OPEN ACCESS – CASE REPORT

A Case Report of Extensive Facial Primitive Myxoid Mesenchymal Tumor of Infancy: An Approach to Diagnosis and Review of Literature

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ABSTRACT

We report a case of a 14-month-old female presenting with a one-year history of rapidly enlarging left hemifacial mass with recurrence despite excision. The tumor consists of bland round to short spindle cells in a myxoid stroma with positive expression to vimentin, CD99, SATB2, cyclin D1 and BCOR, compatible with a sarcoma with BCOR genetic alteration. Next-generation sequencing was performed that detected a BCOR internal tandem duplication, confirming the diagnosis of a primitive myxoid mesenchymal tumor of infancy (PMMTI). This report highlights the importance of attention to histopathologic characteristics, prudent application of immunohistochemical stains and molecular studies in differentiating PMMTI from other soft tissue sarcomas.

Key words: primitive myxoid mesenchymal tumor of infancy, BCL6 co-repressor gene internal tandem duplication, soft tissue sarcoma

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 22 November 2023.
Accepted: 5 January 2024.
Published online first: 9 January 2024.
https://doi.org/10.21141/PJP.2023.20

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INTRODUCTION

Primitive myxoid mesenchymal tumor of infancy (PMMTI) is a rare soft tissue malignancy and newly recognized distinct entity under undifferentiated small round cell sarcomas in the most recent World Health Organization classification of soft tissue and bone tumors. It is characterized by BCL6 co-repressor (BCOR) gene internal tandem duplication (ITD).[1] Since its initial description by Alaggio et al., in 2006, only a few cases have been reported worldwide, hence extensive information is still needed to understand further its biologic and clinical behavior that is fundamental to its successful management, particularly in cases with unresectable conditions. To our knowledge, this report is the first to describe a PMMTI with extensive involvement of the left hemifacial structures in a 14-month-old female. The clinical, radiologic, histologic, immunohistochemical, and molecular features are discussed.

CASE

Clinical history and imaging

A 14-month-old female with unremarkable prenatal and family history was evaluated for a one-year history of left hemifacial mass that was rapidly enlarging, firm, painless, non-movable, and initially measuring 3 x 3 cm on the left zygomaticus at three months of age. Surgical excision was done at seven months and an initial histopathologic diagnosis of lipoblastoma was made in another institution. Postoperatively, recurrence was noticed on the same site that grew rapidly in a span of five months. It was non-erythematous, firm, multinodular, and measured 6 x 8 x 10 cm. extensively involving the periorbital, temporal, zygomatic, maxilla and mandibular area (Figure 1A). A computer tomography scan revealed a large, lobulated heterogeneously enhancing mass in the left zygomatico-maxillary region, which deforms and erodes the bones in the left side of the skull base, left zygomatic bone, left paranasal sinus walls, septa, left orbit, and a portion of

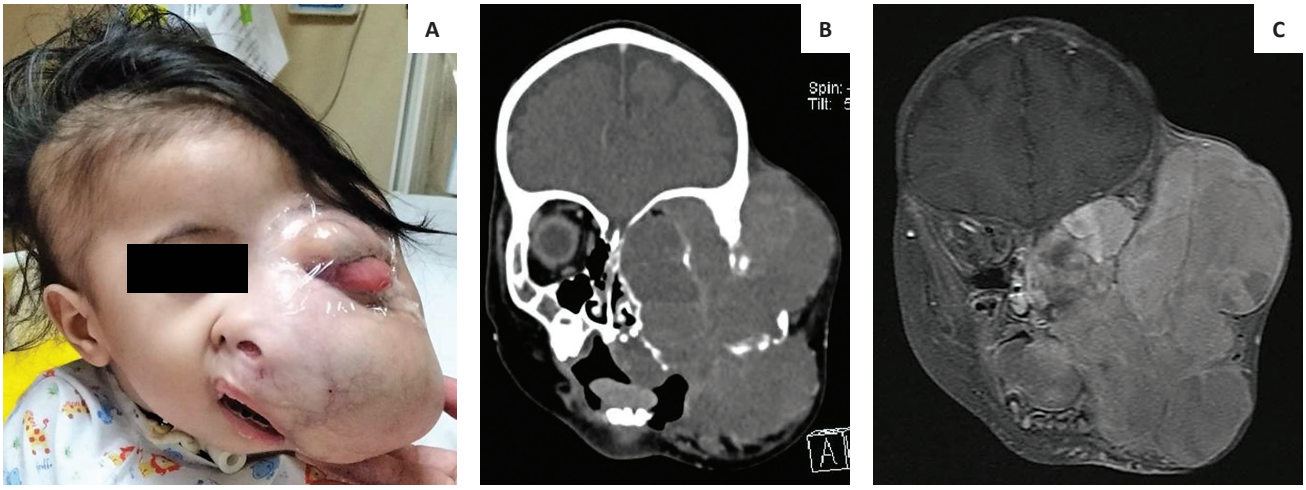

Figure 1. ***Clinical findings and imaging, recurrent lesion.*** **(A)** Gross structure of tumor at 14 months of age; **(B)** Cranial C scan; and **(C)** MRI showing the invasion of tumor to adjacent bone and soft tissue structures.

the body of the left mandible. The adjacent soft tissue structures are poorly defined, the left globe is displaced, and the extraocular muscles and optic nerve cannot be distinguished, indicating potential severe compression or infiltration of these tissues (Figures 1A and 1B). Magnetic resonance imaging showed invasion of the left cavernous sinus and effacement of the anterior aspect of the left middle cranial fossa. Brain parenchymal volume loss is also noted, with no abnormal intracranial parenchymal or meningeal enhancement identified (Figure 1C).

Microscopic findings

Histologic examination of the initial excision biopsy of the lesion disclosed a neoplasm composed of monomorphic, round to slight spindle cells haphazardly arranged in myxoid stroma with prominent, thin-walled blood vessels (Figure 2A). The cells are bland appearing and have ovoid and vesicular nuclei, absent to small nucleoli, and delicate to indistinct, pale, eosinophilic cytoplasm (Figure 2B). The myxoid nodules blend into more fibrous areas composed of vague fascicles of bland short spindle to ovoid cells

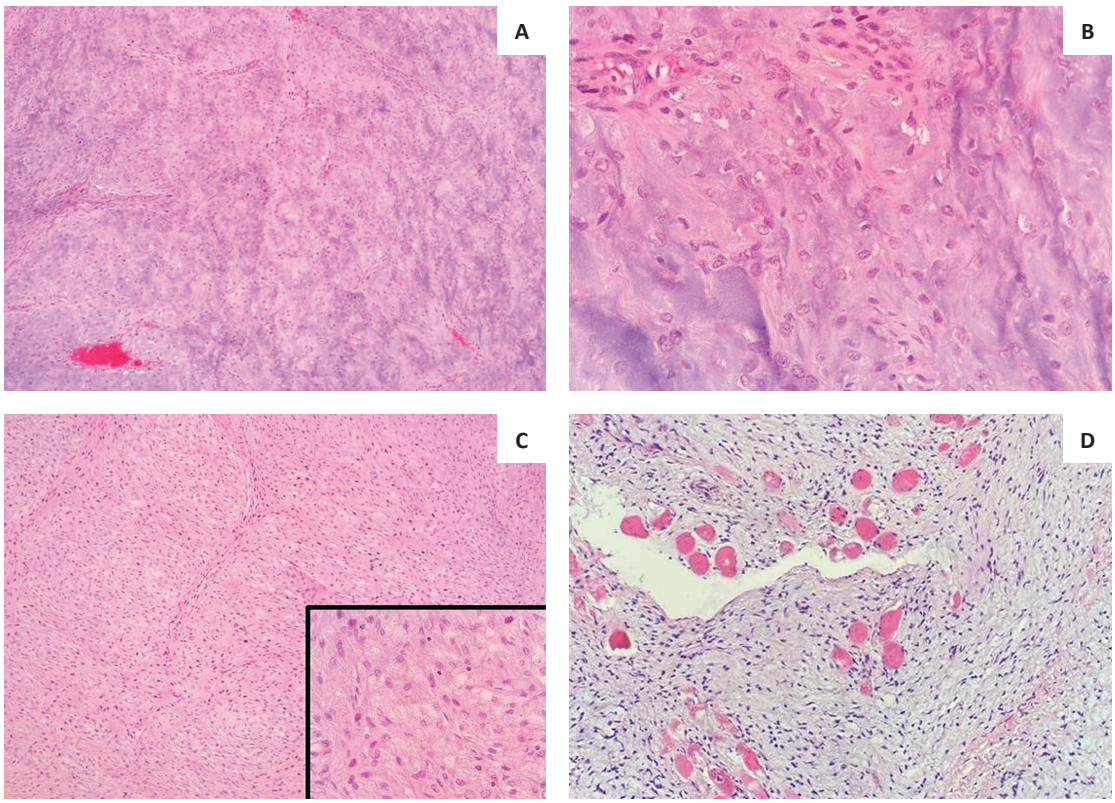

Figure 2. ***Histopathologic findings, initial excision*** *(hematoxylin and eosin stain).* **(A)** Bland round to short spindle cells in myxoid stroma with prominent, thin-walled blood vessels (40x). **(B)** Neoplastic cells with ovoid, vesicular nuclei, absent to small nucleoli, and delicate to indistinct cytoplasm (400x). **(C)** More fibrous areas with vague fascicles of short spindle to ovoid cells (40x, 400x). **(D)** Infiltration of skeletal muscle (200x).

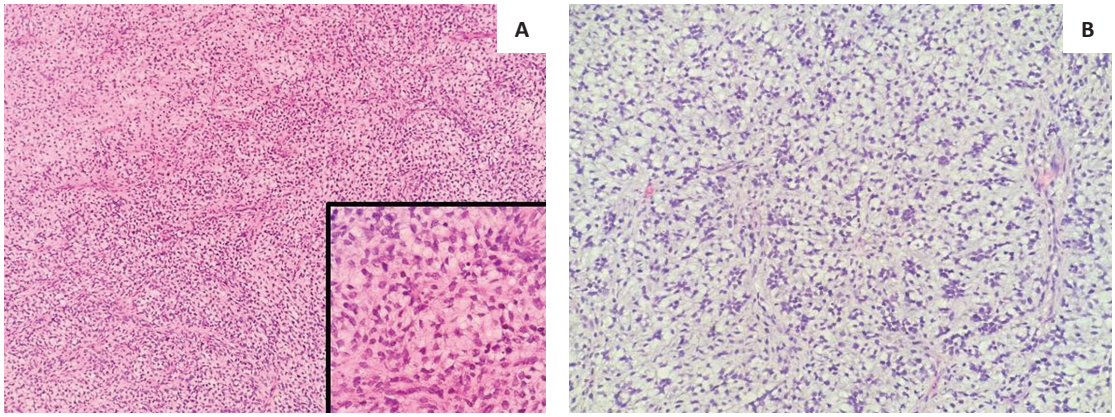

Figure 3. ***Histopathologic findings, recurrence.*** **(A)** Repeat biopsy showed slightly increased cellularity (40x, 400x), and **(B)** focal clustering of cells in myxoid stroma (200x).

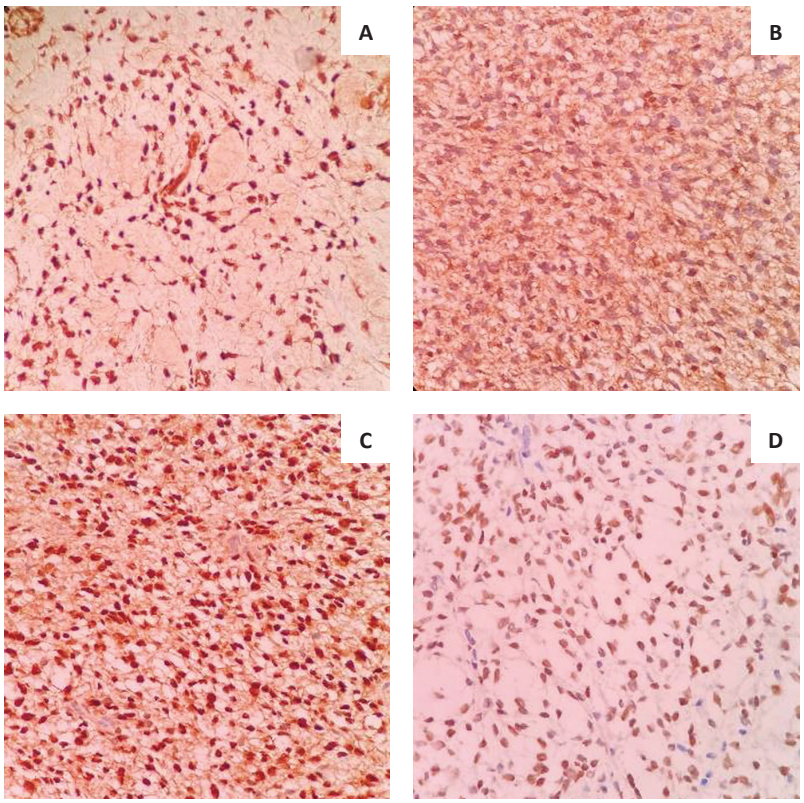

Figure 4. ***Immunohistochemistry (200x)***. **(A)** Retained nuclear staining for INI-1; **(B)** Diffuse, cytoplasmic staining for CD99; **(C)** Diffuse, nuclear staining for Cyclin D1; **(D)** Diffuse, nuclear staining for SATB2.

(Figure 2C). Skeletal muscle invasion was present (Figure 2D). Mitosis is noted at 0 to 4 per 10 high power fields. There were no atypical forms and necrosis was not identified.

An incision biopsy done on the recurrent lesion predominantly displayed similar microscopic features but with increased cellularity and nuclear chromasia (Figure 3A), focal clustering of neoplastic cells (Figure 3B), and slightly increased mitotic activity at 6/10 high power fields.

Immunohistochemical studies

The neoplastic cells showed diffuse immunoreactivity to vimentin, negative staining for cytokeratin, SMA, S100, CD34, ERG, desmin, myogenin, and BCL6, and retained nuclear expression for INI-1 (Figure 4A). Diffuse positivity with CD99, SATB2, cyclin D1 and BCOR immunohistochemistry was noted (Figure 4B, 4C, and 4D; photomicrograph for BCOR immunohistochemistry not available).

Molecular study

Although the immunohistochemical profile and histomorphology were highly suggestive of a sarcoma with BCOR genetic alteration, next-generation sequencing using Archer FusionPlex Pan-Solid Tumor Assay was performed. It detected a BCOR (exon 15) – BCOR (exon 15) breakpoint, indicating the presence of BCOR internal

tandem duplication, and confirming the diagnosis of primitive myxoid mesenchymal tumor of infancy.

Clinical management

With the continuous enlargement of the mass and impending airway/esophageal obstruction, the patient underwent tracheostomy, gastrostomy tube insertion, and porta catheter insertion. The large size and extent of the neoplasm precluded surgical management. Chemotherapy with vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide was initiated. The patient received a total of four cycles of chemotherapy over five months, after which repeat imaging was performed.

Post-treatment reassessment

There appeared to be no changes to the size of the mass on physical examination. Contrast-enhanced craniofacial MRI showed an increase in the size of the mass to 10.3 x 8.1 x 11.6 cm. There was still associated cortical destruction of the adjacent osseous structures and left mastication space, extension to the left orbital space with exophthalmos and superomedial displacement of the conal structures, and extension to the nasal septum. There was progression in the extent of the mass with involvement of the inferomedial aspect of the oral cavity and indentation of the tongue. Abnormal signals with post-contrast enhancement are also seen within the sphenoid sinuses. With this outcome after treatment, chemotherapy was stopped, and the patient was advised palliative care.

DISCUSSION

Primitive myxoid mesenchymal tumor of infancy (PMMTI) is a new category of undifferentiated round cell sarcoma (URCS) that has been proven to be distinct based on histopathology, immunohistochemical markers, and on the nature of the tumor.[1] The molecular hallmark of PMMTI has been recently identified by Kao et al in BCL6 co-repressor (BCOR) gene internal tandem duplication (ITD), the same genetic alteration detected in infantile undifferentiated round cell sarcoma (URCS), clear cell sarcoma of the kidney, group of central nervous system primitive neuroectodermal tumors (CNS-PNET), as well as in certain high-grade endometrial sarcomas, hence suggesting shared pathogenesis.[2,3]

PMMTI typically occurs within the first year of life or may be present at birth, frequently presenting with painless mass ranging from 0.9 cm to 15 cm (mean 6.18 cm). While there is a wide anatomic distribution, the most common sites of occurrence are the deep tissues of the trunk, extremities, and neck. Among the truncal tumors, the paravertebral region is mostly affected.[1,2,4] In the head and neck, cases have been reported around the optic nerve, nasal cavity, throat and scalp.[5-7] In the case presented, the neoplasm arose in an infant at three months of age in the left zygomatic area to subsequently involve the left hemifacial structures extensively. Incompletely resected tumors tend to recur,[5,6] with two cases involving the optic nerve recurring after 8 and 12 months.[5,7] This may be in part due to the difficulty of wide resection in the head and neck region. In the case presented, there was a recurrence five months post-resection with positive margins.

Histologically, PMMTI is characterized by the multinodular appearance and variable cellularity ranging from hypocellular myxoid areas to sheets of primitive spindle and round cells in a myxoid background with delicate vasculature.[1-3,8] In a recent study by Antonescu et al, most of the cases diagnosed as PMMTI displayed predominantly low cellularity, with the myxoid component often in the range of >80-90% of the 13 cases reviewed.[9] Tumor cells have round to ovoid nuclei, with mild to moderate atypia and diffuse hyperchromasia. Necrosis is rarely observed. The mean mitotic rate was 4.1 mitoses (range: 1 to 20 mitoses) per 10 high-power fields. In cases of recurrence and progression, cellularity and cellular atypia were higher. These features were seen in the case presented. The primary neoplasm displayed predominantly mildly cellular myxoid nodules with modest mitotic activity (0 to 4 mitoses per 10 high power fields). The recurrent lesion showed increased cellularity and cytologic atypia, and focal clustering of cells. One case of transformation into an aggressive, undifferentiated sarcoma after chemotherapy and radiation therapy was also reported. Due to its rare incidence, further studies are needed to evaluate the impact of various histologic subtypes and their myxoid component on survival.[4,9,10]

The main differential diagnoses based on histology and age include infantile fibrosarcoma, lipoblastoma, lipofibromatosis, low-grade fibromyxoid sarcoma, embryonal rhabdomyosarcoma, and malignant extrarenal rhabdoid tumor.[8]

Infantile fibrosarcoma (IF) presents as a rapidly enlarging, painless mass and affects children less than 4 years of age with more than 75% diagnosed in the first year of life. It may sometimes arise in the head and neck and has a broad morphological spectrum. It occasionally exhibits monomorphic ovoid to spindle cells in myxoid stroma that resembles PMMTI but is often seen with a hemangiopericytoma-like vascular pattern and a mixed chronic inflammatory infiltrate. The immunohistochemical profile is nonspecific with variable expressions of CD34, S100, SMA and desmin. Pan-TRK antibody may aid in the differential diagnosis as IFs with NTRK rearrangement are immunoreactive, however, this test was not locally available. This lack of characteristic staining pattern in IF and morphologic overlap with PMMTI requires molecular testing to differentiate it from PMMTI. The presence of recurrent ETV6-NTRK3 fusion that confirms its diagnosis[1] was not noted in the NGS testing for this case.

Lipoblastoma is a benign neoplasm of embryonal white fat that similarly occurs in newborns and infants. It occurs in a wide variety of anatomic sites that includes the head and neck and consists of cells with a wide range of maturation states from primitive mesenchymal cells, lipoblasts to mature adipocytes, often with a myxoid background. The presence of primitive mesenchymal cells and myxoid stroma overlaps with PMMTI and it may be difficult to distinguish the two entities in small biopsies as exemplified in this case report. However, the presence of other features (i.e., lipoblasts, mature adipocytes) should aid in the diagnosis. Immunohistochemical studies, which are nonspecific, play a limited role in differentiating lipoblastoma from PMMTI. Lipoblastoma demonstrates

positivity for S100, CD56, and CD34 while the primitive mesenchymal component is often reactive for desmin. The demonstration of rearrangements or amplification of the PLAG1 gene is a characteristic feature.[1] PLAG1 gene aberrations were not noted in the NGS testing for this case.

Lipofibromatosis occurs in children from birth to the second decade of life with a predilection for the hands and feet. The presence of small haphazardly arranged round or oval cells in a myxoid background that is notable in newborn patients may mimic PMMTI. However, it can be easily differentiated due to the presence of interspersed mature adipose cells, capillary-sized vessels, a distinct bundled and fascicular fibroblastic component, and a typical site of predilection. Immunohistochemistry is non-specific with variable expression of CD34 and SMA.[1]

Low-grade fibromyxoid sarcoma (LGFMS) is characterized by collagenous hypocellular areas and cellular myxoid nodules that can histologically imitate PMMTI. However, it can be readily distinguished by its characteristic alternating collagenous and myxoid areas with either an abrupt or gradual transition. It also has a predilection for the proximal extremities and trunk of young adults. Diffuse strong MUC4 reaction and identification of FUS-CREB3L2 fusion confirm the diagnosis.[1] The NGS testing for this case was negative for FUS translocation, dissuading from LGFMS.

Other likely considerations that may occur in the same site and age group, may show round cell morphology and fibromyxoid background including embryonal rhabdomyosarcoma, peripheral nerve sheath tumor, vascular neoplasm, myoepithelial lesions, and malignant extrarenal rhabdoid tumor, but can be readily ruled out based on negative immunohistochemical staining in desmin, myogenin, S100, ERG, CD34, SMA, cytokeratin and retained INI1 expression. In addition, aberrations in CAMTA, EWSR1, and FUS genes were not detected in the NGS testing of this case, which do not support epithelioid hemangioendothelioma, myoepithelial neoplasms, and other undifferentiated round cell sarcomas, respectively.

As with other tumors harboring BCOR gene alterations, PMMTI shows strong and diffuse nuclear positivity for both BCOR and BCL6 as well as in most cases also expresses SATB2, TLE1, and cyclin D1. However, for this case, BCL6 was negative suggesting a variable expression. Moreover, it is positive for vimentin and approximately 50% of cases is reactive for CD99. Even though these immunohistochemical stain markers are nonspecific, they still appear to be very useful in differentiating PMMTI from other tumors, particularly when molecular testing for BCOR internal tandem duplication is not available.[1-3]

The continuous advancement in molecular characterization of human tumors has elucidated the role of the BCOR gene in a variety of mesenchymal neoplasms and more recently in a central nervous system high-grade neuroepithelial tumor. This gene is situated at Xp11.4 and codes for a protein that participates in transcriptional repression by interacting with BCL-6 and promoting epigenetic silencing via polycomb repressive complex 1 (PRC1). Two major genetic alterations have been described namely gene fusions (mainly BCOR-CCNB3, BCOR-MAML3, and ZC3H7B-BCOR) and internal tandem duplications (ITD) of the polycomb-group RING finger homolog (PCGF) ubiquitin-like fold discriminator (PUFD) domain (BCOR-ITD). The presence of the latter distinguishes PMMTI from its histological differential diagnoses. These ITDs were in frame and located in the last exon of BCOR but the nucleotide number and genomic positions were variable.[11] The clinicopathologic importance of the insert size and/or length of the homologous region in positive internal tandem duplication is still unknown due to a limited number of reported cases which restricts a larger multi-institutional investigation.[9]

PMMTI must be differentiated from various analogous pathologies encompassing both benign and malignant conditions due to its different management approach. Available data imply that it has an intermediate biological behavior because it can be locally invasive and infrequently metastasizes.[10] Currently, complete surgical excision with the establishment of negative margins is the gold standard treatment in this pathology. However, consensus treatment protocols for unresectable tumors are still lacking. Based on published cases, chemotherapy resistance is common; however, doxorubicin-containing and ifosfamide-containing regimens seem to be the most effective.[12] Recently, Yang et al., reported a case of a 38-day-old female with right shoulder PMMTI who received an intratumoral injection of bleomycin leading to a distinct boundary between the tumor and adjacent tissue, facilitating its successful resection.[13] The four cycles of doxorubicin and ifosfamide-containing chemotherapy given to the patient, in this case, did not appear to reduce the size and extent of the tumor, and the patient was advised palliative care.

The outcome and long-term survival of patients with PMMTI is mostly unknown.[4, 14] To date, there is only one study published that evaluated the prognosis of 33 BCOR ITD-positive URCS/PMMTI cases which revealed an overall survival of 42% (at 3 years) and 36% (at 5 years). It also found that there was no statistically significant survival difference between cases diagnosed as URCS and PMMTI as well as between those with BCOR ITD and YWHAE fusions.[9]

CONCLUSION

This report emphasizes the importance of cautious attention to histopathologic characteristics, prudent application of immunohistochemical stains together with molecular analysis in differentiating PMMTI from other soft tissue sarcomas. Larger studies are also required to investigate its biologic and clinical behavior and to determine appropriate treatment modalities particularly in unresectable cases.

ETHICAL CONSIDERATIONS

Patient consent was obtained prior to submission.

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

None.

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