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Rhabdoid Tumors in Children: About a Moroccan Pediatric Population

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Abstract

Background: Rhabdoid tumor (RT) is a rare, highly malignant tumor that occurs primarily in the central nervous system (CNS), also known as atypical Rhabdoid/teratoid tumor (AT/RT), kidney (malignant Rhabdoid tumor of the kidney) or soft tissue (malignant extra-renal Rhabdoid tumor extra-cerebral). Infants, usually in their first year of life, may also have a dual location of primary RT, consistent with a genetic predisposition to cancer.

Materials and Methods: This is a retrospective study of a series of RT collected at the Mother and Child Radiology Department of the Hassan II hospital in Fez during a period of 7 years (janvier 2016 to December 2021). Epidemiological, clinical radiological, pathological and therapeutic results were analyzed by Excel.

Results: RT represents a frequency of 1.16 new cases per year followed in the Mother and Child Radiology Department. The median age of the study population was 23 months (01 month-5 years) and the sex ratio was 1.33 (F/M). Abdominal volume increase was the most common cause of consultation for the kidney locations followed by an intracranial hypertension syndrome for the brain locations. Majority of cases were diagnosed at locally advanced and metastatic stages (62.5%of cases). 57% was a renal RT, 14% was a temporal supratentorial cerebral localization, 14% was an orbital localization and 14% was a localization of the soft parts of the left axillary, among these cases two patients had a bifocal localization with an atypical AT/RT at the level of the posterior cerebral fossa.

Four cases in this study underwent surgery; it was complete ans without microscopic residue. One patient received an exclusive radiotherapy. Chemotherapy neoadjuvant was prescribed in four patients and mostly in palliative setting in one patient. Four patients were cured and three patients were died from disease.

Conclusion: RT is rare, highly malignant tumors. The radiologist therefore has an important role for in the management of these patients, both in the diagnostic phase, to affirm or deny the various signs of malignancý as well as in the therapeutic and follow-up phases, to evaluate the efficacý of the treatment and detect signs of recurrence.

Keywords: Rhabdoid tumor • Rhabdoid/Teratoid atypical tumor • Imaging • Pathological diagnosis

Introduction

Rhabdoid tumor (RT) is a rare, highly malignant tumor that occurs primarily in the central nervous system (CNS), also known as atypical rhabdoid/teratoid tumor (AT/RT), kidney (malignant rhabdoid tumor of the kidney), or soft tissue (malignant extra-renal rhabdoid tumor extra-cerebral). The most common sites of extrarenal RTs are the skin, liver, and lungs, although almost any soft tissue, including the orbit, thymus, uterus, bladder, and neck, has been reported. Infants, usually in their first year of life, may also have a dual location of primary RT, consistent with a genetic predisposition to cancer. These infants typically have a CNS RT/RT and a malignant renal rhabdoid tumor or a RT/RT and a rhabdoid tumor of another organ [1].

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Methodology

This is a retrospective study carried out on patients followed for RT in the Mother and Child Radiology Department of Hassan II University Hospital of Fez between 2016 and 2021. We have included any patient less than 15 years old who has RT or AT/RT and whose histological diagnosis was made through a CT scan or ultrasound-guided biopsy or surgical excision. We determined the clinical, radiological and biological data as well as the treatments received. The type of treatment response was specified based on the RECIST V1.1 criteria.

Results

A total of 07 cases of RT and AT/RT were recorded. The annual frequency of these tumors was 1.16 new cases per year. The mean age of our patients was 23 months old with extremes of one month and five years. Female predominance (57.14% of cases) was noted. The mean time between onset of symptomatology and consultation was 27 days with extremes of one day of birth and 90 days. Four patients in our series (57% of cases) presented suggestive symptoms of renal involvement, abdominal volume increase was noted in 03 patients, and right lumbar fossa pain in one patient, intracranial hypertension in two patients. The discovery of an irreducible exophthalmia

patient was indicative of rhabdoid tumor in one patient while the disease was discovered during the etiological workup of a left axillary soft tissue mass in one.

In our study, imagining were mainly based ultrasound for abdominal and left axillary soft tissue. Brain MRI was performed in patients with neuroglial symptoms and irreducible exophthalmia. A chest and abdominal CT scan for assessment of extension was performed in all patients of our series. Histological diagnosis was based on ultrasound-guided biopsy in five patients (71.4%) stereotactic biopsy in one patient (14%) and surgical excision specimen in one patient (14% of cases).

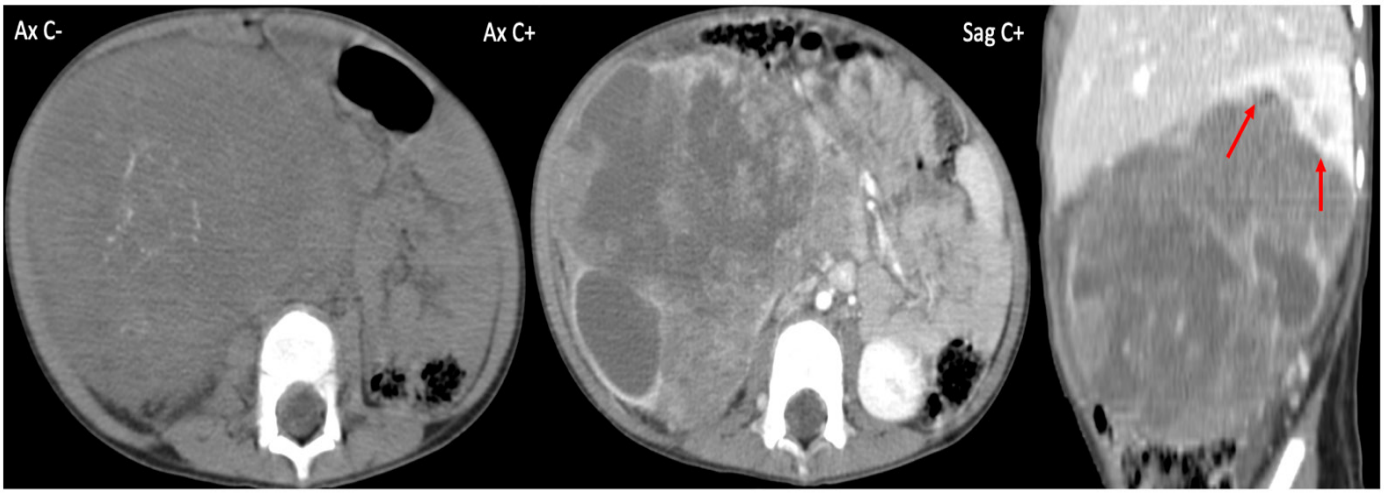

Figure 1. Abdominal CT: Massive right renal mass, polar inferior (red arrow) with irregular contours, heterogeneously enhanced after contrast, including linear calcifications and necrosis areas.

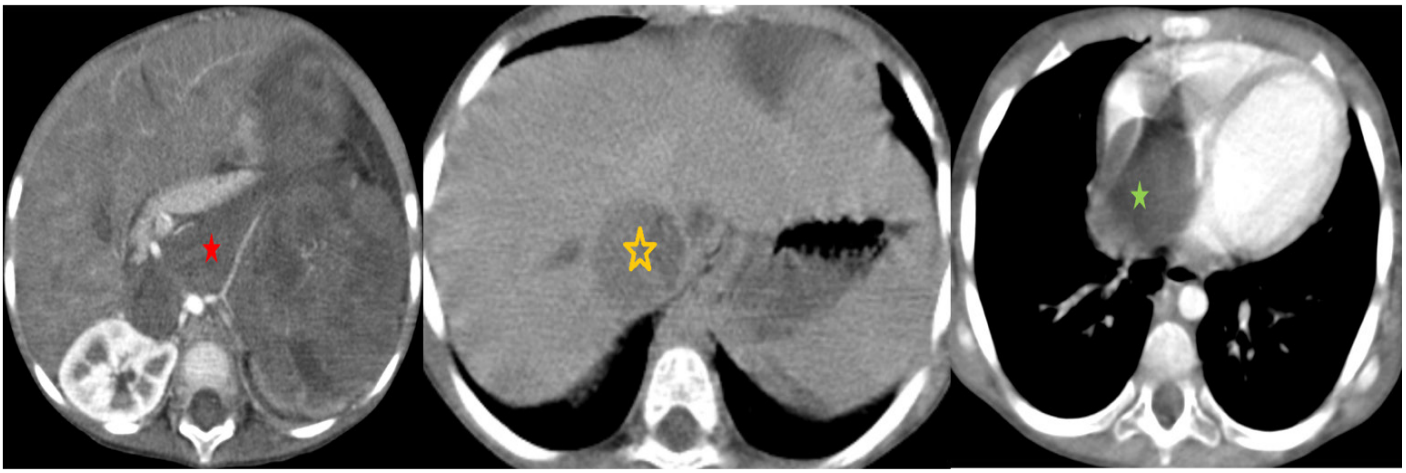

Figure 2. Chest and abdominal CT scan with contrast: Tumor thrombosis of the retrohepatic inferior vena cava extended to the right renal vein and cardiac chambers with LV thrombosis.

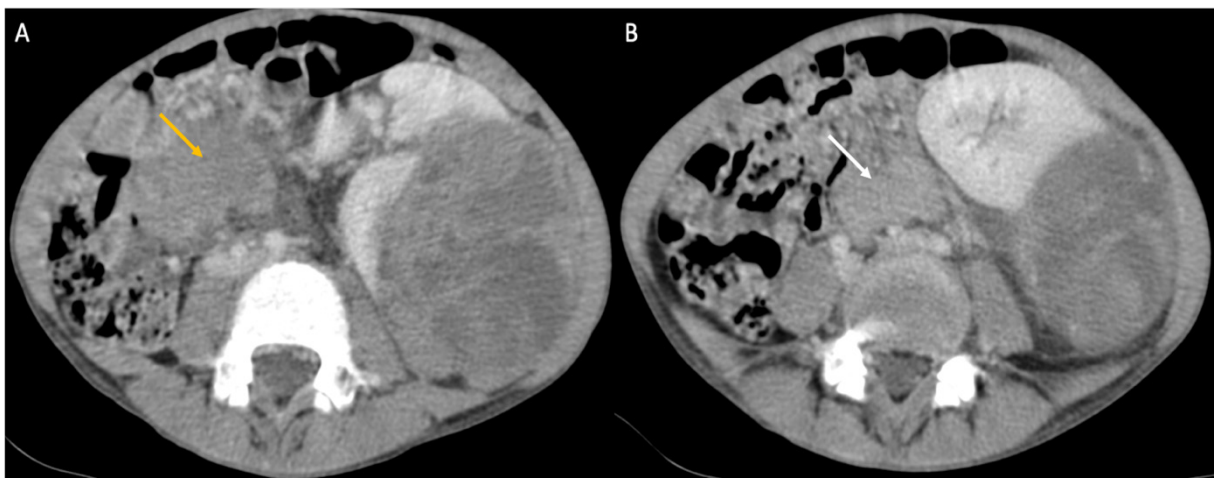

Figure 3. Abdominal CT Scan with contrast: **(A).** Magma of coelio-mesenteric and **(B).** Retroperitoneal adenopathies.

For renal and left axillary soft tissue locations, ultrasound showed a well-limited, heterogeneous mass, including areas of calcification and necrosis. Color Doppler showed a vascular tumor.

On CT, renal RT appeared as large, centrally located, heterogeneous masses with irregular contours.

For renal location, the CT scan showed a large centrally located renal mass, with irregular contours and heterogeneous enhancement, containing areas of necrosis and linear calcifications (Figure 1).

A tumor thrombosis of the retro hepatic vein cava extended to the right renal vein and the cardiac cavities with a thrombus in the left ventricle was discovered in one patient (Figure 2). Mesenteric and retroperitoneal lymphadenopathies were found in three patients (Figure 3) and lung metastases in two patients (Figure 4).

For the supratentorial cerebral location, cerebral Magnetic Resonance Imaging (MRI) showed an intra-axial left temporal tumor described as T1 iso-intense with hemorrhagic areas, T2 hypo-intense, containing calcifications (T2* hypo-intense), massively necrotic, weakly enhanced after contrast

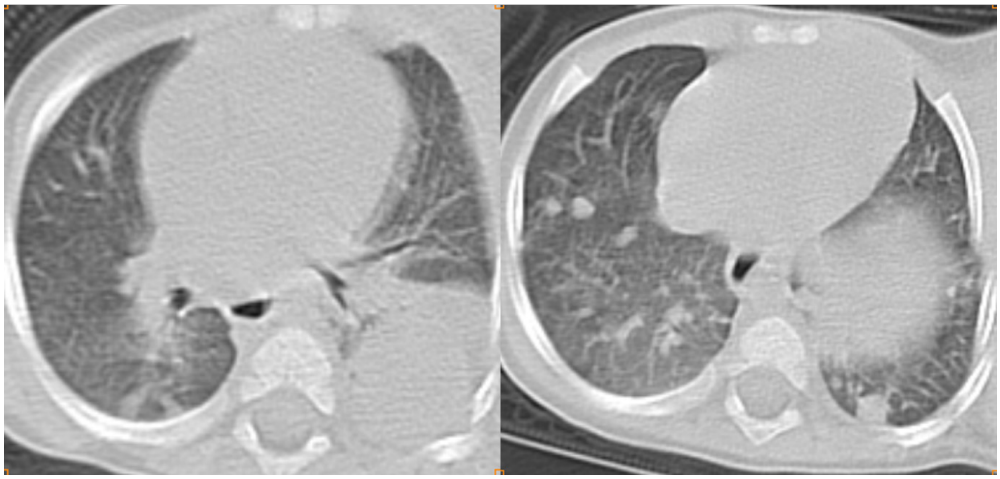

Figure 4. Chest CT scan: Nodules and pulmonary masses, bilateral compatible with secondary locations.

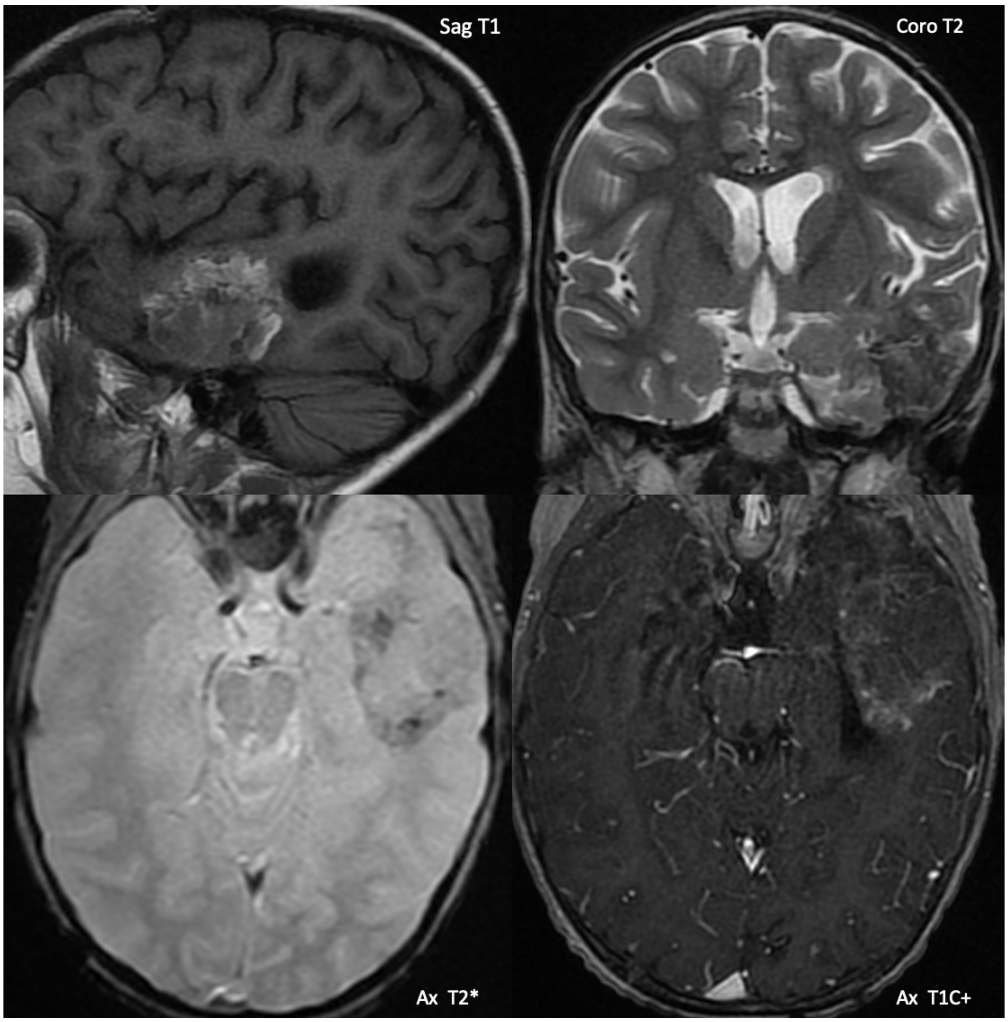

Figure 5. Brain MRI: Intra-axial left temporal tumor process, described in T1 iso-signal with hemorrhagic areas, in T2 hypo signal, containing calcifications in T2* hyposignal, massively necrotic, weakly enhanced after contrast.

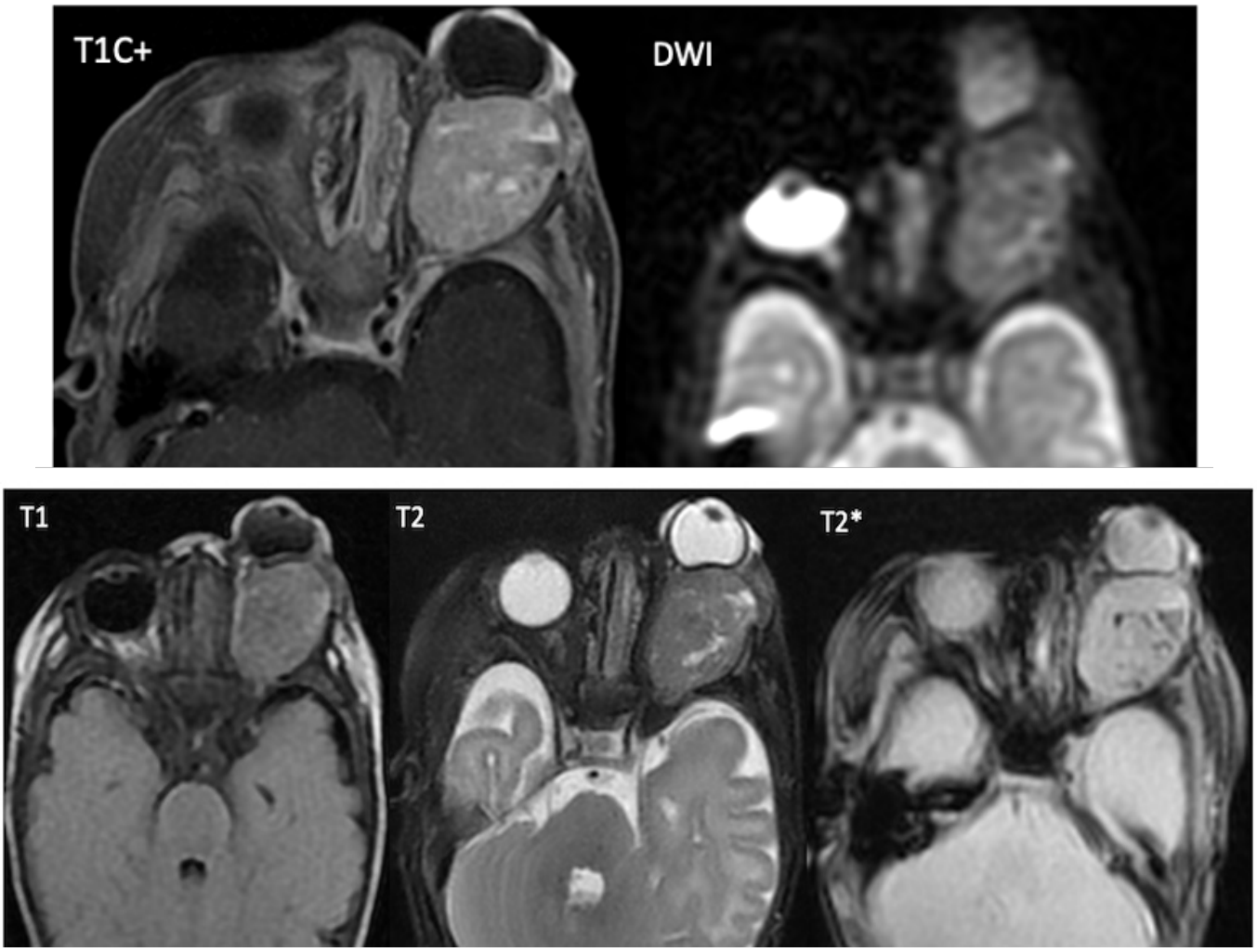

Figure 6. Orbito-cerebral MRI: Well limited left retroorbital process with a double solid-cystic component, the fleshy portion is described in T1 and T2 hyposignal, non restrictive in DWI, moderately enhanced after contrast, containing calcifications (T2* hyposignal). This process is responsible for a stage III exophthalmos; it compresses the optic nerve and respects the homolateral cavernous sinus.

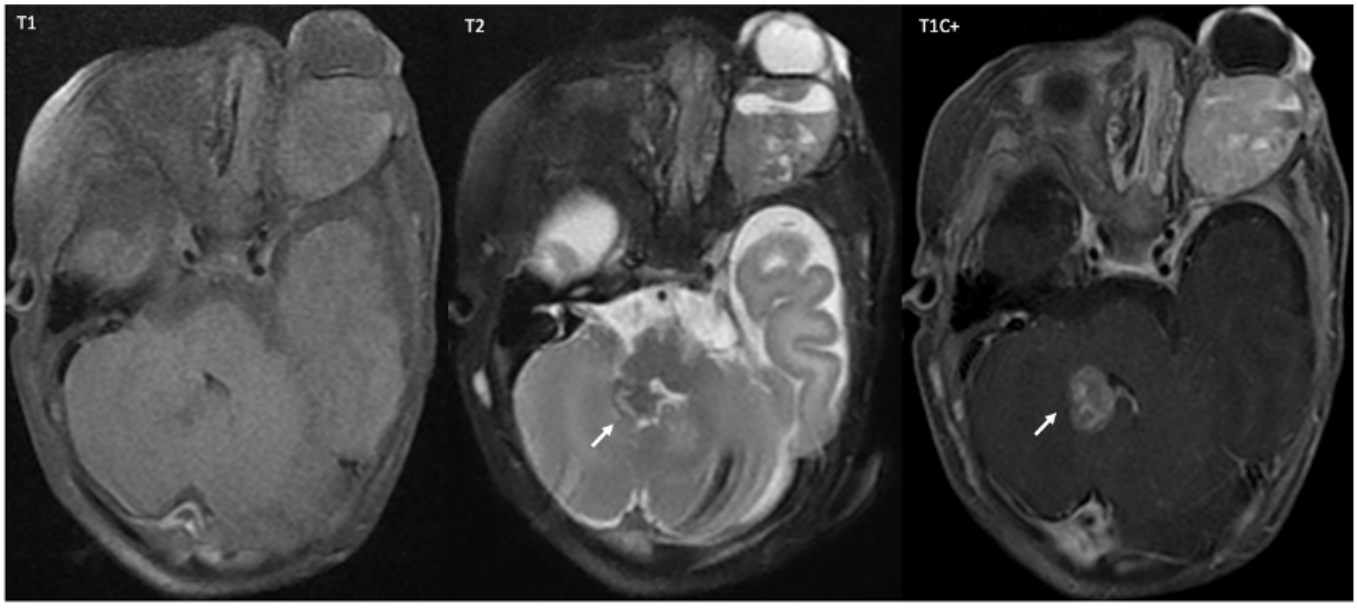

Figure 7. In the same patient On the sections passing through the posterior cerebral fossa, we note the presence of a right vermio-cerebellar lesion, presenting the same semiological characteristics as the retro-orbital lesion previously described, molding the floor of the V4 (arrow) in connection with a double localization of the left orbital rhabdoid tumor.

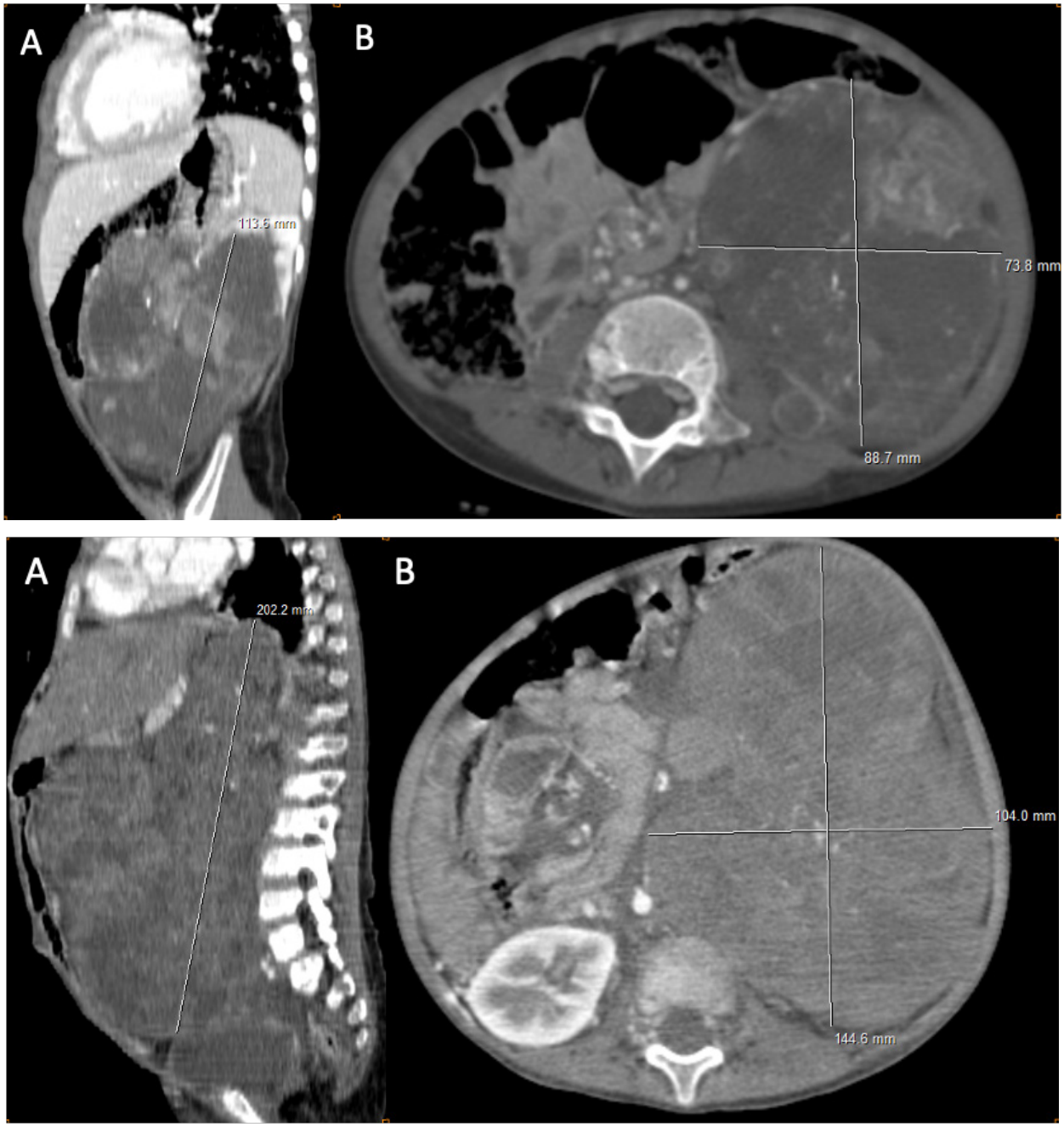

Figure 8. Initial abdominal-pelvic CT before chemotherapy A: sagittal view, B: axial view. Control after neoadjuvant chemotherapy C: sagittal view, D: axial view: Regression of the large locally advanced left renal mass of about 70% of initial volume.

(Figure 5).

In the case of intra-orbital location, MRI had shown a well limited left intra-orbital process, with a solid-cystic component, the solid portion was described as T1 and T2 hypointense, with no restricted diffusion, moderately enhanced after contrast, containing calcifications (T2* hypointense). This mass was responsible for exophthalmos stage III, the optic nerve was compressed (Figure 6). A double location in the posterior cerebral fossa has been found in the same patient (Figure 7).

Neoadjuvant chemotherapy was performed in four patients (57% of cases) according to the GFA-nephro2005 HR protocol. Two Initially unrespectable diseases were converted to resectable disease after neoadjuvant chemotherapy (Figure 8). Surgery was carcinologic without any microscopic residue in all the resected cases.

One patient received exclusive radiotherapy, the clinical and radiological response were good (Figure 9). The total dose was 54Gy. Adjuvant chemotherapy was not performed under any circumstances. In the metastatic setting, first-line metastatic treatment consisted of a triple therapy based on the CAP protocol in one patient with marked disease progression (Figure 10).

Discussion

Rhabdoid tumors are quite rare. In the United States, the annual incidence in children younger than 15 years of age is 0.19 per million for renal tumors, it is 0.89 per million for cerebral teratoid-rhabdoid tumors (AT/RT) and 0.32 per million for tumors at other sites [2].

The fact that we have collected only 07 cases of rhabdoid tumors over a period of 06 years, testifies to the rarity of this tumor also reported in the literature.

Malignant renal rhabdoid tumors occur exclusively in the pediatric population, with 60% of children affected by the age of one and 80% by

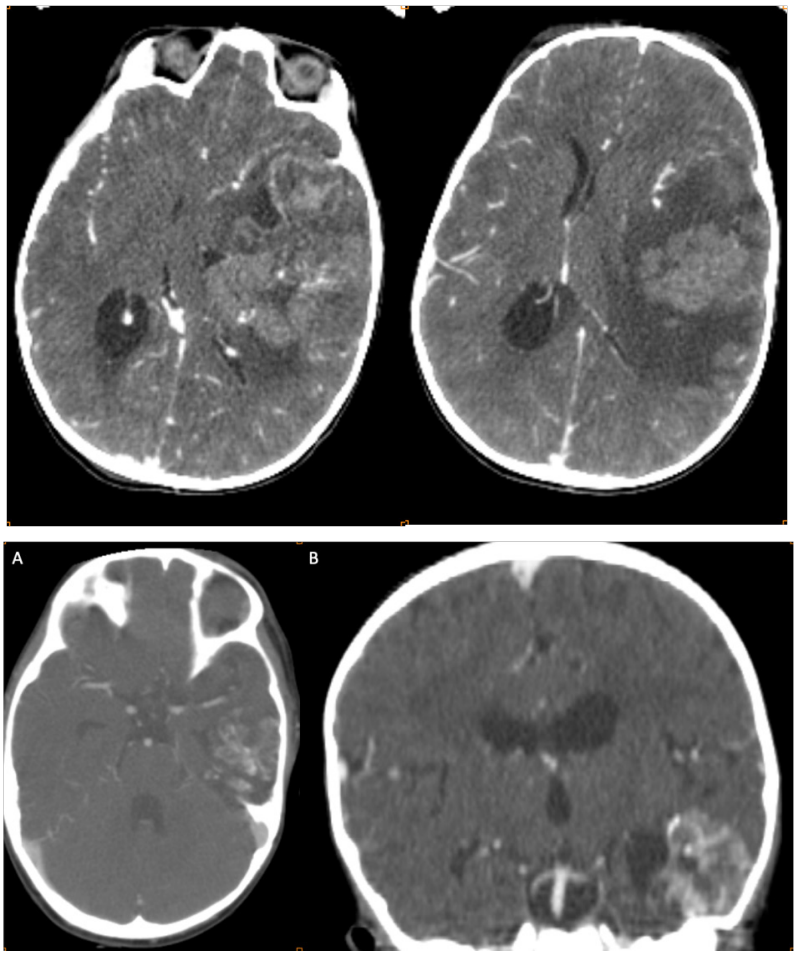

Figure 9. Cerebral CT scan with contrast: A, B axial views. Voluminous intra-axial process, fronto-temporal left, containing calcifications, with poly-lobed contours, surrounded by a large area of peri-lesional edema in fingers of gloves. The whole exerts a mass effect on the homolateral LV which is compressed with dilatation of the contralateral lateral ventricular with evidence of trans ependymal resorption.

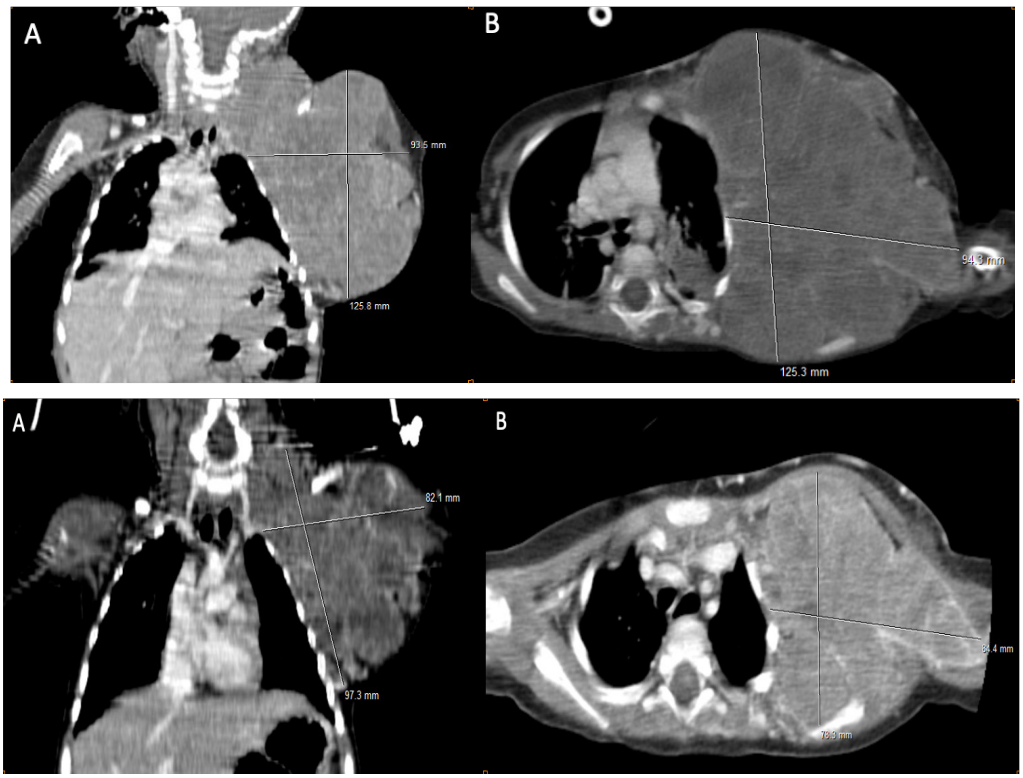

Figure 10. Initial chest CT before exclusive chemotherapy A: coronal view, B: axial view. (Controle: C coronal view, D: axial view: Progression in size of the voluminous tumor mass in the left axillary and supra-clavicular region, massively necrotic and locally advanced).

the age of two; the mean age of diagnosis is 11 months and represent approximately 2% of all malignant renal tumors [3]. According to the U.S. Central Brain Tumor Registry, AT/RTs account for 1.6% of all pediatric CNS tumors and 4.4% of all CNS tumors in children aged 0 to 5 years [4].

Regarding gender, AT/RT is 50% more frequent in boys than in girls [5] and no predominance for malignant rhabdoid tumors of other sites.

In our study the mean age of renal rhabdoid tumors was 2 years and that of AT/RT was 1 year, which is in agreement with the results of the literature. There was a slight feminine predominance with an estimated sex ratio (G/F) of 1.3.

The etiology of rhabdoid tumors is uncertain. An association between rhabdoid tumors and low birth weight, preterm birth and late delivery was reported in a study by Heck JE, et al. [6] in a pediatric population in the state of California. Twin pregnancies were associated with these tumors which was also noted by Nicolaides T, et al. [7] and Bourdeaut F, et al. [8]. Two studies by Nicolaides T, et al. [7] and Cecen E, et al. [9] reported a single case of rhabdoid tumor in a patient born after *in vitro* fertilization. Although some studies suggest a slight increase in cancer risk with the use of assisted reproductive technologies [10], this remains controversial [11].

Histologically, extracerebral RT contains characteristic filamentous cytoplasmic inclusions, large nucleoli and abundant eosinophilic cytoplasm. It is the resemblance of the cytoplasm of these cells to differentiating rhabdomyoblasts that gave the tumor its name [12].

On immunohistochemistry, RT shows polyphenotypic reactivity, with immunopositivity for vimentin, epithelial membrane antigen, smooth muscle actin. To a lesser extent, synaptophysin, cytokeratin, glial fibrillary acidic protein and neurofilament protein are common in AT/RT. The extracerebral RT might be a more differentiated form compared to the CNS one [13].

On molecular genetic analysis, RT is the consequence of SMARCB1 inactivation resulting from biallelic alterations secondary to inactivating mutations, deletions or exon duplications. Inactivation can also result from loss of heterozygosity. Germline alterations are found in 35% of cases, but only a minority is actually genetically inherited, most representing a postzygotic event. The presence of a SMARCB1 mutation in germline or somatic tissue defines Rhabdoid Tumor Predisposition Syndrome Type 1 (RTPS1, OMIM 609322). Affected individuals develop RT earlier, on average at 6 months of age. Other genes are implicated in RT development such as SPEN L945fs, SMARCB1fs and SMARCB1 R201, alteration of these genes is common in renal RT [14].

Imaging has an important role for in the management of patients with this disease, both in the diagnostic phase, to confirm or refute the various signs of malignancý as well as in the therapeutic and follow-up phases, to assess the efficacy of the treatment and detect signs of recurrence.

Ultrasound is the first-line examination for a tumor mass syndrome. On ultrasound, the RT usually presents as a well-limited, heterogeneous mass, containing calcification, areas of necrosis and vascularized on color Doppler. The main limitation is the difficulty of attaching the large mass to the organ. Although cerebral and thoraco-abdominal CT remains necessary in the extension workup. Ultrasound is also useful for radioguided biopsies. Sebire NJ, et al. systematically reviewed the pathologic diagnosis of imaging-guided biopsies of pediatric tumors. They concluded that the cores collected were sufficient to establish a diagnosis in 94% of patients [15].

On CT, renal RT appears as large, centrally located, heterogeneous soft tissue masses involving the renal hilum with indistinct margins. The main differential diagnosis is the much more common Wilms' tumor. Although the imaging may have similar aspects, CT may reveal a number of features that can help guide the diagnosis to a rhabdoid tumor namely: Lobar involvement of the tumor alternating with healthy renal parenchyma; The presence of hemorrhagic and necrotic areas within the tumor; Calcifications have been reported frequently in the literature, they have a calcific density, linear; A subcapsular collection is rarely found in other renal tumors and has been observed in 44% of cases of RT in the literature [16].

In order to perform an extension workup, a thoracic CT scan is mandatory to evaluate pulmonary metastases. CT remains essential in the detection of other secondary, hypatic, or bony locations. The disadvantage of CT in children is the radiation exposure. Synchronous intracranial neoplasm is a distinctive feature of RT, hence the importance of systematic brain imaging even in the absence of focal neurological signs. AT/RT presents on CT as a spontaneously hyper dense lesion due to hypercellularity, heterogeneously enhanced and intense after contrast, calcifications may be present [16].

MRI is very interesting in the context of AT/RT. Intra-axial localization in the posterior cerebral fossa is often reported, but a few studies have reported both infra and supratentorial AT/RT. The imaging characteristics of AT/RT have always been described as non-specific. In conventional sequences, they often appear large, isosignal to the cortex in T2 sequence, associated with calcifications, with heterogeneous enhancement after iodinated contrast injection, containing cystic, necrotic and/or hemorrhagic areas [17].

The AT /RT show an inhomogeneous hypersignal in diffusion (DWI) with a hyposignal in ADC. This can be explained by the high cell density of the tumor. The average ADC value for AT/RT tumors is estimated to be 0.45-0.60 × 10-3 mm^2 s-1. Spectroscopy shows increased choline, decreased N-acetylaspartic acid (NAA) and a high lipid peak. AT/RT shows marked heterogeneity resulting from hemorrhage and necrosis. Necrosis releases lipids, indicating cell membrane degradation and fatty acid release; lipids are an important marker of severe brain injury and aggressive tumors [17].

The most common differential diagnosis for AT/RT in children is a primitive neuroectodermal tumor/medulloblastoma (PNET/MB) [5]. Leptomeningeal metastases have been described in AT/RT. Leptomeningeal dissemination can be observed from the beginning of the disease [18]

For other localizations, it seems that CT is largely sufficient to make a loco-regional and distant assessment due to the unavailability of MRI.

RT have always been considered highly malignant and of poor prognosis. Aggressive surgery is essential for survival. Complete surgical resection and radiotherapy have been reported to have survival benefits [6,8,10].

However, due to the small population studied in the literature, the survival benefits of surgery or therapeutic radiotherapy could not be statistically significantly analyzed.

Conclusion

RT are highly aggressive, despite maximal therapeutic intensity the overall results remain poor, necessitating the discovery and integration of a new targeted therapy, which will likely emerge from a deeper understanding of the molecular biology and further preclinical investigations.

Acknowledgement

None.

Conflict of Interest

None.

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