

Orofacial Rhabdomyosarcoma: Report of a case and review of the literature

Manuel A. Gordón-Núñez¹, Marta R. Piva², Edvaldo D. Dos Anjos³, Roseana A. Freitas⁴

(1) Doctoral and Postdoctoral Scholarships Program 2005-2010, IFARHU-SENACYT, Panamá / UFRN, Natal / RN. Brazil

(2) Discipline of Oral Pathology, Sergipe Federal University - UFS, Aracajú/S, Brazil

(3) Discipline of Buco-Maxillofacial Surgery, Tiradentes University, Aracajú/S, Brazil

(4) Post Graduation Program in Oral Pathology, Rio Grande do Norte Federal University - UFRN. Brazil

Correspondence:

Dr. Manuel Antonio Gordón-Núñez.

Avenida Senador Salgado Filho, 1787

Lagoa Nova, Natal-RN, CEP: 59056-000

gordonnunez28@yahoo.com

Received: 12/12/2007

Accepted: 16/10/2008

Gordón-Núñez MA, Piva MR, Dos Anjos ED, Freitas RA. Orofacial Rhabdomyosarcoma: Report of a case and review of the literature. Med Oral Patol Oral Cir Bucal. 2008 Dec 1;13(12):E765-9.

© Medicina Oral S. L. C.I.F. B 96689336 - ISSN 1698-6946

<http://www.medicinaoral.com/medoralfree01/v13i12/medoralv13i12p765.pdf>

Indexed in:

- Science Citation Index Expanded
- Journal Citation Reports
- Index Medicus, MEDLINE, PubMed
- Excerpta Medica, Embase, SCOPUS,
- Índice Médico Español

Abstract

Rhabdomyosarcomas (RMS) are among the most common soft-tissue tumors in children. These tumors are derived from mesenchymal tissue with a tendency toward myogenic differentiation that probably originates from immature and highly invasive satellite cells associated with the embryogenesis of skeletal muscle. Some of these tumors are associated with high rates of recurrence and metastasis. The diagnosis is made by microscopic analysis and auxiliary techniques such as immunohistochemistry, electron microscopy, cytogenetic analysis, and molecular biology. We report here a case of orofacial RMS in a 4-year-old child and provide an updated review of the literature, focusing mainly on the clinicopathological aspects, diagnosis and treatment of RMS of the head and neck.

Key words: *Rhabdomyosarcoma, childhood, orofacial, immunohistochemistry.*

Introduction

Childhood soft-tissue tumors comprise a heterogeneous group of lesions, including rhabdomyosarcomas (RMS), the most common intracranial solid tumors in this population (1-3).

RMS are malignancies derived from primitive mesenchymal tissues that exhibit a tendency toward myogenic differentiation and probably originate from satellite cells associated with the embryogenesis of skeletal muscle (1, 4). RMS were initially described by Weber in 1854. The highest frequency of these tumors is observed among white and African American children. A slight preference for males has been reported, with these tumors mainly occurring in the first and second decades of life (5). The etiology of RMS is unknown; however, a possible viral involvement in their pathogenesis has been suggested due to the identification of viral particles in malignant RMS tissues. Cytogenetic and molecular studies have identified

chromosomal translocations and mutations in oncogenes, but the participation of these events in the etiology of RMS has not been well established (2, 6).

The head and neck are the most frequently affected regions, followed by the orbit (35% of cases) (7), trunk and extremities, intra-abdominal organs and genitourinary tract (23%). There are reports of cases arising in oral tissues, which correspond to 10 to 12% of all head and neck RMS and mainly involve the tongue, palate and oral mucosa (5). As a result of their aggressive neoplastic behavior characterized by immature and highly invasive cells, RMS are associated with high rates of recurrence and generalized metastases through the hematogenic and/or lymphatic routes. The diagnosis is generally made by microscopic analysis and auxiliary techniques such as immunohistochemistry, electron microscopy, cytogenetic analysis, and molecular biology (8).

Histomorphologically, pediatric RMS are classified into embryonal RMS (66% of cases) which are characterized

by pronounced cellular pleomorphism, alveolar (28%), undifferentiated (4%) and anaplastic RMS (2%). In addition, embryonal RMS are subdivided into botryoid and spindle cell subtypes (4, 5). The introduction of various treatment modalities has increased the survival of patients with RMS and some investigators have associated the prognosis with the location, evolutive stage and histological type of the tumor (9).

We report here the case of a child with orofacial RMS whose survival was limited because of a delay in the diagnosis. In addition, we present an updated review of the literature, focusing mainly on the clinical aspects, diagnosis and treatment of tumors of the head and neck.

Case Report

A 4-year-old black boy was seen in Aracajú city, Sergipe, Brazil, with a lesion located on the right side of the face. A previous incisional biopsy performed by a general pathologist from the same city had resulted in the histopathological diagnosis of juvenile aggressive fibromatosis.

After the initial diagnosis, medical contact with the patient was lost for reasons not specified by the child's parents. Six months later, the parents sought medical care because the lesion exhibited progressive growth and painful symptoms (Figure 1). The boy was examined by the physician who initially attended him. A panoramic radiography revealed involvement of the ramus and body of the mandible, with the observation of a radiolucent lesion without defined limits and severe bone destruction (Figure 2A). Computed tomography confirmed the presence of an extensive infiltrative lesion accompanied by severe bone destruction and displacement of adjacent structures (Figure 2B). Since the child's family refused a second incisional biopsy, the lesion was removed surgically en bloc and part of the material collected was sent to the Laboratory of Pathological Anatomy, Postgraduation Program in Oral Pathology, Federal University of Rio Grande do Norte, Natal, Brazil. Histopathological analysis of the hematoxylin/eosin-stained material showed fragments of a tumor characterized by the proliferation of clear cells compactly arranged in solid masses and cords but without exhibiting a specific organizational pattern; the cells were sometimes separated by fibrous fillets and some of them were clustered in rows (Figure 3A). Cells with hyperchromatic nuclei, cellular and nuclear pleomorphism, and cells with slightly eosinophilic cytoplasm were also observed (Figure 3B). Mitotic figures, some of them aberrant, were noted (Figure 3C).

Since the histopathological findings were not characteristic of a specific tumor, immunohistochemistry was performed using myogenic and non-myogenic markers (desmin, smooth muscle actin, myoglobin, vimentin and S100 protein). Staining was only positive for desmin (Figure 3D). A diagnosis of Rhabdomyosarcoma (RMS) was established on the basis of the clinical and histopathological characteristics.

Unfortunately, the patient died 2 months after the last surgical procedure without allowing the institution to provide any other adjuvant therapy. The patient's parents received a detailed informed consent form stating that the case might be used for didactic purposes, which they signed authorizing the use of the data and images for publication.



Fig. 1. Lesion with swelling and facial asymmetry.



Fig. 2. (A) Panoramic radiograph showing ramus and body mandibular impairment, radiolucent lesion without defined limits and severe bone destruction, (B) CT – extensive infiltrative lesion with severe bone destruction and displacement of adjacent structures.

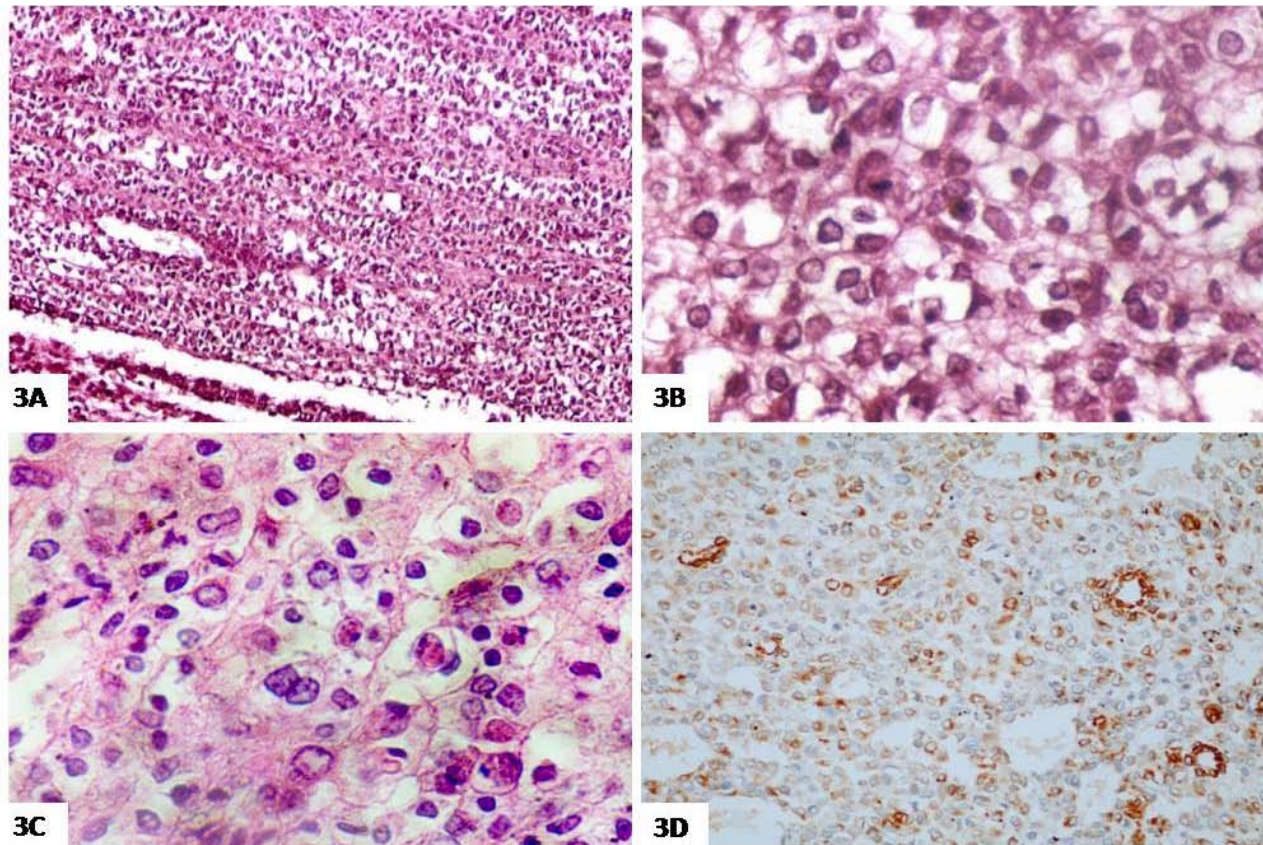


Fig. 3. (A) Clear cell proliferation clustered in rows, separated by fibers of the connective tissue. Hematoxylin and eosin stain. 200x; (B) Cells with slightly eosinophilic cytoplasm, with hiperchromatic nuclei and pleomorphism. Hematoxylin and eosin stain. 400x; (C) Cellular and nuclear pleomorphism, mitosis figures. Hematoxylin and eosin stain. 400x; (D) Desmin immupositivity. Immunoperoxidase stain. 200x.

Discussion

The estimated incidence of RMS in Brazil is 7.8 cases per one million children younger than 15 years, with an incidence peak between 2 to 6 years of age (10). Approximately 35% of childhood RMS occur in the head and neck region, with involvement of the oral cavity being rare. These tumors exhibit a fast and aggressive growth, reaching large dimensions, and are generally painless (7). Childhood RMS located in the head and neck region have been associated with a more favorable prognosis than those arising at other anatomical sites, possibly due to the early evolutive stage of the tumor at the time of its detection at these sites (11). The case reported here agrees with the literature with respect to patient age and the fast and aggressive growth of the tumor accompanied by severe bone destruction.

According to the literature, clinical establishment of the differential diagnosis of RMS is difficult (5), a fact that can markedly affect the patient's prognosis. Unfortunately, in the present case the lack of cooperation of the patient's guardians and the lack of institution of adjuvant chemotherapy and/or radiotherapy at first admission, as well as the delay in the diagnosis of the first biopsy material,

may have favored the rapid progression of the tumor and subsequently aggravated the severity of the condition, resulting in the child's death.

Patients with RMS may present signs and symptoms such as pain, paresthesia, loss of teeth and trismus as a result of factors such as advanced tumor stage, infiltrative growth and tumor location (12). In the present case, involvement of some mandibular teeth was observed and the patient complained of painful symptoms associated with the tumor.

Differences exist in terms of the most common location of RMS in the oral cavity. However, analysis of the cases reported in the literature indicates that most of them occur in the palate and tongue. No preferential location was seen in the present patient, with the orofacial tumor involving the ramus and body of the mandible, an uncommon location of RMS and therefore making this case unusual.

Similar to the difficulties in defining a clinical diagnosis, the histopathological diagnosis of RMS is sometimes a delicate task since the tumor may exhibit nonspecific characteristics similar to those of other neoplasms, a fact requiring staining methods that are more specific than histopathological examination of hematoxylin/eosin-

stained specimens, particularly when the tumor is poorly differentiated. However, in some cases the histomorphological and immunohistochemical findings may not be sufficient to establish a precise diagnosis or are difficult to interpret within the clinical context (2). The case reported here illustrates this diagnostic difficulty as demonstrated by the different diagnostic hypothesis of the initial biopsy specimen raised by the physician who attended the patient at the first time. Since the initial diagnosis was made using an incisional biopsy fragment, the specimen may not have been representative of the architectural features of the tumor, a fact preventing the correct diagnosis on that occasion.

Although sufficient amount of tissue was obtained for analysis during the second biopsy, the findings of nonspecific spindle-shaped and round cells, sometimes exhibiting clear cytoplasm and pleomorphism, upon analysis of hematoxylin/eosin-stained material led to the initial diagnosis of a malignant neoplasm of possible mesenchymal origin. Only immunohistochemical analysis using antibodies for the identification of the cytological origin of the tumor permitted the establishment of the final diagnosis of RMS.

Although no histological features suggestive of a specific RMS type were observed, considering the young age of the patient the possibility of embryonal RMS was raised, the most common type in this age group. On the other hand, the presence of diverse morphological features suggested pleomorphic RMS; however, this rather aggressive tumor type does not occur in children (1). In addition, it is known that embryonal RMS exhibits marked cellular pleomorphism. Franca et al. (7) reported the case of a patient with solid alveolar RMS. After immunohistochemical analysis, the subtype was changed to undifferentiated RMS due to its negativity for myogenin, desmin, muscle-specific actin, leukocyte common antigen, and cytokeratins. Considering this information and the positivity for desmin observed in the case reported here, the tumor might have been a not otherwise specified (NOS), a category recently added to the classification of RMS that was created for tumors that could not be classified into an specific subtype (4).

Myogenin and desmin are sensitive and specific immunohistochemical markers for head and neck RMS. Muscle-specific actin has also been considered as a marker for these tumors, but it is less sensitive (1, 13). Other immunohistochemical markers have been used to help with the difficult diagnosis of RMS, including myogenic nuclear regulatory proteins such as MyoD1 and myogenin that act as transcription factors and stimulate myogenesis (14). MyoD1 is a marker of the myoid lineage which is expressed by fetal myoblasts and is important for the transition from cell proliferation to differentiation. A variety of differentiated cell types can be converted into skeletal muscle after transfection with MyoD1 through the activation of muscle-specific genes (15). Myogenin

is a myoid differentiation marker. In this respect, it has been reported that the loss of normal proliferation and differentiation control may theoretically lead to the formation of RMS (16).

Analysis of MyoD1 and myogenin expression should permit the identification of primitive, relatively undifferentiated tumors such as RMS. However, since MyoD1 and myogenin are markers of skeletal muscle differentiation, they may also be expressed in other tumors that exhibit this differentiation type, such as rhabdomyomatous Wilms' tumor, and in regenerative muscle fibers entrapped within any infiltrating tumor (14).

Unfortunately, in the present case MyoD1 and myogenin immunostaining could not be performed to help with the diagnosis of the tumor. However, we believe that the use of these markers would have made only a didactic contribution, since the morphological findings and desmin immunopositivity provided sufficient evidence to establish the final diagnosis of RMS. Molecular biology techniques are currently used for the classification of RMS subtypes and may represent a valuable tool for the determination of histological tumor type based on specific genetic criteria, especially permitting the planning of appropriate therapeutic management and estimation of prognosis (8).

Treatment of RMS consists of surgical resection, when possible, associated with multiagent chemotherapy and/or radiotherapy. This treatment represents risks and is primarily defined by the extent, location and stage of the tumor (5). In the case reported here, the fast growth of the tumor and the severe impairment of general health of the patient did not permit the introduction of a neoadjuvant chemotherapy or radiotherapy protocol after surgical removal since the patient died within a short period of time, even before the final diagnosis was available.

In conclusion, the present case illustrates the difficulty in the diagnosis of RMS and emphasizes the importance of urgent medical care to detect any fast-growing lesions in children, to diagnose severe lesions in a timely fashion, and to establish an appropriate treatment plan aimed at improving prognosis and patient survival, since a correct initial management is important for the satisfactory prognosis of any tumor.

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