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Spindle Cell Variant of uterine embryonal Rhabdomyosarcoma: therapeutic and diagnostic challenges in low resource setting

Le Rhabdomyosarcome embryonnaire, variante à cellules fusiformes de l'utérus : enjeux diagnostiques et thérapeutiques en milieu à ressources limités

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Cas clinique

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ABSTRACT

The spindle cell variant of embryonal rhabdomyosarcoma is a rare variant and better differentiated from all other types of embryonal rhabdomyosarcoma variants. It usually occurs in childhood and is generally associated with a good prognosis when diagnosed early with the complete panel necessary, but it becomes a whole different story at the advanced stage, despite its low malignant potential. A 3-year-old girl with stage 4 embryonal spindle cell rhabdomyosarcoma underwent 15 cycles of chemotherapy with actynomycin-D, cyclophosphamide and vincristine, the course was marked by disease progression and death. Spindle cell embryonal rhabdomyosarcoma is a rare variety, and its prognosis depends on the stage of presentation, and rapidity of diagnosis.

RESUME

La variante fusiforme du rhabdomyosarcome embryonnaire est une variante rare et la mieux différenciée de tous les autres types de rhabdomyosarcome embryonnaire. Il survient généralement dans l'enfance et est associé à un bon pronostic lorsqu'il est diagnostiqué tôt avec une prise en charge adéquate, cependant, l'histoire n'est plus la même lorsque le diagnostic est posé à un stade avancé, malgré son faible potentiel malin. Une fillette de 3 ans atteinte d'un rhabdomyosarcome embryonnaire à cellules fusiformes de stade 4 a subi 15 cycles de chimiothérapie à base d'actinomycine-D, de cyclophosphamide et de vincristine, l'évolution a été marquée par la progression rapide de la maladie et le décès. Le rhabdomyosarcome embryonnaire à cellules fusiformes est une variété rare, et son pronostic dépend du stade de présentation et de la rapidité du diagnostic.

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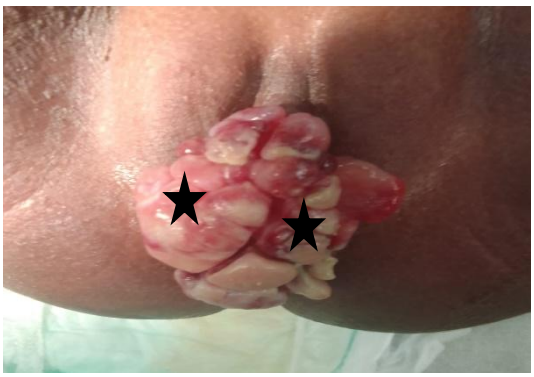
Introduction

Rhabdomyosarcoma (RMS) is a malignant tumour of immature skeletal muscle cells [1]. It is the most common soft tissue sarcoma of childhood, accounting for 3 % of cancer cases among children aged 0 to 14 years and 1 % of cases among young adults aged below 20. The overall 5-year survival ranges from 70 % for children to 50 % for adolescents and young adults [2]. RMS occurs mostly in the genitourinary tract, with the head and neck as the second most common sites.

The Intergroup Rhabdomyosarcoma Study Group (IRSG) subdivides rhabdomyosarcomas into three histological subtypes: (i) embryonal RMS (ERMS), botryoid and fusiform variants; (ii) alveolar RMS (ARMS), including the solid variant; and (iii) undifferentiated RMS [3]. Treatment modalities are based on risk stratification, considering the presence of metastases, alveolar histology, and age at the time of presentation. The mainstays of treatment involve surgery, radiation therapy, and chemotherapy. We report the case of a 3-year-old girl diagnosed with an advanced stage uterine rhabdomyosarcoma with an unfavourable outcome in the face of an aggressive histological type whose diagnosis and management is a challenge in our setting.

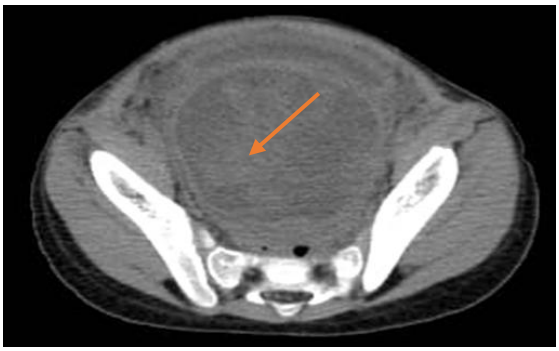
Case presentation

A 3-year-old girl with no personal or family history of cancer presented with an exteriorization of a centimetric mass through the vaginal orifice of around 3 months' duration, reddish in color and bleeding on contact, according to the first evaluation by her mother. Physical examination revealed a large grape-like centimetric vaginal exophytic lesion (**picture 1**).



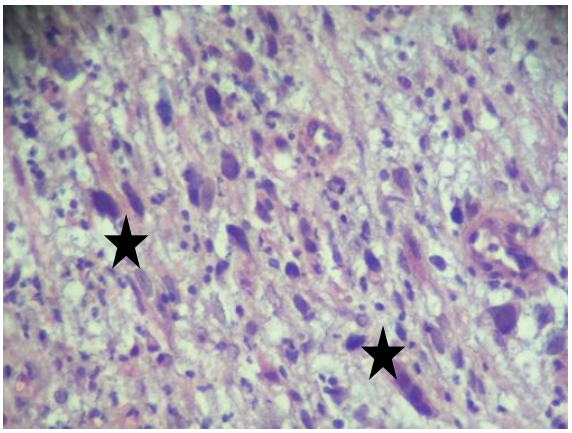
Picture 1: front view of the tumor protruding through the cervix and vulva, with a grape-like appearance (stars)

A biopsy was taken and the initial histopathological analysis concluded that it was a fibro-vascular polyp of the vaginal mucosa. Evolution was marked in between 2 months by alteration of general states, persistent pain and urinary tract retention due to a rapid growth of the vaginal mass compressing neighbourhood organs. Computed tomography of the abdomen revealed a solid cystic mass measuring 70*68 mm involving the uterus, the cervix, pushing back the bladder and rectum. (**picture 2**).



Picture 2: *transverse CT-scan section of the tumour with a grape-like appearance (arrow)*

After two different slide microscopies, a spindle cell embryonal rhabdomyosarcoma was diagnosed (**picture 3**).



Picture 3: proliferation of rhabdomyoblasts with elongated eosinophilic cytoplasm giving the cell a snowshoe or comet-tail appearance (stars)

The Patient was referred to paediatric oncology where she received 10 cycles of neoadjuvant chemotherapy (Vincristine, Actinomycin-D and Cyclophosphamide-VAC). Afterwards, re-assessment through body CT revealed no reduction in mass size, and she received five more cycles of VAC chemotherapy. The evolution was marked by the onset of chronic kidney disease, followed by a uremic coma, and the unfortunate death of the little girl less than 3 months later.

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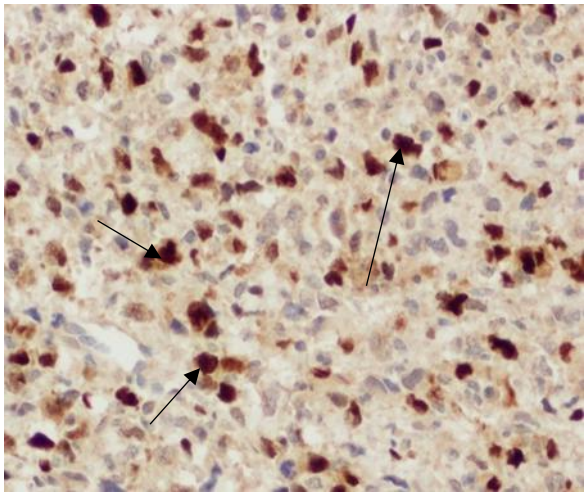

Picture 4: *immunohistochemistry technic showing nuclear expression of Myogenine antibody in rhabdomyoblast (arrows)*

Discussion

Embryonal RMS is a rare skeletal muscle malignant tumour affecting children. It can occur all over the body but the genitourinary variant is frequent. It's appeared as a rapidly growing malignancy tumour, seen in 40% of cases of RMS, must frequently between the ages of 0 and 4 years. Most cases occur sporadically without recognized predisposing risk factors, although in a small proportion of cases there may be a genetic link between RMS and other primary tumours, most notably Sertoli-Leydig tumour [4].

The vagina is the most common site and it grossly appears as a grape-like structure located below the mucosal surface of organs. Our patient was diagnosed with an RMS tumour that involved the uterus, cervix and vagina with partial extrusion of the mass through the introitus. She presented with vaginal bleeding and a vaginal mass. Some patients present with additional symptoms, including leucorrhoea, bleeding and foul-smelling discharge [5].

The spindle cell variant of embryonal rhabdomyosarcoma was first recognized as a rare entity having a male predilection, but in recent decades there has also been a significant increase in occurrence among girls. It accounts for 3 to 4.4 % of all subtypes of rhabdomyosarcoma [6], and has a better prognosis in children, but when the diagnosis is made late the prognosis is poor, as was the case in our patient [7]. The microscopic exam shows elongated spindle-shaped cells arranged in a diffuse, fasciculate or storiform pattern, mimicking sometimes smooth muscle fibers (picture 3). In high grade cases, atypical cells and mitotic figures are easily appreciated. Amidst the spindle cells, is a second population of immature rhabdomyoblasts, usually comprising a small population of the tumour. Due to the heterogeneity of the collagen architecture of these tumours, the diagnosis is often difficult and sometimes confused with leiomyosarcoma, fibrosarcoma, or a malignant peripheral nerve sheath tumour with heterologous differentiation (malignant triton tumour) in hematein-eosin stain [8]. Meanwhile cells express myogenic antibody (nuclear expression as seen in picture 4) This expression gives the diagnosis of certainty and differentiates it from other differential diagnoses

The pathogenesis of embryonal RMS of the genital tract is unclear. However, several reports implicate germline mutations involving the DICER1 gene. The DICER1 gene codes for endoribonuclease, which plays an important role in the biogenesis of microRNAs and the control of protein translation. An analysis by Apellaniz-Ruiz *et al.* suggests that almost all cases of gynaecological embryonic RMS may present with alterations in the DICER1 gene [9]. This pathological germline variation in DICER1 may create a predisposition to the hereditary cancer syndrome - DICER1 syndrome, characterised by the development of a multitude of tumours [9]. Our patient did not seek genetic counselling due to the absence of genetic services in our clinical environment.

According to available literature, the diagnosis of this tumour is difficult to make, but as far as the management of this tumour is concerned, there are a variety of approaches. Nuclear MRI is the gold standard for determining where the tumour originates from (endometrium, myometrium, or cervix) as well as the spread and involvement of neighbouring structures [10]. Due to socio-economic reasons, few centres in our area have the possibility of having an MRI, which is quite an expensive test for an average citizen whose salary is 91.64 euros. In most cases we use computed tomography scan which is quite limited in the evaluation of the extension [11]. In most cases we use computed tomography scan which is quite limited in the evaluation of the extension [11]. The stage is established using two systems: the Intergroup Rhabdomyosarcoma Study Group clinical categorization method [12] and the TNM staging approach for rhabdomyosarcoma [13], in our case we use the TNM staging system .

With no consensus on the management for embryonic RMS, a multimodal approach to treatment appears to improve patient outcomes. This consists of a combination of surgery, systemic chemotherapy and considerations for radiotherapy [14]. The optimal number of cycles of adjuvant chemotherapy required varies,

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depending on clinical and radiological response. There are many reports of neoadjuvant chemotherapy being used to reduce tumour size prior to surgery [14]. In this case, neoadjuvant therapy was used, including 15 cycles of the VAC protocol (vincristine, actinomycin-d and cyclophosphamide), but the evolution was unfavourable. As shown in the Surveillance, Epidemiology, and End Results (SEER) programme on embryonal rhabdomyosarcoma from 1988 to 2016, children under 4 years of age have a poor prognosis, in the advanced stage, poor surrogate survival criteria at 3 years [15].

Conclusion

The spindle cell variant of embryonal rhabdomyosarcoma is a rare variant of the embryonal subtype of rhabdomyosarcoma, which occurs more frequently in children and adolescents. It has a low malignant potential, but the prognosis after treatment is better if the correct histopathological diagnosis is made at time. This, by bypassing the various histological pitfalls, and combining immunohistochemical chemistry and mutational research, which will have a major impact on the therapeutic strategy.

Conflicts of interest: None

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