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Case Report

Management challenges of sinonasal alveolar rhabdomyosarcoma in infanthood: case report and literature review

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ABSTRACT

Alveolar rhabdomyosarcoma (aRMS) is an aggressive soft tissue malignant neoplasm. It's not known to occur often in the sinonasal region of an infant when compared with other histological types. And due to its aggressive nature in deep-seated locations, it's often difficult to manage efficiently, thus associated with worse prognosis. In this article, a rare case of an infant with right sided sinonasal aRMS was reported. Eight month old child with two month history of right sided nasal blockage, watery discharge and a growth in the right nose. There was no epistaxis, palatal or neck swelling. On examination, a polypoid mass was completely occupying the right nasal cavity. There were no palpable cervical lymph nodes. Diagnosis of allergic rhinosinusitis with nasal polyposis was made. The mass progressed with associated ipsilateral cheek swelling extending to the nasal bridge. A greyish white, friable mass was biopsied and was diagnosed histologically as aRMS. The child had a debulking surgery and adjuvant chemotherapy. She later developed tumour lysis syndrome and died. Management of infanthood sinonasal aRMS is challenging especially in low socioeconomic region like ours. A multi-disciplinary approach with intensified multimodality therapy is crucial to improving the management outcomes and quality of life. In all, it is advisable to take closer look at any swelling in the paediatric age group by carefully evaluating it with high degree of suspicion, early diagnosis and individualized treatment.

Keywords: Alveolar rhabdomyosarcoma, Sinonasal region, Intensified multimodality therapy, Adjuvant chemotherapy, Tumour lysis syndrome

INTRODUCTION

Rhabdomyosarcoma (RMS) is an aggressive soft tissue malignant neoplasm of skeletal muscle origin.[1,2] It has a higher male predominance and bimodal peak incidence, with the first peak occurring between the age of 2-6 years and the other around adolescence age group. It accounts for about one-fourth of all head and neck sarcomas and about 6% of all malignancies in paediatric age group of less than 15 years.[1,3] Another study that made attempt at analyzing the clinical features of RMS in infanthood found a higher incidence in the first year of life when compared with an overall incidence per year in children and adolescents.[4]

Other than in the head and neck region, RMS may be found in the retroperitoneal region, genitourinary tract, and the extremities. Within the head and neck region, RMS can be further classified into three subtypes (orbital, parameningeal, and nonorbital-nonparameningeal) based on the anatomical classification and varying prognostic significance. The parameningeal type involves

infratemporal fossa, pterygopalatine area, sinonasal region, and middle ear cleft. The nonorbital-nonparameningeal subtype involves scalp, face, parotid, and oral cavity. Orbital subtype are sorely associated with RMS of the eye region. Out of the three subtypes, parameningeal RMS is associated with poor prognosis because of the propensity to spread to the cranium through the skull base while the nonorbital-nonparameningeal subtype has better prognosis.[1,3] Microscopically, the common histopathological types are the embryonal, alveolar, pleomorphic, and botryoid.[2,5] Many of the reported cases in the literature presented the embryonal RMS (eRMS) as the commonest type that arises from the nasal cavity, post nasal region and paranasal sinuses. Younger children tend to have the eRMS; while adolescents, teens and young adults experience the aRMS.[6,7] In addition, Thompson et al found more adults presenting with aRMS when compared with other age groups.[8]

aRMS is a highly aggressive soft tissue malignant neoplasms. It's not known to occur often in the head and neck region when compared with other histological types. And due to its aggressive nature and deep-seated locations, aRMS is often difficult to manage efficiently, thus associated with worse prognosis.[1,7,9]

The intergroup rhabdomyosarcoma study group (IRSG) designed grouping guidelines for RMS management. This comprises of four groups based on tumour resectibility:[10]

Group 1 describes a localized tumour that can be completely removed by surgical excision.

Group 2 describes a local tumour that had a gross resection, however there was no clear resection with or without evidence of regional spread into the lymphoid tissues.

Group 3 describes a local tumour that cannot be completely resected, leaving a gross residual disease.

Group 4 describes a tumour with distant metastatic disease at the time of diagnosis.

Metastasis of RMS is either direct, by hematogenous route and/or by lymphatic routes.[1] Therefore, combined approach to treatment which includes excisional biopsy and adjuvant chemoradiation therapy has been associated with increase survival.[10,11]

Ear, nose and throat (ENT) forms of RMS are not unexpected, however, those arising from the nose and paranasal sinuses are uncommon. In this report, we presented a case of an infant with alveolar RMS arising from the right nasal cavity and review relevant literature on the clinical presentations and management modalities.

CASE REPORT

We reported a case of an eight month old female child referred to our ENT clinic in a secondary health centre with two month history of right sided nasal blockage, watery nasal discharge and progressively increasing fleshy growth in the right nose. There was no similar history on the left nostril. There was no associated epistaxis, palatal bulge or neck swelling. Perinatal history was not contributory. There was no fever, weight loss, refusal of feeds. On nasal examination, a polypoid mass was found completely occupying the right nasal cavity, it didn't bleed to touch or shrink on application of decongestant nasal drops. Left nasal cavity was patent and no mass lesion was seen though, the nasal septum was slightly deviated to the left. The ear, oral cavity and oropharynx appeared normal. There were no palpable cervical lymph nodes. A diagnosis of allergic rhinosinusitis with nasal polyposis was made. However, differential diagnoses of odontogenic tumour, neurofibroma, dermoid tumour, solitary fibromatosis and gingival granular cell tumour were entertained. She was placed on steam inhalation, oral antibiotics and oral antihistamine and decongestant. However, the nasal mass progressed with associated right sided cheek swelling extending to the nasal bridge (Figure 1). Contrast-enhanced paranasal sinus computed tomography scan (CTS) revealed an isodense mass lesion filling up the right nasal cavity, right maxillary sinus and anterior ethmoidal sinus with erosion of the maxillary bone and deviation of the nasal septum to the contralateral side. No similar lesion was seen in the left nasal cavity or the paranasal sinuses. There was no extension into the nasopharynx and skull base (Figure 2).

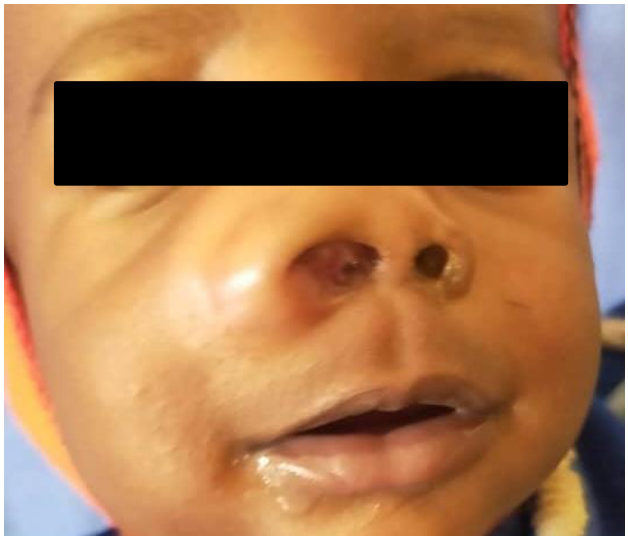

Figure 1: Eight month old with right sided nasal growth with right cheek swelling.

A per nasal biopsy was carried out under general examination and a greyish white, friable mass was biopsied. The intraoperative nasal bleeding was very mild and was arrested by application of pressure with an

anterior nasal pack. IRSG classification in this case was group 3 because the tumour could not be completely excised. The specimen was sent for histopathology analysis. The report revealed infiltrating nests and sheets round, oval to polygonal cells disposed in alveolar pattern. The cells have pleomorphic nuclei with scanty eosinophilic cytoplasm which gave an impression of an aRMS (Figure 3). Immunohistochemical study was not available and the parents could not afford transferring of the tissue to centres where the tumour makers were available. Patient did not have the benefit of carrying out necessary investigations to rule out distant metastasis due to financial issues.

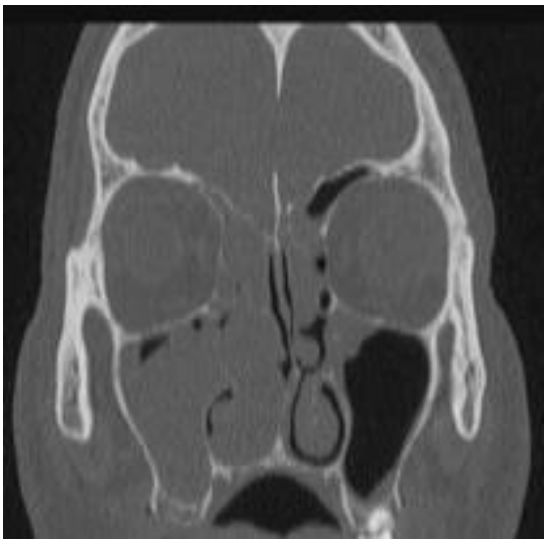

Figure 2: Coronal view of the CTS of the paranasal sinuses showing the lesion in the right nasal cavity and right antrum with extension into the ethmoidal air cells.

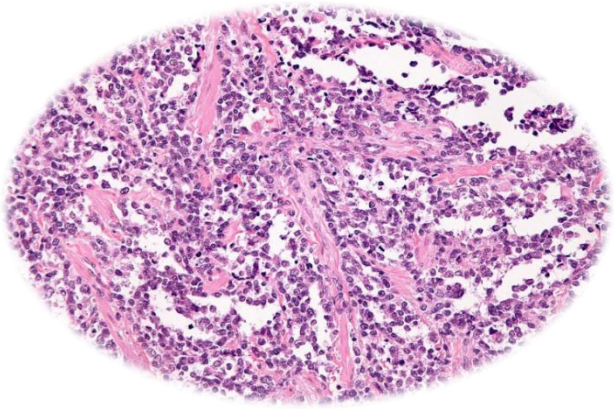

Figure 3: Histopathologic photomicrographs of aRMS.

The child had a debulking of the tumor extension into the right sided maxillary and ethmoidal air cells. She was subsequently placed on cytotoxics by the pediatric oncologists. Six cycles of adjuvant chemotherapy with VIE regimen was prescribed: vincristine 0.45 mg (1.5 mg/m^2, weekly), ifosphamide 360 mg (1 g/m^2, three times weekly) and etoposide 36 mg (100 mg/m^2, five times weekly). Although she was initially started on first line medications with no desirable improvement hence the decision to commence second line drugs. The first four cycles were administered with significant improvement without any severe adverse effects. However, few days after the completion of the 4th cycle, she was rushed into the emergency room in hypovolemic shock with complaints of fever and vomiting. Despite the vigorous resuscitation, patient later succumbed and died due to features related to tumour lysis syndrome (TLS).

DISCUSSION

Sinonasal RMS is an uncommon but aggressively malignant tumor that affects different age groups. The eRMS forms the commonest account for about 75% of cases with good treatment outcome. aRMS, especially in the sinonasal region is not a common disease in infanthood.[6,7,12] This is because it occurs primarily in patients between the age of 10 and 25 years, and involves tumor cells that are mostly undifferentiated in nature, with a propensity to develop distant metastasis faster resulting into poorer outcomes.[2] In the subtype of aRMS, about 80% of cases concealed two signature chromosomal translocations which resulted into the formation and overexpression of chimerical genes. The anomalous expression has been postulated to be part of the tumorigenic behavior by affecting growth control, apoptosis, and differentiation.[13]

Cases of aRMS masquerading as acute lymphoblastic leukemia and lymphoma had been reported.[13] Our reported case was an eight month old girl with right sided nasal blockage, watery nasal discharge and a polypoid growth in the same nasal cavity. The diagnosis of allergic rhinosinusitis with nasal polyposis was made initially due to the similar clinical features. Child was also referred to us after two months of onset of symptoms. This could only mean that there had been some alternative interventions which amounts to late presentation. After making a diagnosis of RMS, systematic clinical evaluation with an attempt at ruling out metastasis was very important because they sometimes presented with painless cervical lymph node enlargement and evidence of distal metastasis even at the first presentation.[2] Surprisingly, such was not recorded in the case reported which also hampered suspicion of a malignant tumour at the first clinic visit.

Radiological evaluation in RMS included contrast-enhanced computerized tomographic and magnetic resonance imaging scan of the head and neck region which was very useful in confirming the location, size, local infiltration of the tumour into surrounding tissue and bony erosions. Bone scan, chest and abdominal imaging will also be needed for evaluating features of distant metastasis. [18F]-fluoro-2-deoxyglucose positron emission tomography combined with CTS (FDG-

PET/CTS) is very helpful for staging and restaging of the tumour especially in the assessment of response to therapy.[14] Our patient could not afford to do other investigations outside CTS, we had to depend on our clinical acumen to rule out evidences of both regional and distant metastasis throughout the treatment period.

Histopathological diagnosis and immunohistochemical analysis remained the means of confirming diagnosis of the subtypes.[7] Generally and as stated in the histological findings our report, diagnosis of RMS and its subtypes can be confirmed by detection of cross striations characteristic of skeletal muscle under light or electron microscope. Studies have elaborated the importance of the investigative modalities for confirming the diagnosis of RMS other than haemotoxylin and eosin aided histological diagnosis. Staining for smooth muscle actin, desmin, and myoglobin for immunohistochemistry will further confirm the diagnosis. Molecular and genetic markers including evaluation with fluorescence in situ hybridization (FISH) methods were also useful for differentiating the subtypes of RMS.[7,10,15] In our reported case, we could only do the conventional histological analysis because of the financial handicap as well as institutional factors and constraints. We did not have the privilege of getting an immunohistochemistry done.

On histological analysis, aRMS can be confirmed by microscopic visualization of small round rhabdomyoblasts arranged in nests or cards separated by connective tissue trebaculae with focal areas of alveolar architecture.[7,14] However, the alveolar subtype also appeared as loosely arranged, mitotic cells with septae that gave a similar morphologic appearance of the normal alveoli of the lungs as well as spindle cell neoplasm. This made immunohistochemical analysis very important in the definitive diagnosis. RMS is characteristically positive for actin, desmin, Z-band protein and Myo-D1.[2]

Generally, the choice of treatment of RMS is based on various factors which includes the histopathological type, clinical stage of the tumour at first presentation, site of tumour, recurrence, prior therapy among others. Studies had reported a significantly high recurrence rate of the tumor after surgical intervention alone. Though there was no clear cut universal protocol for the specific management of infanthood RMS due to peculiarities associated with physiologic immaturity of various organ systems in their premodial stage of development.[11,16] Nevertheless, treatment should be individualized.[16] IRSG recommended initial complete excision of RMS (as far as there will be no or minimal effect on the functions and cosmesis of the structures around the tumour) to be followed by adjuvant therapy. IRSG helps in grouping and prognosticating the disease and it is very useful for preparing a treatment plan. Protocol for the management of soft tissue sarcomas in children according to Children's Oncology Group (COG) as well as European Paediatric Soft Tissue Sarcoma Study Group (EPSTSSG) have also made attempt at basing the staging and treatment of RMS according to its local extension of the tumour, regional and distant metastases, and amount of residual tumour post-surgical resection. Though there is no agreement on a protocol for optimal treatment yet, complete resection of the mass confer a better prognosis and then, residuals can be treated with cytotoxic drugs like vincristine, actinomycin-D, cyclophosphamide and/or the platinum-based. RMS can be radio-sensitive, therefore radiotherapy is another treatment modality of choice. In fact, combined therapy protocols which involves chemotherapy and radiotherapy have been often employed. Neck dissection are also indicated in the presence of occult metastasis to lymph nodes.[2,3,10,12,17] A complete resection is said to have been achieved when the tumour is resected along with (at least) 0.5 cm margin of cancer free tissue.[7] The tumour in our report was in IRSG group 3 because of its extensive local spread with inability to excise the tumour completely. So the patient only had debulking of the nasal mass followed by three regimen chemotherapy. Surgery was the first-line in operable ENT forms. Non-operable forms should be managed by neo-adjuvant chemotherapy. Depending on regression of the tumour and general health status, surgery should be carried out followed by radiation therapy.[18] However, considering the fact that most of the tumors of group 3 in the head and neck region were non-resectable, the mainstay of treatment was an intensified multimodality therapy with at least a combination of radiotherapy and chemotherapy involved.[6] A total maxillectomy in a growing child was not advisable and might not be able to completely remove the tumour without residual disease in this case. Radiotherapy was not instituted in this patient in combination with chemotherapy because of financial constraints. Distance from functional radiotherapy centres was also a contributing factor. Three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, proton beam radiotherapy and brachytherapy were far better techniques of implementing radiotherapy in RMS for better outcome and less complications.[12,14] The introduction of brachytherapy in the management of head and neck tumors had gradually become more preferable due to less complication and tissue-sparing advantages. Some specialist reserved radiotherapy for cases presenting with residue or recurrence after initial primary treatment.[7,14]

In cases where aRMS reoccured or persisted despite combined treatment modality, second-line therapy with combination of temozolomide and irinotecan can be considered for repeat of treatment. The use of brachytherapy in head and neck tumors had become increasingly popular owing to its superiority in tissue sparing approach. Newer researches into the use of immunotherapy like regorafenib in advanced cases of RMS is also ongoing.[14]

The ablative surgery mold technique with after loading brachytherapy and immediate surgical reconstruction (AMORE) protocol for salvage treatment of non-orbital

head and neck RMS especially in childhood RMS entails a regimen that combines vincristine and actinomycin-D with an alkylating agent like cyclophosphamide or ifosfamide.[12,19] These cannot go without high level of toxicity and death related complications especially with the use of full dose of the antineoplastic drugs. Therefore, dose reduction without affection of the final treatment outcome has been reported with less fata toxicities Moreover, to avoid cardiac and renal damage, anthracyclines and ifosfamide are omitted in infants particularly those less than 3 months old.[16]

When compared with other subtypes, aRMS had been reported to have poorer outcomes with a greater frequency of disseminated metastases.[10] The pathway for distant metastasis of aRMS is via hematogenous dissemination, more commonly to the lungs and bones.[2] Distal metastasis should be ruled out at time of diagnosis especial in our environment where patient often present late. Although, there are still gaps in knowledge on the peculiarities of the aetiopathogenesis of aRMS in infants, there are some specific factors that determine or are specific of poor prognosis and survival of patients. They include delay diagnosis and treatment, onset of disease before the first year of life, presence of metastasis, and genetic translocation of PAX3-FHR.[1] Other factors are primary tumor site, tumour burden, extent of disease at diagnosis, clinical grouping, histopathologic types, response to treatment, and margins of surgical resection.[2,10] In cases where aRMS is involvement with metatstatic lymph nodes as well as clinical and/or laboratory signs of acute TLS are also associated with less favorable prognosis.[13,14] In our study, the child developed TLS after the fourth cycle of chemotherapy which later led to her demise. Availability of intensified multimodality therapy has been reported to improve the outcome of RMS treatment even in the face of factors militating against the prognosis.[7]

CONCLUSION

aRMS of nasal cavity and paranasal sinus, the parameningeal subtype is not a common diagnosis in infanthood and not likely to be coming readily to one's mind when thinking of the differentials of unilateral nasal swellings. Time of presentation and how long it took to make definitive diagnosis are very important as diagnosis at early stage and aggressive treatment will improve outcome and increase survival rate. Developing an alveolar rhabdomyosarcoma in the sinonasal region is also unfavorable and challenging especially in infanthood. A multi-disciplinary approach with close coordination among head and neck surgeons, histopathologists, medical oncologists, and radiation oncologists is crucial to improving the management outcomes and quality of life of patients with alveolar rhabdomyosarcoma. In all, it is advisable to take closer look at any swelling in the paediatric age group by carefully evaluating it with high degree of suspicion and early diagnosis. Treatment plan should be individualized and take into consideration the age of the patient, the stage of the disease, and the tumour size. Our patient had adjuvant (second line) chemotherapy for the treatment of alveolar rhabdomyosarcoma which produced a significant improvement at the initial stage of therapy but unfortunately the patient did not survive the complications of the disease and adverse effects of treatment.

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