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Ethmoid Maxillo Orbital Alveolar Rhabdomyosarcoma: Case Report and Review of the Literature

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Abstract **Case Report**

Introduction: Rhabdomyosarcoma is a soft tissue sarcoma, of unknown etiology. It is divided into two entities: embryonic rhabdomyosarcoma and alveolar rhabdomyosarcoma. The latter is common in adults and very aggressive. It's a lymphophilic tumour with 15 to 50% lymph node involvement. Immunohistochemistry is crucial for differentiating an alveolar form an embryonic one. However molecular biology must be performed before any treatment. Management is multidimensional, combining chemotherapy, radiation therapy and surgery. The objective of this presentation is to show the aggressive character of alveolar rhabdomyosarcoma as well as the evolution, therapeutic strategies with a review of the literature. Case presentation: 27-year-old patient consults for swelling in the right eye associated with exophthalmia, pain and redness of the eye with a decrease in visual acuity. Clinical examination noted a mass of the right eye with exophthalmia, and the radiologic examination of CT and magnetic resonance imaging revealed an ethmoido-maxillo-orbital process. Histology and the immunohistochemistry of the biopsy confirmed that it is an alveolar rhabdomyosarcoma with expression of desmin and myogenin. The extension assessment came back negative. Neoadjuvant chemotherapy with Vincristine, Actinomycin, Cyclophosphamide, Ifosfamide and Etoposide and 54 Gy radiotherapy was performed with good clinical response, visual acuity in both eyes and radiological stability, and the patient was monitored. With a follow-up of 4 months, she presents a local relapse confirmed by an anatomical pathology examination with chemotherapy like Adriamycin, Cisplatin, Ifosfamide/ Adriamycin, Ifosfamide and a waiver of Right eye. After two other locoregional relapses, she was admitted to the palliative care unit. Conclusion: Alveolar rhabdomyosarcoma is an aggressive tumour that requires multimodal management. Despite the combination of chemotherapy, radiation therapy and surgery, the prognosis remains poor.

Keywords: Rhabdomyosarcoma, Alveolar, Ethmoid, Maxillary, Orbit.

INTRODUCTION

Rhabdomyosarcomas (RMS) come from immature cells at the origin of striated skeletal muscles [1], of mesenchymal origin, of unknown etiology [2]. They represent 6% of solid tumors and 50-60% of malignant mesenchymal tumors in children and adolescents [3]. It is the most common soft tissue sarcoma in children, adolescents and young adults [4]. The most frequent localizations are in the head and neck (40%), genitourinary tract (25%) and limbs (20%) [5]. This pathology is historically divided into two subtypes, embryonal rhabdomyosarcomas, found in 70-80% of cases, and alveolar rhabdomyosarcomas, in 20-30% of cases [6], which are more frequent in adults and more aggressive [5]. Alveolar rhabdomyosarcoma is a tumor of high malignancy that differs from other sarcomas by its locoregional aggressiveness, its metastatic evolution and its unfavorable prognosis regardless of the undertaken treatment [2]. The diagnosis is only made on histological examination. It shows poorly differentiated cells, without cross-striation and agglomerated around fibrovascular septa in formation, poorly defined, without connection between them but with the appearance of alveoli. There may be massive aspects of compacted round cells without stroma and without alveolar architecture. This is a "solid" alveolar form that is very difficult to differentiate from embryonal or undifferentiated forms. The diagnosis can then be established by the detection of specific fusion transcript of the alveolar RMS in the

tumor cells. The detected presence of an alveolar area in the tumor makes it classified as alveolar RMS [7]. Early diagnosis and appropriate multidisciplinary treatment can improve the survival rate; with an overall survival of 54% in localized forms [8].

CASE PRESENTATION

Our work concerns a 27 year old female patient, who consulted for a tumor of the right eye. The anamnesis does not find any known pathological history. The patient has never been operated, without notion of facial trauma. The onset of the symptomatology dates back to 6 months ago with the progressive installation of exophthalmos of the right eye associated with pain and redness of the eye with a decrease in visual acuity. The whole evolving in a context of conservation of the general state. The general examination found a patient in good general condition, weighing 64 kg for a height of 1.75 m. The clinical examination found a mass of about 5 x 4 cm externalized with exophthalmos and redness of the right eye. Examination of the cervical lymph nodes did not reveal any palpable adenopathy. The examination of the right eye and the rest of the somatic examination were unremarkable.

An orbital CT scan showed the presence of an ethmoido-maxillo-orbital tissue process, enhancing after injection of contrast medium, causing lysis of the floor and roof of the orbit and the planum, filling of the right frontal sinus and its recess. The endo-orbital extension takes place at the level of the internal part of the retro-orbital cone with the internal rectus muscle being pushed back. This process is in contact with the inferior rectus muscle and the optic nerve (Figure 1). Magnetic resonance imaging shows a process in the right nasal cavity with a significant locoregional extension towards the right orbital cavity, the maxillary sinus and the ethmoidal cells with bone rupture. This process measures 41 mm in craniocaudal diameter, 30 mm in transverse axis and 30 mm in anteroposterior axis. It is a tissue-like process that clearly takes up contrast medium without any necrosis focus. The extension study showed a large invasion of the right orbit with infiltration of the medial rectus muscle respecting the eyeball. The optic nerve was pushed outwards without macroscopic invasion. Inside, there was extensive invasion of the nasal cavity and the anterior and posterior ethmoidal cells. Outside and backwards, there is an invasion of the maxillary sinus with fluid retention in the maxillary sinus. Respect for the base of the skull, particularly at the anterior level. In the face, there is also infiltration of the deep fatty spaces of the face, particularly the infra-temporal fossa. The patient underwent a surgical biopsy. Anatomopathological examination and immunohistochemical study revealed an alveolar rhabdomyosarcoma with expression of desmin and myogenin, without expression of anti NSE bodies, cytokeratin, PS100, CD99, CD45 and chromogranin (Figure 2, 3 et 4). The extension workup including a thoraco-abdomino-pelvic CT scan did not reveal any secondary location. Positron emission tomography and computer tomography were not available. The patient's file was presented at a multidisciplinary consultation meeting and surgery was not possible at the outset due to the local tumour extension to level of the ethmoid. She received 3 courses of neoadjuvant chemotherapy with VAC-IE (Vincristine, Actinomycin, Cyclophosphamide, Ifosfamide and Etoposide) with a good radiological response. Orbital MRI after 3 courses of neoadjuvant chemotherapy showed a 96% response with persistence of a small formation in the right orbit in contact with the right medial oculomotor muscle measuring 14 x 11 x 9.6 mm. The patient then followed a 54 Gy radiotherapy with a good clinical response with good visual acuity in both eyes and radiological stability. Four months after the end of the radiotherapy, in front of the appearance of a decrease of the right visual acuity and a diplopia in the right eye, the magnetic resonance imaging showed the appearance of an extra conical tissue formation in contact with the internal wall of the right orbit with extension to the homolateral anterior ethmoidal cells. This formation is quite well limited in T2 hyper signal and T1 hypo signal with moderate enhancement after gadolinium injection. It measures 17 x 15 mm extended over a height of 20 mm. Outside, this formation is in contact with the eyeball with loss of the separation line and the medial rectus, greater and lesser oblique muscles which are infiltrated at their insertion on the eyeball. The PET scan shows a right orbital hyper metabolism in favor of local recurrence. She received two courses of API - AI (Adriamycin, Cisplatin, Ifosfamide) chemotherapy with preoperative magnetic resonance imaging which showed a clear regression of the right orbital tumor process. An exenteration of the right eyeball was performed and the pathological anatomy examination showed a lesion measuring 1.7 x 1.2 x 1 cm, snow white and friable, with hemorrhagic changes. This lesion did not seem to infiltrate either the eyeball or the optic nerve. Histological examination showed a proliferation of round cells, with sparse cytoplasm and hyperchromic nuclei, compatible with rhabdomyosarcoma already diagnosed. This proliferation is flush with the limits of the excision. The anterior and internal wall cuts show tumor cells. The cross section of the ethmoidal sinus shows absence of tumor proliferation. Six months after the eyeball exenteration, she consulted with bilateral cervical lymphadenopathy whose biopsy confirmed lymph node relapse. A workup was performed and chemotherapy was started with Navelbine-Endoxan and then Etoposide-Ifosfamide after a locoregional progression with the appearance of right temporal masses associated with multiple bilateral cervical and right parotid lymph nodes. The patient was admitted to a palliative care unit with the cessation of chemotherapy after a 24-month follow-up since diagnosis.

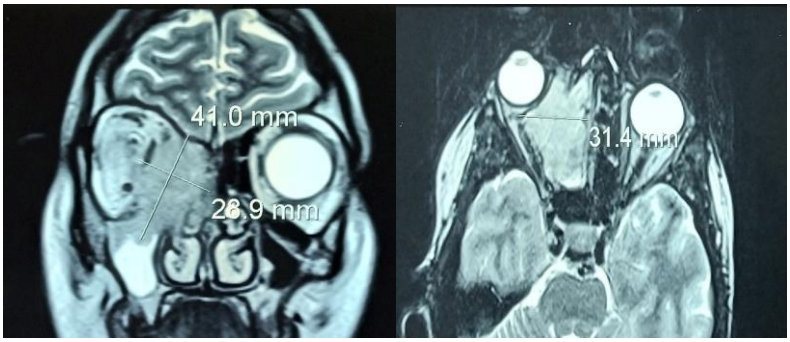

Figure 1: Transverse and sagittal CT scan showing the ethmoido-maxillo-orbital tumor process

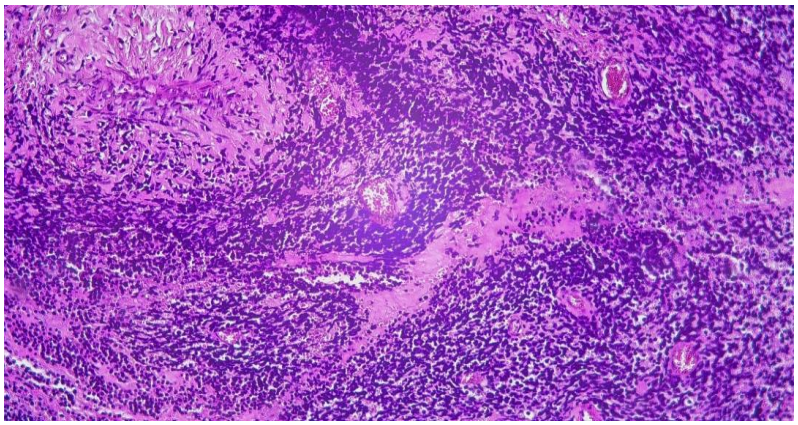

Figure 2: Histological appearance of HE x10 round cell rhabdomyosarcoma

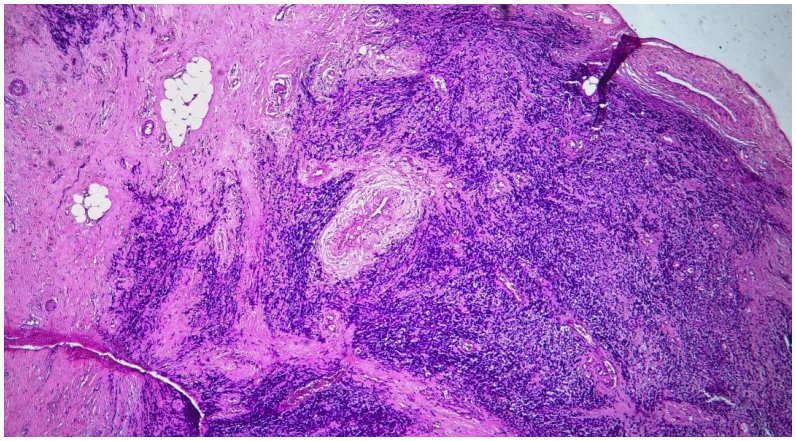

Figure 3: Histological appearance of HE x20 round cell rhabdomyosarcoma

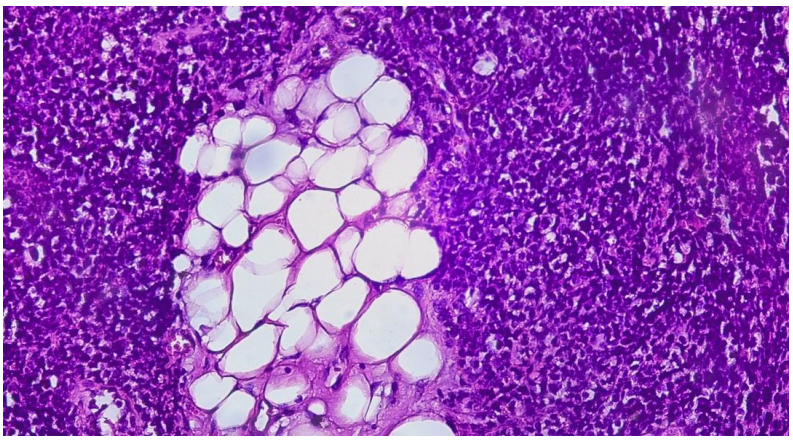

Figure 4: Histological appearance of HE x 40 round cell rhabdomyosarcoma

DISCUSSION

Rhabdomyosarcoma is the most common soft tissue sarcoma in children, with the head and neck location representing approximately 40% of cases. In adults this histology is much rarer (less than 3% of all soft tissue sarcomas) but is still the most common soft tissue sarcoma histology, especially in the facial region [2]. Rhabdomyosarcoma are preferentially localized to the naso-sinus cavities and the masticatory space [2]. Although they are of muscular origin, many rhabdomyosarcoma are found in anatomical situations without striated muscle fibers: main biliary tract, bladder, mesentery, parotid gland [9] and in our case, the naso sinus and the orbit. A distinction is made between rhabdomyosarcoma of para-meningeal and non-para-meningeal location (neck, orbit) which are rare in adults. The former have a higher rate of adenopathy and initial metastases and are less surgically accessible because of the possibility of endocranial invasion. Adult rhabdomyosarcoma have a particular lymphophilia (15 to 50%), especially in para-meningeal locations (>40%) of lymph node involvement at diagnosis [6]. Rhabdomyosarcoma is a proliferation of poorly differentiated round or spindle-shaped cells with a striated muscle differentiation line [10]. Cytologically, rhabdomyosarcomas vary greatly in their constitution and cellular architecture and are histologically classified into three types: embryonal (the most common), alveolar and pleomorphic or polymorphic [11]. The often homogeneous proliferation of round cells with clear cytoplasm may pose problems of differential diagnosis with other small round blue cell tumors such as lymphomas [9]. Immunohistochemistry is of great help, looking for labelling of rhabdomyoblasts by myosin, actin, desmin, myoglobin, myogenin and Myo-D [10]. In 90% of cases, it reveals intense and diffuse myogenin positivity, which indicates the alveolar nature of the rhabdomyosarcoma [12, 13].

Alveolar rhabdomyosarcoma accounts for 20-25% of rhabdomyosarcoma, more common in the limbs (60%) [14]. The cells are poorly differentiated, without cross-striation and agglomerated around fibrovascular septa in formation, poorly defined, unrelated but with the appearance of alveoli [14]. Massive aspects of compacted round cells without stroma and without alveolar architecture may exist. This is a "solid" alveolar form that is very difficult to differentiate from embryonal or undifferentiated forms. The diagnosis can then be established by the detection of specific fusion transcript of the alveolar rhabdomyosarcoma in the tumor cells. The detected presence of an alveolar area in the tumor makes it classified as alveolar rhabdomyosarcoma [7].

Molecular biology studies before any treatment are part of the diagnostic strategy. Indeed, it can rectify or refine the diagnosis and can establish prognostic elements. It looks for a fusion transcript on the tumor, by reverse transcriptase polymerase chain reaction, with specific genetic abnormalities specific to certain types of rhabdomyosarcoma: the translocation (2; 13) (q35; q14): this results from the fusion of two genes: PAX3 (transcription factor during neuromuscular development) and FKHR (ubiquitous transcription factor). The resulting transcript is specific to the alveolar form but is found in only 55% of cases [15]. The translocation (1; 13) (p36; q14) results from the fusion of two genes: FKHR and PAX7. This transcript is present in 22% of alveolar rhabdomyosarcoma [16].

The workup should therefore be comprehensive, including a biological workup, thoracoabdominal CT scan, liver ultrasound, bone scan, and fluorodeoxyglucose positron emission tomography [17]. In general, given the major metastatic risk, adult RMS should be treated with neoadjuvant chemotherapy combined with locoregional therapy (surgery and radiotherapy) as is done in pediatric cases [2]. However, the chemotherapy protocols used in adults tend to become similar to those used in pediatrics given the excellent therapeutic results obtained in this population in terms of survival [2]. Chemotherapy protocols most often combine Vincristine, Actinomycin, Cyclophosphamide, Etoposide, Ifosfamide, and Doxorubicin. The tolerance of these very heavy protocols is a limiting factor in adults over 25 years of age [2]. After 12 weeks of neoadjuvant chemotherapy, surgical treatment is performed depending on operability. However, radiotherapy can be performed before surgery. As rhabdomyosarcomas are very radiosensitive tumors, radiotherapy is also an integral part of the treatment. The dose used in pediatrics is 50.4Gy for embryonal and alveolar rhabdomyosarcomas [2]. In adults, given a higher rate of non-embryonic histologies, dose escalation would be of interest and would be facilitated by conformal techniques [2]. Our patient received a dose of 54 Gy at the tumor site. Irradiation is usually performed postoperatively. It concerns the tumor site and the lymph nodes. In high risk metastatic forms, where surgery may be mutilating, curative treatment with exclusive radiochemotherapy should be discussed, especially if chemotherapy has resulted in major tumor regression. Alveolar RMS has a poor prognosis despite treatment combining surgery, chemotherapy, and radiation therapy [4]; with overall survival at 54% in localized forms [14]. Enzinger and Shiraki reported two survivors out of 102 patients at five years. Half of the patients developed metastases three months after surgery [4].

CONCLUSION

Alveolar rhabdomyosarcomas are frequent in children. In adults they are rare, but the location of the head and neck are frequent. The alveolar type of rhabdomyosarcoma represents a quarter of the rhabdomyosarcomas. The management is multidisciplinary, including multidrug therapy, surgery

and external radiotherapy. Despite improvements in therapeutic management, the prognosis of adult head and neck rhabdomyosarcomas remains very poor.

Conflicts of Interest: The authors declare no conflicts of interest.

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