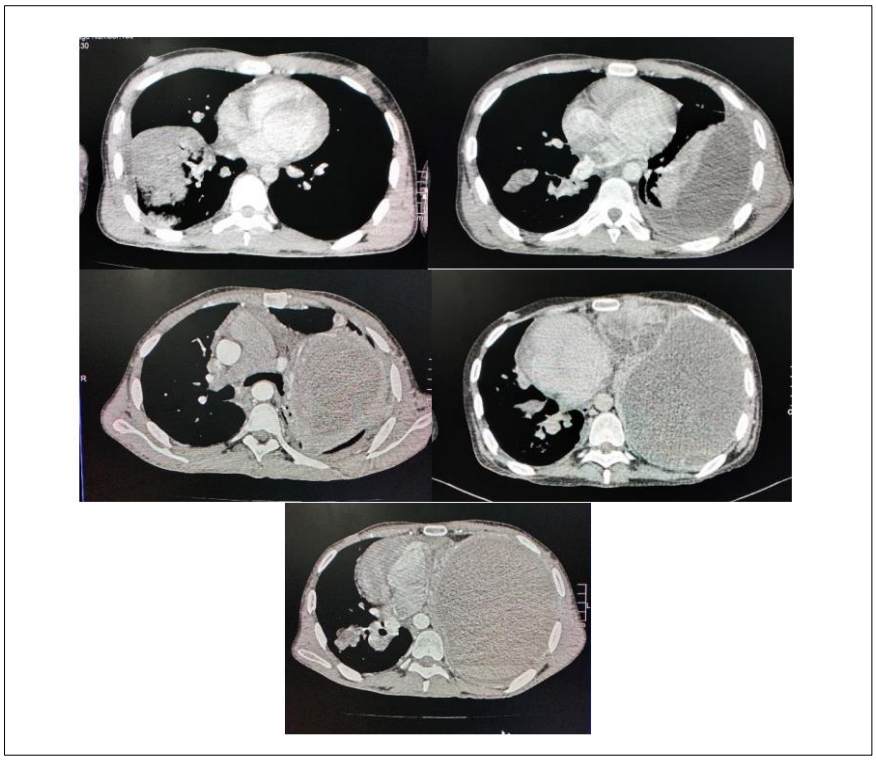

Figure 4: Chest CT in August 2022

- The cytology study of pleural fluid in September 2022 revealed malignant cells, confirmed by a histological study in October 2022.

Surveillance TAP-CTs from October 2022, February 2023 and April 2023 reported stable disease.

In July 2023, he consulted for swelling of the right upper limb. A Doppler ultrasound revealed a deep thrombosis associated with swelling of the forearm, giving the appearance of a pseudo mass of probably secondary origin.

Hospitalized the same month for haematuria and edema of the right upper limb, the abdominopelvic ultrasound performed during this hospitalization showed right renal, left adrenal and pleural lesions (left pleurisy) and the CT-TAP, an increase in number and size of pleural and pulmonary nodules and masses, lymphadenopathy of the left mammary chain, stability of the right renal lesion and a secondary lesional process with bone lysis in the right forearm.

MRI of the right forearm in August 2023 revealed a lesional process of the muscular compartment of the right forearm, with locally infiltrating radioulnar bone lysis associated with Thrombosis of the right basic vein extended over 30mm.

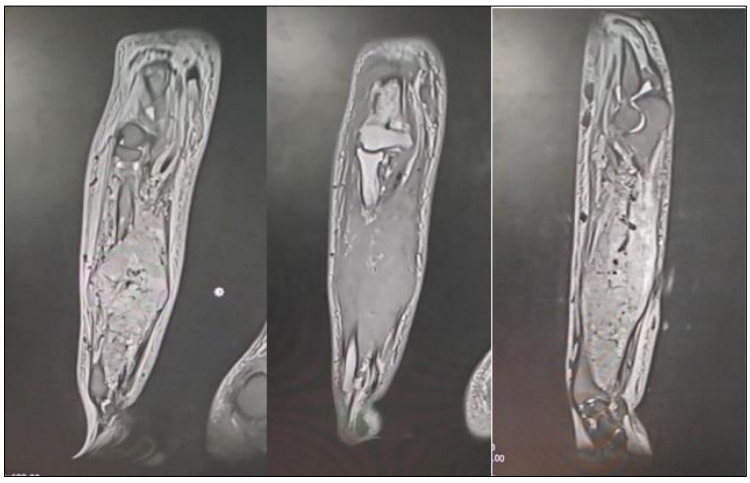

Figure 5: Forearm MRI in August 2023

Hospitalized at the end of August 2023 for respiratory distress, pleural puncture and talcation being contraindicated due to the partitioning of pleurisy, pleural nodules and masses and his general condition, the patient, discharged against medical advice, died a few days later at his home.

DISCUSSION

EMC, first described by Stout and Verner [12], was first defined by Enzinger and Shiraki in 1972 as a rare soft tissue sarcoma with a distinct histologic identity [13].

Approximately 80% of these tumors occur in the extremities, its location is in fact ubiquitous. The lower extremity is the most common location of the EMC [14, 15], which was confirmed in our case.

The clinical signs are not specific; often it involves pain or swelling that can ulcerate the skin and restrict range of motion, the perfect clinical picture for our patient.

Radiological images are non-specific; lesions show low density on CT, low signal intensity on T1-weighted MRIs, and high signal intensity on T2-weighted MRIs [16].

Macroscopically, it appears as a mass of approximately 1 to 25 cm (mainly 6 to 13 cm), firm, homogeneous, gray or gelatinous in cross-section, well bounded by a fibrous capsule and generally presents a configuration multilobular or nodular with a relatively well-defined margin and an incomplete fibrous capsule [6-21].

Immunohistochemically, tumor cells always express vimentin; in about a third of cases, S100 protein (typically weak and focal labeling) and often CD 99. Cytokeratin and EMA are sometimes focally expressed [20]. Other markers are not expressed, except sometimes NSE, synaptophysin, more rarely chromogranin, suggesting possible neuroendocrine differentiation [7-20].

Genetically, around 80% of EMC is associated with the recurrent specific chromosome translocation t(9;22)(q22;q12), leading to a genetic rearrangement between the EWS gene, located on chromosome 22, and the TEC gene, located on chromosome 9 (20) . The rearrangement can be detected by RT-PCR on fixed tissue. Other translocations are rarely observed: t(9; 15)(q22;q12), t(9;17)(q22;q11.2), t(9;17;15) (q22;q11;q22), t(2; 13) (q32; p12) and t (11; 22) (q11; p11) [22, 23].

Pulmonary metastases are common, occurring 62 to 82% of sarcoma patients [24, 25], but EMC can also metastasize to the abdomen, bones and peritoneum [20]. Our patient presented with synchronous pulmonary metastases and, in the course of his disease, developed visceral metastases above and below the diaphragm (pleura, liver, adrenal gland and kidney), soft tissue metastases (frontal scalp and right forearm) as well as supra-diaphragmatic lymphadenopathy.

Brain metastases from soft tissue sarcomas only affect a minority of patients with soft tissue sarcomas, with a prevalence between 1 and 6% [26, 27]. Cardiac metastases are extremely rare [28].

The development of metastases decreases the probability of survival [6-8], but this is variable. Median survival after detection of metastases has been reported to range from 1.7 years [8], to 5.5 years [6], with individuals surviving up to 14 years after spread of EMC to the lungs [5]. Our patient survived almost 10 years after the diagnosis of the secondary sites of his disease.

Treatment consists first of surgery of the primary tumor and/or metastasis, radiotherapy and chemotherapy, as the first line has not been proven [11]. The response to chemotherapy is generally poor and the results of radiotherapy are discordant [29].

Localized disease is treated with extensive local resection, while metastatic disease is often treated with systemic chemotherapy. In a retrospective review, chemotherapy was able to produce stable disease for more than six months in 25% of patients [8]. Our patient benefited from surgical treatment followed by adjuvant chemotherapy, his disease was only stabilized for approximately two years before progressing under an adapted protocol due to the unavailability of a molecule.

A 10-year survival of between 65 and 78%, aggressive variants have been described [30], the presented case documents nine years of follow-up of metastatic EMC. Recent case series in the literature have reported therapeutic responses with Sunitinib, but the survival benefit to date is unknown [31, 32].

Tyrosine kinase inhibitors may have better activity than chemotherapy in this disease: a clinical benefit of sunitinib was observed in 8 out of 10 patients with the EWSR1–NR4A3 translocation (6 PR); high expression and activation of RET, a known target of sunitinib was noted [32]. A phase 2 trial of pazopanib in patients with unresectable or metastatic chondrosarcoma reported a median overall survival of 17.6 months and a median progression-free survival of 7.9 months [33].

The main factors of poor prognosis are: advanced age of the patient, tumor size greater than 10 cm, proximal site, incomplete initial surgical excision, absence of surgical resection and discovery of metastases. At initial diagnosis [6-20]. Our patient had a poor prognosis due to the size of the tumor (10 x 15 cm) and synchronous pulmonary metastases.

CONCLUSION

This work reports an unusual case of highly aggressive EMC that proved multi-metastatic in its clinical evolution over nearly 9 years of follow-up. This observation demonstrated that EMC has the potential for a more invasive transition during its prolonged clinical course, which can lead to a dismal prognosis.

In addition, this work informs us about the difficulties of developing countries in managing certain diseases due to the unavailability of certain drugs.

Early consultation would spare us this type of evolution, and we recommend consulting a doctor at the slightest swelling, regardless of the site, in order to clarify its histological nature, avoid untoward progression and, if possible, achieve a complete therapeutic response.

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