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Carcinomatous pachymeningitis secondary to leg ewing sarcoma: an unusual metastatic site

Abboud Fatima Zahra[1], Chebihi Hassani Ghita[1], Ait Erraisse Mohamed[1], Youssoufi Moulay Ali[2], Bouhafa Touria[1], Hassouni Khalid[1]

[1] Department of Radiation Oncology, University Hospital Hassan II, Morocco
[2] Medical Physics Unit, Oncology Hospital, University Hospital Hassan II, Morocco

SUMMARY

Introduction: We report here a case of carcinomatous pachymeningitis in a patient followed for Ewing's Sarcoma (ES) of the leg. Methods: A 17-year-old patient followed for leg Ewing's sarcoma undergoing neoadjuvant chemotherapy who presents for the management of acute and atrocious headaches of rapidly progressive onset. He had a brain MRI that showed carcinomatous pachymeningitis, the diagnosis is confirmed by a lumbar puncture of the Cerebrospinal Fluid (CSF) that showed the presence of cancer cells related to Ewing's sarcoma. Results: The patient was proposed for chemotherapy and craniospinal irradiation (CSI), but he died before starting his treatment. Conclusions: Carcinomatous pachymeningitis in Ewing's sarcoma is an unusual metastatic localization and its prognosis is pejorative.

Key words: carcinomatous pachymeningitis, Ewing's sarcoma, cerebrospinal fluid

Address for correspondence:

Abboud Fatima Zahra, Department of Radiation Oncology, University Hospital Hassan II, Morocco, Tel: +212627782466, email: abboud.fatimazahra@gmail.com

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INTRODUCTION

Carcinomatous Meningitis (CM) appears late in the natural history of cancer and represents an extremely pejorative progressive event. Without treatment, the median survival time is estimated at four to six weeks [1, 2]. The incidence of CM is increasing due to medical advances that are prolonging the survival of patients [1, 3]. It is diagnosed in 5% to 10% of cancers and complicates 5% of breast cancers (essentially triple-negative and overexpressing HER2), 5 to 18% of bronchopulmonary cancers (adenocarcinomas and small cell bronchial cancers mainly) and 25% of melanomas [4-7]. The diagnosis of carcinomatous meningitis is based on the presence of carcinomatous cells in a sample of cerebrospinal fluid or on the combination of suggestive clinical signs and evocative abnormalities on the cerebrospinal image, in a cancer context [4, 8]. It is a very devastating diagnosis, with a median patient survival of about 3 months [9]. The treatment is very controversial. From a literature review, different modalities of treatment have been used, such as intrathecal (IT) and/or systemic chemotherapy and radiotherapy, but none of them show a significant benefit for overall survival [9].

We report the case of a patient followed for Ewing's sarcoma who has had carcinomatous pachymeningitis secondary to his disease, and who represents an unusual metastatic location in the case of Ewing's sarcoma.

METHODS: CASE REPORT

We report here the case of a 17-year-old patient with a history of progressive swelling of the right leg evolving 3 months before his consultation in a context of altered general condition and functional impotence of the right lower limb. The clinical examination on admission found a patient with a performance status of 2. On examination of the right leg a painful swelling taking the entire upper third of the leg at its outer surface, with no opposite inflammatory signs, with limited movement of the right knee due to pain. Neither on neurological examination of the right lower limb, there was neither motor disorder (segmental muscle strength is rated at 5/5) nor sensitivity. On examination of the lymph node areas, there was no palpable adenopathy. A CT scan of the right leg was performed and objectified a mass of the upper fibula. The patient received a biopsy of this mass and the pathological analysis found the invasion of the biopsiac fragments of the fibula by a morphologically undifferentiated round cell

tumor process involving discussion of Ewing's sarcoma. The immunohistochemical study confirmed the diagnosis of Ewing's sarcoma of the right fibula.

The search for rearrangement of the EWS gene was carried out by Fluorescent In Situ Hybridization (FISH). This rearrangement was found on 60% of the tumor cells. The MRI of the right lower limb objectized a lesional process centered on the upper two-thirds of the fibula (epiphysometaphysodiaphysis), in hyposignal T1, hypersignal STIR heterogeneous, significantly elevated, containing necrotic areas, measuring approximately 32*197 mm, this process is responsible for lysis of the fibula cortex, with extension to the soft tissue and invasion of the muscles of the outer right leg compartment, coming into contact with the outer cortex of the ipsilateral tibia, without bone invasion or periosteal reaction of the latter. This process encapsulates the anterior tibial artery over a circumference of 180°, at its upper third, extended over 7 cm, which remains permeable. It also has contact with the fibular artery (less than 90°); it remains at a distance from the posterior fibular arteries. There is also a secondary bone lesion of the right tibial metaphysis. The bone scan did not find any other secondary bone lesions other than the 2 lesions of the right tibia found on the MRI.

The patient had a bone marrow biopsy and the immunopathological analysis found infiltration of the bone marrow by sarcomatous cells related to Ewing's sarcoma. The chest and abdominal-pelvic CT scans did not find any visceral secondary locations. Laboratory evaluations including complete blood count, electrolytes and basic metabolic profile were normal.

After being assessed, the patient was put on neoadjuvant chemotherapy: seven cycles based on CAV-IE for two months.

The control MRI of the right lower limb found a progression of the tumor process of the right fibula, with the progression of the secondary bone lesion of the tibia.

Subsequently, the patient applied for an amputation of the right leg with the insertion of a prosthesis afterward, but since he refused the amputation, external radiotherapy on the right leg was scheduled at home.

After two cures of external radiotherapy on the right leg, the patient reports a notion of atrocious headaches of rapidly progressive installation and rebellious to analgesics with photophobia and vomiting in a jet. A brain MRI was performed urgently in the patient and objectified a diffuse pachymeningeal thickening, hypo-signal T1 (Figure 1), iso-signal T2 and FLAIR (Figures 2 and 3), hyper-signal on the diffusion sequences (Figure 4), takes the gadolinium (Figure 5), arriving at 17 mm of maximum thickness, sus, and sub-tentorial. It associates a peri-lesional focal edema parietal right.

The patient underwent a first lumbar puncture, with normal pathological analysis, then a second lumbar puncture, which objectified the presence of sarcomatous cells in the cerebrospinal fluid related to Ewing's sarcoma. A third lumbar puncture also confirmed the diagnosis of carcinomatous meningitis in our patients.

After confirming the diagnosis of carcinomatous pachymeningitis, systemic chemotherapy and craniospinal irradiation (at a total dose of 30 Gy in 10 fractions per fraction, one fraction per day and 5 fractions per week, spread over two weeks, using a linear accelerator, with 6 MeV energy photons) were programmed in our patient. Intrathecal chemotherapy

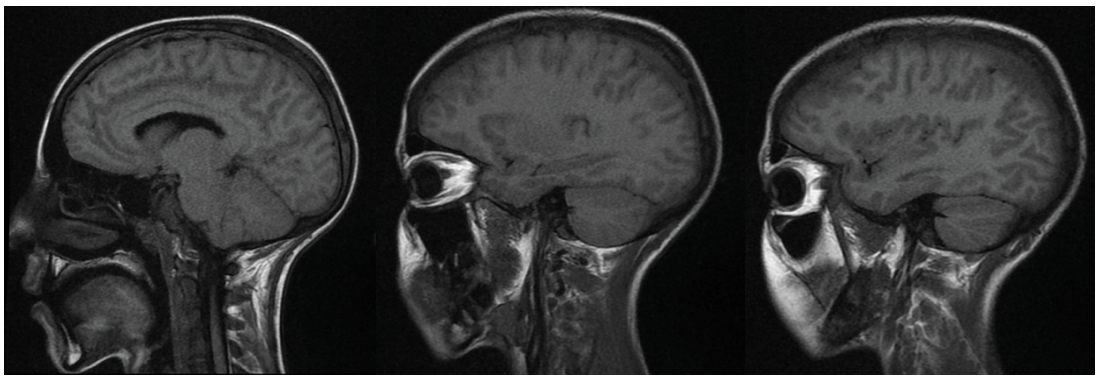

Fig. 1. Image showing sections of the brain MRI, T1 sequence, in the sagittal plane showing the thickening of the meninges in ypo-signal

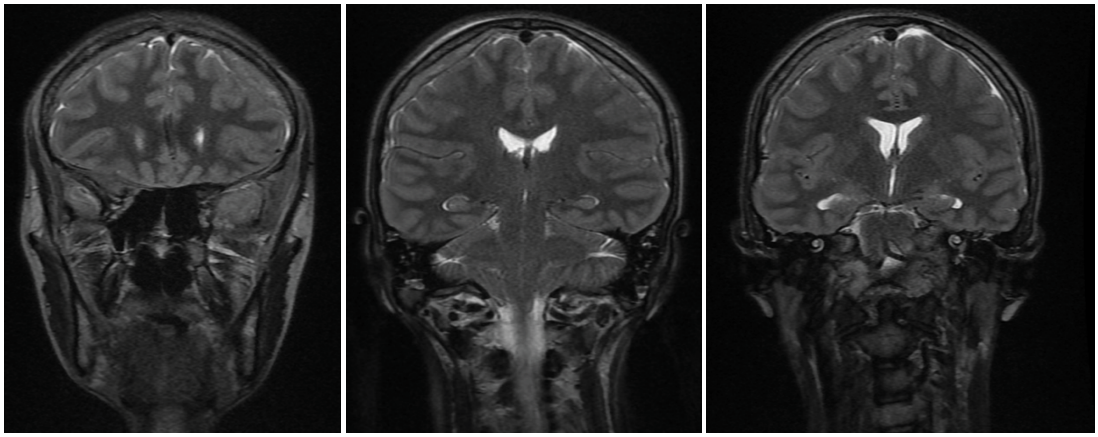

Fig. 2. Image showing sections of the brain MRI, T2 sequence, in the frontal plane showing the thickening of the meninges in iso-signal

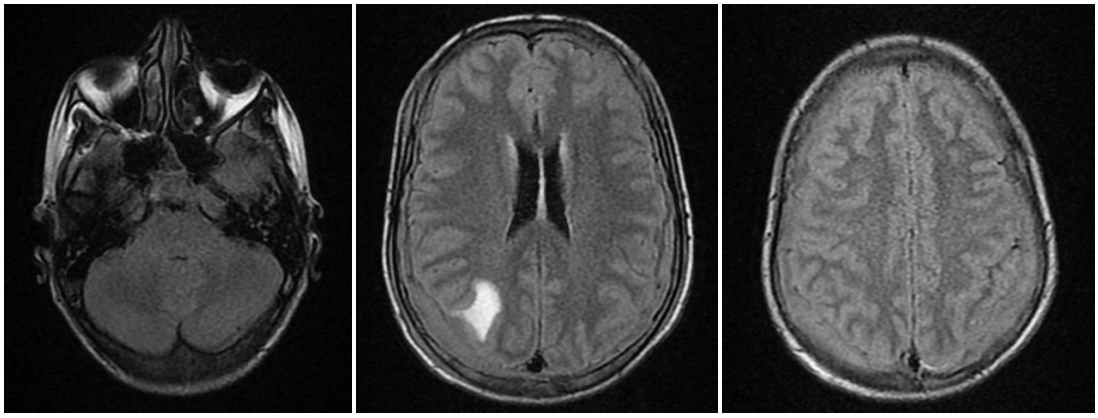

Fig. 3. Image showing sections of the brain MRI, FLAIR sequence, in the axial plane showing the thickening of the meninges in iso-signal

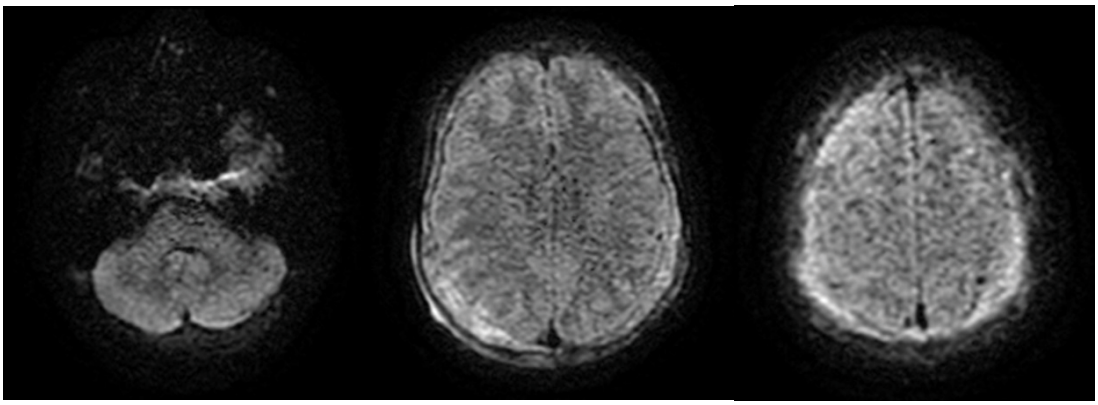

Fig. 4. Image showing sections of the brain MRI, diffusion sequence, in the axial plane showing the thickening of the meninges in hyper-signal

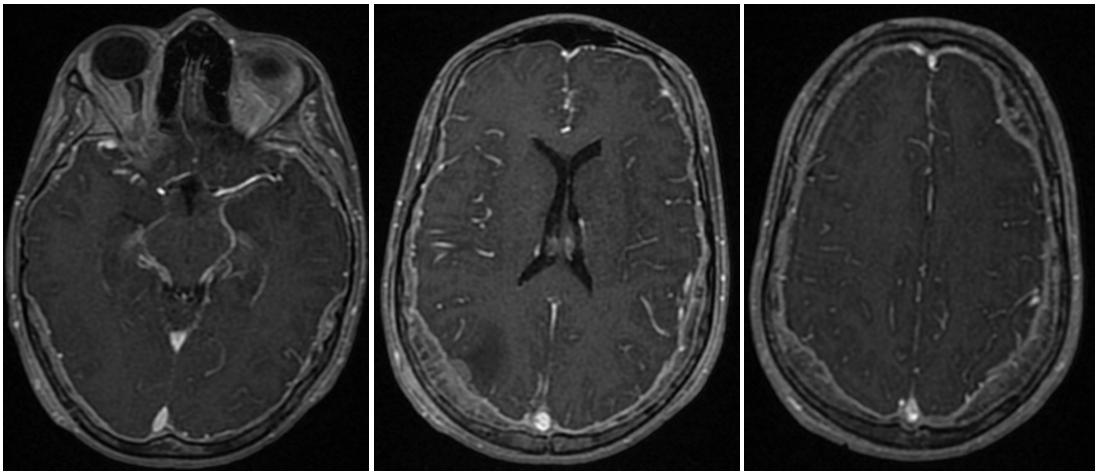

Fig. 5. Image showing sections of axial brain MRI, T1 sequence with gadolinium injection, showing contrast uptake

has not been proposed for the patient, given the deterioration of his general condition.

RESULTS

The patient died before starting chemotherapy or craniospinal radiotherapy.

DISCUSSION

Carcinomatous Meningitis (CM) is an infiltration of the leptomeninges by malignant cells. The largest providers of carcinomatous meningitis are breast cancer (12%-35% of carcinomatous meningitis), bronchopulmonary cancer (10%-26%), melanoma (5%-25%), and less frequently gastrointestinal cancer (4%-14%) and cancers of unknown primary importance (1%-7%) [4, 5].

Carcinomatous meningitis secondary to ES is rare; therefore, it is difficult to diagnose. Some histological characteristics are associated with an increased risk of carcinomatous meningitis [5]. The dissemination of neoplastic cells to the neuromeningeal space is mainly done by blood [5] or from vertebral or peri-vertebral metastases [10]. More rarely, it is done by contiguity since the primitive sound [4, 10]. In half of all cases, carcinomatous meningitis is associated with secondary brain lesions [5, 11].

CM usually affects multiple areas of the neuroaxis, manifesting clinically as a range of multifocal neurological signs and symptoms including cranial and spinal nerve neuropathies, altered mental

status and cerebellar dysfunction [12]. Although symptoms of intracranial hypertension (headache and confusion) are frequently reported presentations, they are nonspecific and rarely aid diagnosis, contributing to the diagnostic challenge in our case. Furthermore, the absence of other symptomology despite extensive metastases is an interesting finding.

Key investigative tests include Lumbar Puncture (LP) and gadolinium-enhanced brain MRI (Gd-MRI).

The CSF typically demonstrates a low glucose (30%-50% of cases), an elevated protein (70%-90%) and lymphocytic pleocytosis (50%-60%). Opening pressures should routinely be measured as this can be elevated in 50% of cases [7]. Definitive diagnosis requires the identification of malignant cells in the CSF. This is achieved in 50%-70% of cases on initial LP, increasing to >90% after three LPs [13].

The presence of malignant cells in the CSF confirms the diagnosis of CM but, in general, assignment to a particular tumor is not possible [14]. Only 45%-55% of CM patients have an initial positive CSF cytology [15]. Of a series of 90 patients, 5% had positive CSF cytology only from either the ventricles or cisterna magna [16]. In a series of 60 patients with CM with positive lumbar CSF cytology and no evidence of CSF flow obstruction, a discordance rate of 30% was observed between ventricular and lumbar cytology obtained simultaneously [17]. In the presence of spinal signs or symptoms, the lumbar CSF was more likely to be positive and, conversely, in the presence of cranial signs or symptoms, the ventricular CSF was more likely to be positive. Not obtaining CSF from a site of symptomatic or radiographically demonstrated disease was found to correlate with false-negative cytology results, as did withdrawing small CSF volumes (less than 10.5 mL), delayed processing of specimens, and obtaining fewer than two samples [18]. To improve the sensitivity of CSF cytologic analysis, one should collect a non-hemorrhagic CSF sample of at least 10.5mLfroma site compatible with the clinical manifestations or directed by radiologic findings. A second CSF assessment collected in a similar manner increases the sensitivity of CSF cytology to 80% in patients with positive CSF (approximately 50% of all patients with CM) [17, 18]. The time of processing of the CSF samples should ensure the viability of malignant cells (50% of viable cells after 30 minutes, 10% after 90 minutes) [19]. CSF fixation in dedicated tubes allows longer intervals between CSF sampling and laboratory analysis. Even after correcting for these factors, approximately 25%-30% of patients with clinical CM and normal neuraxis imaging have persistently negative CSF cytology [2, 8, 9, 20-23]. Post mortem analyses have shown that cytology remained negative in up to 40% of patients with clinically suspected CM then proven at the time of autopsy [15]. This rate increased to more than 50% in patients when CM is focal.

Although hypoglycorrhachia has been reported in CM, it is more commonly seen in infective aetiologies, with tuberculosis meningitis associated with the lowest glycorrhachia [24]. The marked similarity in CSF analysis between TB meningitis and CM in the absence of malignant cytology can be diagnostically challenging.

In terms of imaging, the brain scanner is much less effective than MRI in diagnosing pachymeningitis. He may not visualize moderate lesions. In larger forms, it shows a hyperdense thickening of the dura mater that increases after injection of contrast agent [25]. So the brain scan is not an examination to be performed in case of suspected carcinomatous meningitis, its sensitivity is only 30% [26].

MRI is the reference examination, to diagnose pachymeningitis, assess its intensity and spread of lesions and detect a possible complication (thrombosis of the upper longitudinal sinus or parenchymal extension). The thickening of the dura mater appears hyposignal on T1 and T2 weighted sequences and increases significantly (hypersignal) on T1 sequences after injection of gadolinium. In sequence T2, the hyposignal linked to the density of the fibrous tissue can be bordered by a thin peripheral hypersignal border indicating the hypervascularization of the injured dura mater [27]. A diffuse hypersignal in T2 is also described [25, 28]. The field of exploration must cover the entire central nervous system (brain and bone marrow) and must include an injection of contrast agent (gadolinium monodose) [29-32]. The examination should preferably be performed before the lumbar puncture. MRI shows meningeal contrast capture in nearly 90% of cases. It can be a pachymening contrast shot, diffuse, or focused, more or less associated with masses. The search for secondary parenchymal lesion(s) in the brain or spinal cord is systematic, as is the search for bone lesion(s) [26].

Oncological treatment should always be assessed according to the patient's clinical condition, systemic evolution, and desire given the pejorative prognosis of this location. There is no effective treatment, but current available options are corticosteroids, radiation therapy, and chemotherapy. Corticosteroids do not reverse neurologic deficits but can improve headache and pain. Radiation therapy includes cranial irradiation and whole-brain radiation to target symptomatic sites for palliative purposes.

The main objective is still quality of life with stabilization or even reduction of neurological symptomatology [3, 7] but targeted chemotherapy/therapy can still be offered in subjects with low neurological symptoms, maintaining a correct overall condition (Karnofsky index of more than 60%) and systemic therapeutic possibilities [1, 8]. However, since external radiotherapy has not shown any survival benefit, treatment-related morbidity should be avoided. Rudnicka et al. evaluated the impact of radiotherapy on survival in 67 patients with carcinomatous meningitis due to breast cancer [20]. Three-quarters of patients were treated with panencephalic irradiation, and one-quarter with craniospinal irradiation. Craniospinal radiotherapy has shown a positive impact on survival in single-factor analysis, but not in multifactor analysis, unlike systemic treatment and intrathecal chemotherapy. Morris et al. also showed no improvement in the probability of survival following panencephalic radiotherapy in 125 patients with carcinomatous meningitis secondary to non-small cell lung cancer [33]. In addition, radiotherapy started late (i.e., after the onset of neurological symptoms) probably does not allow them to regress significantly [34].

Regarding chemotherapy, Methotrexate (MTX) and cytosine

arabinoside (Ara-C) were historically the mainstays of medical treatment for carcinomatous meningitis caused by any primary cancer. They remain the main drugs used in intrathecal therapy in carcinomatous meningitis. Topotecan has also been used with equivocal results [35]. Liposomal Ara-C is another option with similar results in efficacy, but with the advantage of reduced frequency of intrathecal therapy [36]. The following schedules have been recommended.

If the patient is fit enough intravenous chemotherapy with pemetrexed is recommended if the patient has not already received the drug. There is some evidence in preclinical studies of its efficacy [37].

CONCLUSION

In summary, we presented a case of carcinomatous pachymeningitis due to Ewing's sarcoma, which represents an unusual metastatic site of this disease.

COMPETING INTEREST

The authors state that they have no Conflict of Interest.

AUTHORS' CONTRIBUTIONS

All authors read and approved the final version of the manuscript.

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