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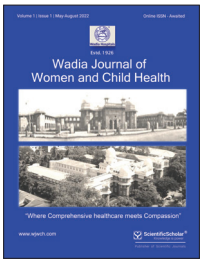

Case Series

Known monster, unknown "avatars": Pediatric rhabdomyosarcoma case series with uncommon presentation

Purvaja Kubde[1], Purva Kanvinde[1], Ritika Khurana[1], Sunil Jhondhale[1], Sneha Shinde[1], Swathi Krishna[1], Parmarth Chandane[2], Sangeeta Mudaliar[1]

[1]Department of Paediatric Hematology-Oncology, [2]Division of Pediatric Pulmonology, Bai Jerbai Wadia Hospital for children, Mumbai, Maharashtra, India.

***Corresponding author:**
Purvaja Kubde,
Department of Paediatric Hematology-Oncology,
Bai Jerbai Wadia Hospital for Children, Mumbai,
Maharashtra, India.

purvajakubde@gmail.com

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ABSTRACT

Rhabdomyosarcoma (RMS) is a rare soft-tissue tumor, accounting for 3% of all childhood cancers. RMS can arise virtually anywhere in the body, as it originates from the embryonal mesenchyme. Embryonal RMS (ERMS) and alveolar RMS are the most prevalent types. In this case series, five children with unusual sites of presentation of ERMS have been reported. The first case is a 6-year-old male who presented with episodes of recurrent hemoptysis for 2 months and computed tomography chest showed lung mass. The second case is a 3-year-old male, who presented with right abdominal distention and was diagnosed as a liver ERMS which is a very rare site for RMS. The third case is a 1-year-old male child who presented with isolated right inguinal lymph node swelling. The fourth case presented with recurrent admissions for respiratory distress requiring intubation and was misdiagnosed as recurrent viral infection, but on further, investigation was diagnosed as a laryngeal ERMS. Our fifth case is a 6-year-old male child who presented with infraumbilical mass, diagnosed as a retroperitoneal ERMS. The 5-year survival rate of such tumors is 70% in children with localized disease who receive combined-modality therapy. Therefore, an awareness of the typical signs and symptoms, radiological features, and histomorphological features in a case of pediatric RMS can help a physician to consider this tumors in the differential diagnoses, even at unusual sites.

Keywords: Embryonal rhabdomyosarcoma, Lung rhabdomyosarcoma, Liver rhabdomyosarcoma, Retroperitoneal rhabdomyosarcoma, Laryngeal rhabdomyosarcoma

INTRODUCTION

Although rhabdomyosarcoma (RMS), a malignancy derived from primitive mesenchyme, is the most common soft-tissue malignancy of childhood, the annual incidence in children aged 14 years or younger is only 2.7 cases/million children.[1] All children with RMS require multimodality therapy with systemic chemotherapy, in conjunction with either surgery, radiation therapy (RT), or both to maximize local tumor control. Several factors affect the disease nature and resectability, hence affecting prognosis. Site of tumor is one such important determinant, others being the histological type and more recently the molecular studies, such as fusion status. RMS is most frequently found in the head and neck area, followed by the genitourinary tract, extremities, and biliary tract.

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Embryonal RMS (ERMS) is the most common histological subtype which carries a fair prognosis while alveolar RMS is the more aggressive subtype.[2] Alveolar RMS has a high rate of metastasis and unfavorable prognosis; it is characterized by a chromosomal alteration – a fusion between the FKHR (also known as FOXO1) gene and either the PAX3 or PAX7 gene. Around 20% of cases showing alveolar histology have no detectable PAX gene translocation.[1] These patients have clinical behaviors, gene alteration patterns, and transcriptomic profiles that align with patients who have ERMS and are now classified together with ERMS, as fusion-negative RMS.

Due to the limited number of cases, there is not much data on course, therapeutic challenges and prognosis of RMS occurring at sites other than the ones mentioned above. We intend to report our experience with five RMS patients who had tumor at atypical sites and presented with uncommon features.

CASE SERIES

Case 1 – a unilateral mediastinal mass

A 6-year-old boy presented with history of recurrent episodes of hemoptysis for 2 months, with no associated systemic symptoms or a history of tuberculosis contact. On examination, child had decreased air entry on the right side of the chest. Chest X-ray showed a heterogeneous opacity in the right hemithorax [Figure 1a] and computed tomography (CT) chest confirmed a large mass replacing the lower lobe of right lung, supplied by the right pulmonary artery, and extending to the right mainstem bronchus. A few heterogeneous hilar lymph nodes were also seen [Figure 1b]. Differential diagnosis of a unilateral mediastinal mass as neuroblastoma, ganglioneuroma, lymphoma, or a primitive neuroectodermal tumor (PNET) was kept and CT-guided biopsy was performed. Histopathology and immunohistochemistry of lung mass lesion revealed malignant round blue cell tumor, positive for desmin, and myogenin [Figure 1c and d]; hence, diagnosis of lung ERMS was established. Fusion studies for FOXO1-PAX3/PAX7 were negative. The child was stratified as group E (High risk) as per EpSSG (European Soft Tissue Sarcoma Study Group) RMS 2005 protocol. At present, he is on neoadjuvant chemotherapy and planned for surgical resection and RT later.

Case 2 – a liver mass

A 3-year-old boy presented with history of abdominal distension for 15 days. He was diagnosed with type 1 choledochal cyst at 2 years of age, requiring excision with hepaticojejunostomy. Physical examination revealed a mass (5 × 4 cm) in the right hypochondrium that was firm with poor mobility and no obvious tenderness. Laboratory test results showed normal complete blood counts and liver

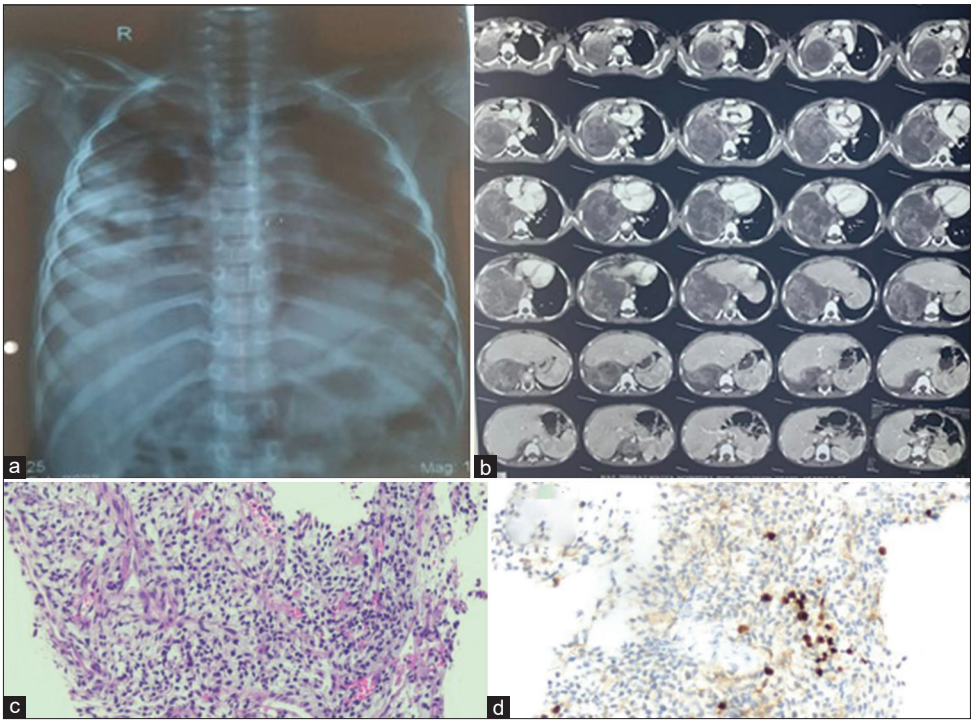

Figure 1: (a) Chest X-ray on presentation. (b) Computed tomography chest showing a large mass replacing right lower lobe, supplied by the right pulmonary artery, extending to the right mainstem bronchus. (c) Histopathology showing malignant round blue cell tumor, (d) Immunohistochemistry demonstrating positivity for desmin.

function tests. In addition, the viral markers for hepatitis B and C were negative, and he had normal levels of alpha-fetoprotein. CT abdomen showed a heterogeneous solid cystic mass arising from the right lobe of liver, abutting the head of pancreas, with dilatation of intrahepatic biliary radicles. A core needle biopsy demonstrated typical rhabdomyoblasts with oval nuclei and eosinophilic cytoplasm. Immunohistochemical analysis was positive for vimentin, desmin, and myogenin; hence, the diagnosis was established to be hepatic and biliary tract ERMS. Fusion studies could not be done due to inadequate sample. He was stratified as per EpSSG protocol as group E (High risk) and underwent right hepatectomy with Whipples procedure after receiving neoadjuvant chemotherapy with vincristine, cyclophosphamide, and actinomycin D for 30 weeks. Post-surgery, while on maintenance therapy with vinorelbine and cyclophosphamide, child had relapse of symptoms and he succumbed to the disease.

Case 3 – inguinal lymphadenopathy

A 1-year-old male child presented with a palpable right inguinal lymph node for 3 months. Ultrasonography showed a well-defined hypoechoic lesion involving the iliacus EpSSG RMS 2005 protocol and sartorius muscles with enlarged inguinal lymph nodes. A right inguinal lymph node biopsy revealed ERMS with diffuse anaplasia [Figure 2a-c]. Fusion studies were negative. Positron emission tomography (PET) scan showed F-18 fluorodeoxyglucose (FDG) uptake in the right inguinal soft-tissue lesion with hypermetabolic inguinal lymph node involvement. Child was stratified as group F (High risk) as per EpSSG RMS 2005 protocol. Having an elder sibling being treated for adrenocortical tumor, he was evaluated for Li Fraumeni syndrome which was then confirmed on genetic analysis. At present, he is on neoadjuvant chemotherapy and awaiting surgery.

Case 4 – subglottic obstruction

A 3-year-old boy presented with history of recurrent cough associated with respiratory difficulty for 5 months, requiring intensive pediatric care unit admission and intubation for severe respiratory distress. He had three admissions in the past for similar complaints. Bronchoscopy revealed subglottic mucosal cicatrisation with narrowing requiring dilatation of subglottic segment [Figure 3a]. High-resolution computed tomography chest showed focal severe narrowing of subglottic segment due to a nodular enhancing lesion indenting the trachea along its anterior wall with non-necrotic lymph nodes seen in the right paratracheal region. The child required a tracheostomy in view of complete obstruction on of the subglottic region due to mass lesion the mass. PET scan showed fluorodeoxyglucose (FDG) avid soft-tissue lesion in subglottic region with hypermetabolic

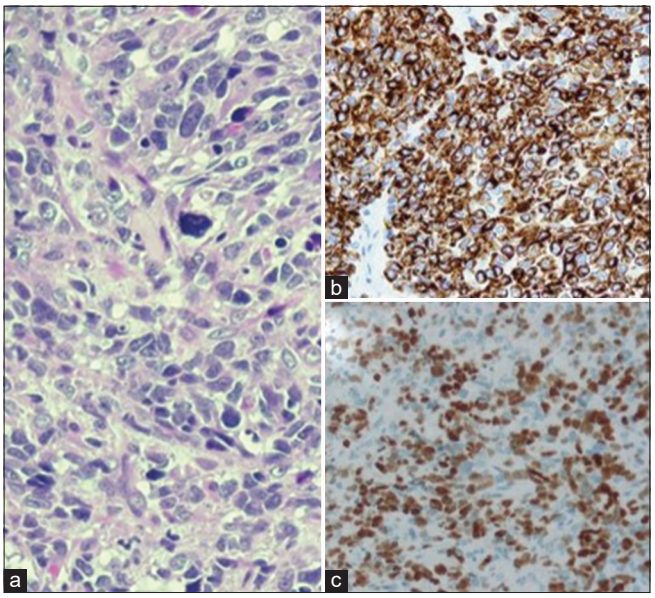

Figure 2: Histopathology examination with (a) hematoxylin and eosin stain showing a small round blue cell tumor with immunohistochemistry showing (b) desmin and (c) myo D1 positivity.

upper paratracheal nodes [Figure 3b]. A biopsy taken from the nodular subglottic mass revealed a small round blue cell tumor, with no anaplasia, showing positivity for desmin and myogenin; hence, the diagnosis of a subglottic ERMS was established. Fusion studies were negative. The child was stratified as group F (High risk) as per EpSSG RMS 2005 protocol. At present, he is on chemotherapy and is planned for radiotherapy.

Case 5 – retroperitoneal mass

A 6-year-old boy presented with a localized infraumbilical swelling for 15 days. On presentation, there was no history of bowel or bladder disturbances. On physical examination, a firm non-tender mass measuring 6 × 7 cm was felt in the infraumbilical region. He had normal levels of alpha-fetoprotein and B-HCG. CT abdomen and pelvis showed retroperitoneal multiloculated cystic mass, extending from left common iliac region to pelvic region [Figure 4]. A CT-guided biopsy of the lesion revealed a retroperitoneal ERMS with no anaplasia. Fusion studies were negative. He was stratified as group E (High risk) and has been started on neoadjuvant chemotherapy.

DISCUSSION

Childhood RMS is a soft-tissue malignant tumor of mesenchymal origin. It accounts for approximately 2.7% of cancer cases among children aged 0–14 years.[1] The 2020

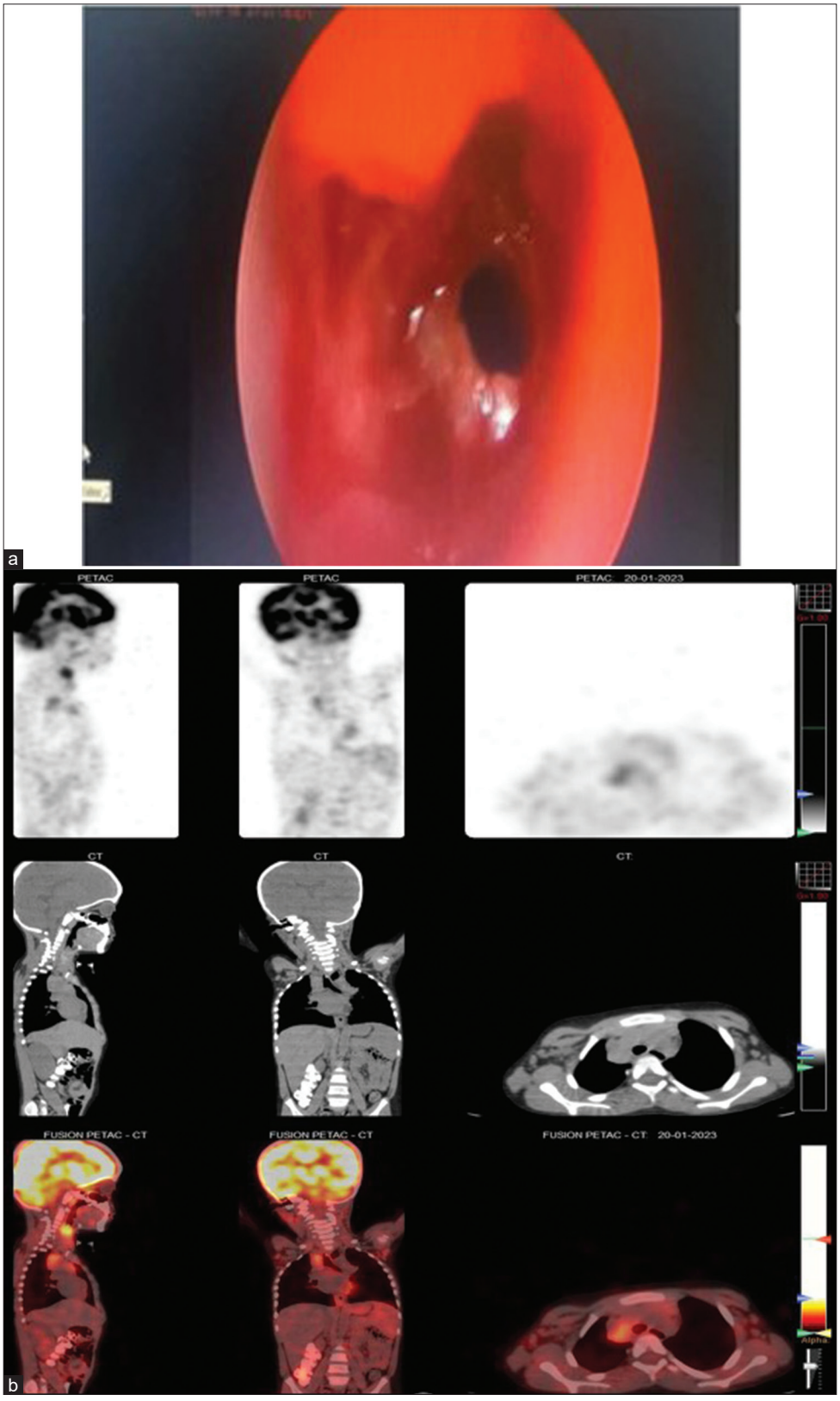

Figure 3: (a) Laryngoscopy image showing subglottic mucosa cicatrisation on with narrowing and nodular lesion. (b) Positron emission tomography scan showing F-18 fluorodeoxyglucose avid soft-tissue lesion in subglottic region with hypermetabolic upper paratracheal nodes.

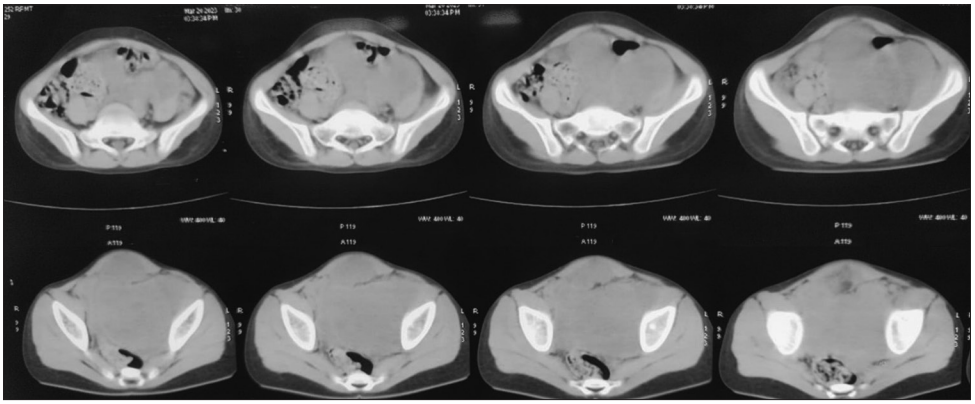

Figure 4: Computed tomography abdomen and pelvis retroperitoneal multiloculated cystic mass, extending from left common iliac region to pelvic region.

World Health Organization classification distinguishes four histological subtypes of RMS, including embryonal, alveolar, spindle cell/sclerosing, and pleomorphic.[2] RMS may occur anywhere in the body. The most common primary sites include head and neck region (parameningeal) (approximately 25%), genitourinary tract (approximately 31%), and extremities (approximately 13%).[3,4] Other less common primary sites include the trunk, chest wall, perineal/anal region, and abdomen, including the retroperitoneum and biliary tract.[5] However, rare sites of origin as explained above can be seen. Most cases of RMS occur sporadically, with no recognized predisposing risk factor. Genetic predisposition factors reported for RMS include Li-Fraumeni syndrome, DICER1 syndrome, Neurofibromatosis type I, Costello syndrome, Beckwith-Wiedemann syndrome, and Noonan syndrome.

We report a case series of five patients who had rare sites of involvement by RMS such as lung, liver and biliary tract, right thigh muscle with inguinal lymph node, subglottic region of larynx, and retroperitoneum. The incidence of RMS is highest in children aged 1–6 years, lower in children aged 10–14 years, and lowest in those aged 15–19 years. Our patients presented between 1 and 6 years of age and all of them were males. All five patients were diagnosed on histopathology as ERMS. Fusion study of four patients showed negative fusion status. Fusion study of one patient could not be done due to inadequate sample. All patients were stratified as per EpSSG RMS 2005 protocol as high risk. One patients with the right thigh muscle ERMS showed TP53 mutation, other patients were tested and showed no significant pathological variant on genetic analysis. Four out of five patients are currently on neoadjuvant chemotherapy. One patient with liver and biliary tract ERMS had relapsed while on maintenance therapy and succumbed to febrile neutropenia with septic shock.

RMS rarely originates in the lung and only 32 cases are reported as primary pulmonary RMS in the pediatric age group.[6] Among the other cases, the ages of the patients ranged from 5 months to 16 years old. Nine of the cases developed in a background of congenital cystic adenoid malformation, while the others including our case developed in a normal lung. RMS should be considered in the differential diagnosis of any lung mass with small round blue cell morphology in the microscopic evaluation and should be distinguished from metastatic RMS of other sites, pleuropulmonary blastoma, lymphoma, neuroblastoma, PNET, and malignant peripheral nerve sheath tumor.

Primary intrahepatic RMS is extremely rare. Since 1956, a total of 20 cases of hepatic RMS have been reported. RMS rarely affects the liver as a primary pediatric malignancy and has a poor prognosis, with a mean survival time of 9.25 months.[7] The liver as a rare location of RMS has an insidious onset which makes it easy to misdiagnose. There are no reports that have described the typical clinical symptoms and imaging findings of hepatic RMS, so histopathological diagnosis is the gold standard.

Primary laryngeal sarcomas constitute <1% of all malignant laryngeal tumor.[8] The most common symptoms and signs, including hoarseness, dyspnea, stridor, dysphagia, and polypoid appearance, provide limited diagnostic information. RMSs have been misdiagnosed as hemangioma and laryngopharyngeal reflux. Our case was also initially diagnosed as recurrent viral lower respiratory tract infection with post intubation subglottic stenosis as the overlying mucosa was cicatrized. Therefore, bronchoscopy was not performed on initial presentation. This is usually the main reason for delayed diagnosis of laryngeal ERMS. Thus, early suspicion and prompt diagnosis is important.

Despite the advent of modern imaging, and the associated increase in incidental diagnoses, retroperitoneal RMS remains a rare malignancy, occurring in 0.5–1.0/100,000 population.[9] The rarity of these tumors and the complexity of their treatment require multidisciplinary management

in specialized centers to improve oncologic and clinical outcomes**.** For patients with initially unresectable retroperitoneal/pelvic tumors, complete surgical removal after induction chemotherapy, with or without RT, offers a significant survival advantage. Retroperitoneal RMS can expand massively in the confines of the retroperitoneum before detection and diagnosis, making these resections challenging.

All children with RMS require multimodality therapy with systemic chemotherapy, in conjunction with either surgery, RT, or both modalities to maximize local tumor control. Surgical resection is performed before chemotherapy where possible if it will not result in disfigurement, functional compromise, or organ dysfunction. If this is not possible, only an initial biopsy is performed.

CONCLUSION

RMS is usually a highly malignant tumor with extensive local invasions and early hematogenous and lymphatic dissemination. Physicians need a strong index of suspicion, especially when the tumor presents in uncommon locations, to make an early diagnosis. Early detection and multimodality treatment are critical for a positive outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. National Cancer Institute. NCCR Explorer: An Interactive Website for NCCR Cancer Statistics. Bethesda, MD: National Cancer Institute. Available from: https://www.cancer.gov/types/soft-tissue-sarcoma/hp/rhabdomyosarcoma-treatment-pdq [Last accessed 2022 Dec 06].
2. WHO Classification of Tumours Editorial Board. WHO Classification of Tumours. Soft Tissue and Bone Tumours. 5th ed., Vol. 3. France: IARC Press; 2020.
3. Crist W, Gehan EA, Ragab AH, Dickman PS, Donaldson SS, Fryer C, *et al*. The third intergroup rhabdomyosarcoma study. J Clin Oncol 1995;13:610-30.
4. Maurer HM, Gehan EA, Beltangady M, Crist W, Dickman PS, Donaldson SS, *et al*. The intergroup rhabdomyosarcoma study-II. Cancer 1993;71:1904-22.
5. Casanova M, Meazza C, Favini F, Fiore M, Morosi C, Ferrari A. Rhabdomyosarcoma of the extremities: A focus on tumors arising in the hand and foot. Pediatr Hematol Oncol 2009;26:321-31.
6. Hafiz B, Bamefleh H. Primary pulmonary alveolar rhabdomyosarcoma in a pediatric patient: A case report with literature review. Cureus 2022;14:e21270.
7. Okazaki M, Tajima H, Ohbatake Y, Shinbashi H, Nakanuma S, Makino I, *et al*. Pleomorphic rhabdomyosarcoma of the liver in an adult: A rare case report. BMC Surg 2020;20:81.
8. Mungan S, Arslan S, Küçüktülü E, Ersöz Ş, Çobanoğlu B. Pleomorphic Rhabdomyosarcoma arising from true vocal fold of larynx: Report of a rare case and literature review. Case Rep Otolaryngol 2016;2016:8135967.
9. Ransom JL, Pratt CB, Hustu HO, Kumar AP, Howarth CB, Bowles D. Retroperitoneal rhabdomyosarcoma in children. Results of multimodality therapy. Cancer 1980;45:845-50.