Case Report

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Pathology Section

Rhabdomyosarcoma with Bone Marrow Metastasis Masquerading as Acute Leukaemia: A Case Report

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ABSTRACT

Rhabdomyosarcoma (RMS) is a malignant mesenchymal tumour with skeletal muscle differentiation. Three subtypes of RMS are recognised, namely embryonal, alveolar, and pleomorphic. Of these, the alveolar and embryonal subtypes are common in childhood and adolescence. The present case illustrates an example of paediatric RMS with diffuse bone marrow metastasis. A 12-year-old male child was referred as a case of bicytopenia under evaluation and initially had complaints of cough, cold and fever for one month. There was also a history of breathing difficulty, weight loss, loss of appetite and lethargy. The child developed respiratory distress and required oxygen support. A Computed Tomography (CT) scan of the chest revealed left moderate pleural effusion, consolidation of the left upper and lower lobes, and mild pericardial effusion. The child underwent bone marrow aspiration and flow cytometry. The bone marrow aspiration showed 35% blasts, and the flow cytometry report was suggestive of acute erythroid leukaemia/acute megakaryoblastic leukaemia. Meanwhile, the child developed haemorrhagic pleural effusion, and a Contrast-enhanced Computed Tomography (CECT) scan of the chest showed a large mediastinal mass encasing the airway and large vessels (aorta, pulmonary vein and superior vena cava). The child was planned for an Ultrasonogram (USG) guided biopsy under high-risk consent. During the course of the procedure, the child developed sudden cardiac arrest and was declared dead. Biopsy tissue from the mediastinal mass was received, and based on microscopic and immunohistochemistry analysis, the final diagnosis of RMS with diffuse bone marrow metastasis was made. The present case is known for its diagnostic challenge due to the lack of characteristic clinical presentation.

Keywords: Bicytopenia, Immunohistochemistry, Mediastinal mass, Pericardial effusion

CASE REPORT

A 12-year-old male child presented with complaints of cough, cold and fever for one month, along with a history of breathing difficulty, weight loss, loss of appetite and lethargy. The cough was productive and blood-stained. The fever was high-grade, intermittent, and not associated with chills or rigor. The child had no history of contact with Tuberculosis (TB). Upon respiratory system examination, decreased air entry was noted in the left basal region. A CT chest scan revealed moderate left pleural effusion, consolidation of the left upper and lower lobes, and mild pericardial effusion. Multiple supraclavicular nodes measuring 0.5×0.5 cm were palpable on the left-side of the neck. An USG showed multiple enlarged lymph nodes with distorted architecture in levels 3A, 3B and 4. Fine Needle Aspiration Cytology (FNAC) was performed on the left supraclavicular node, which showed sheets of neoplastic cells with enlarged vesicular nuclei, prominent nucleoli, and scant eosinophilic cytoplasm intermixed with lymphoid cells in a haemorrhagic background, suggestive of a lymphoproliferative lesion (image not shown). Following this, serological [Table/Fig-1], haematology [Table/Fig-2] and biochemistry [Table/Fig-3] investigations were conducted.

S. No.	Serological investigations	Result
1	Widal	Negative
2	Scrub typhus	Negative
3	Mantoux test	Negative
4	ICTC	Non reactive

[Table/Fig-1]: Serological investigations done.
ICTC: Integrated counseling and testing centre

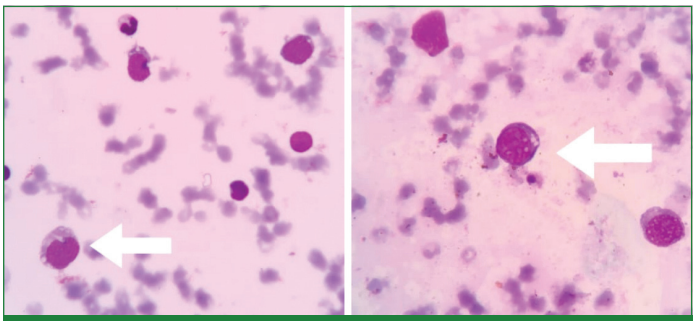
Haematological investigations	Units	Patient values	Normal values
Total count	cells/mm^3	6900	4.5-13.5
Haemoglobin	g/dL	6.3	12-15
PCV	%	19	35-49
DC-POLY	%	30	-
Lymphocytes	%	55	-
MXD	%	13	-
Platelets	cells/mm^3	17000	150000-450000
MCV	fl	81	80-94
MCH	pg	21	26-32
MCHC	g/dL	32	32-36
Red blood cells	cells/mm^3	320	400-540
RDW-CV	%	16.8	11.5-14.5

[Table/Fig-2]: Haematological investigations done.
PCV: Packed cell volume; DC-POLY%: Percentage of polymorphonuclear neutrophils (PMNs), within a differential count (DC); MXD%: Mixed white blood cells %

Biochemical investigations	Units	Patient values	Normal values
Urea	mg/dL	22	15-40
Creatinine	mg/dL	0.4	0.52-0.69
Sodium	mEq/L	140	134-146
Potassium	mEq/L	4.4	3.4-4.8
Calcium	mg/dL	10.4	9.4-10.3
Phosphorous	mg/dL	5.1	4-7
Total bilirubin	mg/dL	1.3	0.1-0.9
Direct bilirubin	mg/dL	0.5	0.1-0.29
SGOT	IU/L	50	14-35
SGPT	IU/L	31	8-22
Total proteins	g/dL	5.6	5.7-8
Albumin	g/dL	3.6	3.4-5.4
Uric acid	mg/dL	4.6	3.1-6.4

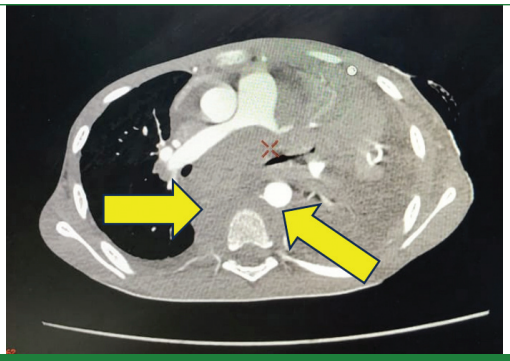
[Table/Fig-3]: Biochemical investigations done.

A blood transfusion was performed to correct bicytopenia, namely anaemia and thrombocytopenia. Three units of Packed Red Blood Cells (PRBC) and one unit of platelets were transfused. Given the persistent bicytopenia, haematological malignancy was suspected, and a Bone Marrow Aspiration (BMA) was done, which showed normocellular marrow with 35% blasts. The blasts were large cells with an increased nuclear-cytoplasmic ratio, a round nucleus, and basophilic vacuolated cytoplasm [Table/Fig-4]. Megakaryocytes were decreased but exhibited normal morphology. The features were suggestive of acute leukaemia, and a bone marrow biopsy along with flow cytometry was recommended for confirmation. Flow cytometry analysis revealed a large cell cluster in the Cluster Differentiation 45 (CD45) negative region with low-side scatter. These gated cells exhibited negative expression for T cell, B cell, myeloid and monocytic markers, suggesting acute erythroid leukaemia or acute megakaryoblastic leukaemia. Due to the unavailability of further markers, the flow cytometry results were not confirmatory for the diagnosis of leukaemia. Additional markers, such as glycophorin and CD61, were unavailable. Therefore, a request for a bone marrow biopsy to confirm the diagnosis using immunohistochemistry was suggested. However, due to the patient's unstable condition, the bone marrow biopsy was not performed. A work-up for tumour lysis syndrome was conducted, which showed elevated serum uric acid; consequently, the child was started on hyperhydration and allopurinol. The pleural effusion worsened, and intercostal drainage revealed haemorrhagic fluid. A CECT chest scan demonstrated a large mediastinal mass encasing the airway and large vessels {aorta, pulmonary vein and Superior Vena Cava (SVC)} along with massive left pleural effusion and pericardial effusion [Table/Fig-5]. The child was scheduled for a USG-guided biopsy of the mediastinal mass under high-risk consent. During the procedure, the child developed a bout of haemoptysis and nasal bleeding. Subsequently, the child experienced sudden bradycardia and desaturation. Resuscitative measures were unsuccessful, and the child was declared dead. A biopsy from the mediastinal mass was sent for histopathological examination. Grossly, three grey-tan soft tissue cores measuring a total of 0.1 cc were received. Microscopic examination revealed a small round blue cell tumour arranged in trabecular patterns, sheets and linear cords separated by desmoplastic stroma [Table/Fig-6]. A preliminary impression of a small round cell tumour was made, and to confirm the diagnosis, IHC markers for small round blue cell tumours were performed [Table/Fig-7].

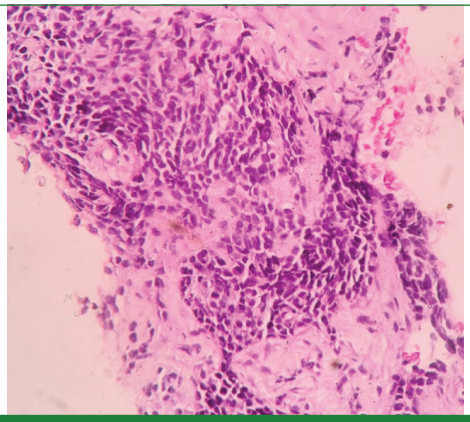


[Table/Fig-4]: BMA showing atypical cells (white arrow) with increased nuclear cytoplasmic ratio, round nucleus and deep basophilic vacuolated cytoplasm (H&E, 100x).

Of these, chromogranin exhibited only weak positivity [Table/Fig-8], thus excluding the possibility of neuroblastoma. INI was retained (image not shown), excluding the possibility of a malignant rhabdoid tumour. Glycophorin and Pan-cytokeratin (panCK) were negative (image not shown), ruling out acute erythroid leukaemia and thymoma, respectively. Desmin exhibited strong cytoplasmic positivity in the tumour cells [Table/Fig-9], while myogenin showed strong nuclear positivity in the tumour cells [Table/Fig-10]. The final diagnosis of rhabdomyosarcoma presenting as diffuse bone marrow metastasis was established.



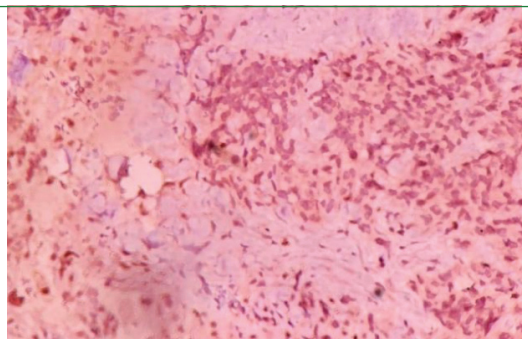
[Table/Fig-5]: CECT chest showing large mediastinal mass (yellow arrow) encasing the large vessels.



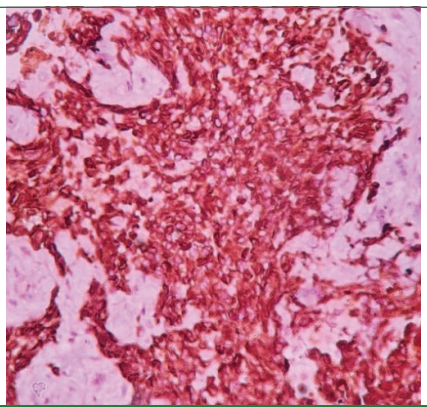
[Table/Fig-6]: Histological image showing small round cell tumour (H&E, 40x).

Differential diagnosis for small round cell tumour	IHC done
Rhabomyosarcoma	Desmin, myogenin
Acute erythroid leukaemia	Glycophorin
Neuroblastoma	Chromogranin
Thymoma	panCK
Malignant rhabdoid tumour	INI1

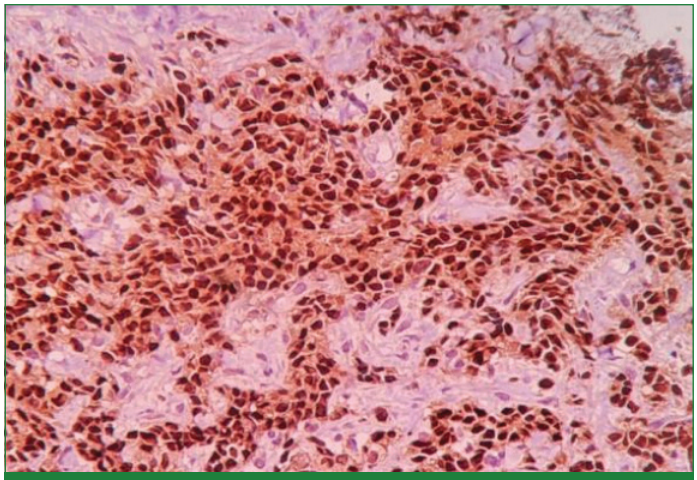
[Table/Fig-7]: Immunohistochemistry investigations.
panCK: Pan-cytokeratin; INI1: Integrase interactor 1



[Table/Fig-8]: Chromogranin showing weak cytoplasmic positivity (IHC, 40x).



[Table/Fig-9]: Desmin showing strong cytoplasmic positivity in the tumour cells (IHC, 40x).



[Table/Fig-10]: Myogenin showing strong nuclear positivity in the tumour cells (IHC, 40x).

DISCUSSION

The RMS is a malignant neoplasm of skeletal muscle lineage that is more common in children than in adults [1]. Paediatric RMS often occurs in the head and neck, genitourinary tract and extremities [2].

Approximately 20% of RMS patients will have metastasis at the time of diagnosis [3]. The most common sites of metastasis are the lungs through the haematogenous route; other sites include the bone marrow, liver, breasts and brain [4]. The outcome of metastatic disease is unsatisfactory. Karyotyping and Fluorescent In-situ Hybridisation (FISH) studies are also used, in addition to IHC, in arriving at the final diagnosis [5]. The FISH for FOXO1 gene rearrangement and reverse transcription-Polymerase Chain Reaction (PCR) for PAX3/7-FOXO1 fusion transcripts have become routine ancillary tools for the diagnosis of Alveolar Rhabdomyosarcoma (ARMS). Prognosis is closely tied to the location of the primary tumour and the extent of distant metastasis.

Bone marrow metastasis is uncommon, accounting for only 6-16% of all RMS cases. Even rarer is the presentation of a patient with diffuse bone marrow metastasis without evidence of a primary tumour at the initial presentation. In one review of the literature, a total of 39 cases were found with this presentation pattern. In cases associated with diffuse bone marrow involvement without evidence of a primary tumour, such as in the present case, it can often be misdiagnosed as acute leukaemia [6]. When bone marrow involvement appears as the first manifestation of RMS, such cases pose a diagnostic challenge to clinicians, as signs and symptoms are usually non specific. These may include fever, weight loss, nausea, vomiting, lethargy, bone and articular pain, and sometimes anaemia and hypercalcemia.

Bone marrow aspiration may reveal blast-like cells with deep blue cytoplasm, irregular cytoplasmic membranes, cytoplasmic blebs, and vacuoles resembling the morphology similar to that of proerythroblasts and megakaryoblasts. In such cases, a bone marrow biopsy is necessary to confirm the diagnosis, with IHC markers like glycophorin for erythroid leukaemia and CD61/CD41 for megakaryoblastic leukaemia. The similarities in clinical presentation, compounded by morphological likeness, can result in incorrect or delayed diagnosis [7].

These blast-like cells are usually negative for CD45. The presence of blast-like cells showing negativity for CD45, a common backbone marker used in flow cytometry, suggests an alternative to sarcoma, such as Rhabdomyosarcoma (RMS) with an unknown primary site [8]. In sarcomas with unknown primary sites, misdiagnosis can lead to delayed treatment and increased mortality. The immunophenotype was CD56+/CD45- and was useful for the correct diagnosis in many of the cases reported in the literature. Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) can be utilised to detect the primary lesion and differentiate RMS from acute leukaemia, and Vincristine, Doxorubicin, Cyclophosphamide-Ifosfamide and Etoposide (VDC-IE) were found to be effective in demonstrating a response [8].

Similar cases of RMS metastasis to bone marrow reported in the literature had the initial presentation as cytopenias [9-12]. Additionally, cases have been reported showing that, although RMS is common in the younger age group, similar presentations are observed in the adult age group [1,9-11]. There have also been cases reported with a previous history of malignancy that was treated and underwent remission, which later presented as RMS with bone marrow metastasis [9,11]. RMS metastatic to bone has a poor prognostic outcome, and early novel treatments or approaches are needed for these patients [13].

Treatment with drugs like vincristine, doxorubicin, cyclophosphamide and dexamethasone led to improvements in cytopenia and regression of the mass [12]. It is advisable to perform a Positron Emission Tomography/Computed Tomography (PET-CT) to find the primary tumour after ruling out haematological malignancy in a bone marrow biopsy with IHC.

Immunohistochemical staining with the marker desmin helps differentiate RMS from other small round blue cell tumours. The presence of translocation t(2;13) (q35;q14) is pathognomonic for the diagnosis of RMS.

Bone marrow infiltration by solid tumour or lymphoma cells is often patchy, and bone marrow staging based on bone marrow aspirates or trephine biopsies (typically obtained from the right and left posterior iliac crests) comes with a degree of sampling error. In such cases, bone marrow metastases may be detected more reliably using 2-(18F) fluorodeoxyglucose PET/CT [14].

The present study is compared with similar cases reported in the literature and summarised [Table/Fig-11] [1,4,6,8,15,16].

S. No.	Article	Age/sex	Clinical features	Radiology (primary tumour)	Mode of diagnosis
1	López-Andrade B et al., 2019 [1]	56/F	Persistent back pain and epistaxis	Soft-tissue mass englobing D10 reported in CT	Bone marrow biopsy- 90% of large cells are CD45-, CD56+, Positive for IHC markers desmin and myogenin. The diagnosis of ARMS bone marrow infiltration associated with haemophagocytosis and cell cannibalism was made.
2	Huang D et al., 2022 [4]	11/M	Back discomfort after a fall a few days prior to presentation	X-ray and Magnetic Resonance Imaging (MRI) foot showed soft-tissue swelling	With MRI foot and bone marrow biopsy, diagnosis of stage IV RMS with primary in the right foot was confirmed.
3	Ataseven E et al., 2020 [6]	3/F	Right arm pain, limp while walking and abdominal pain	CT abdomen- huge mass in left pararectal fossa and multiple bone metastasis	Bone marrow biopsy- Blastic cells positive for myogenin and desmin. The diagnosis of RMS with primary in left pararectal fossa with bone marrow metastasis was made.
4	Imataki O et al., 2017 [8]	15/M	Left femoral pain for 2 weeks	Fluorodeoxyglucose-18 Positron Emission Tomography (FDG-PET)- accumulation of FDG18 in basal penile muscle MRI- irregular lesions on his pelvis and bilateral femurs	Karyotype of bone marrow cells- t (2;13) (q 35; q 14) Immunohistochemistry positive for myogenin in bone marrow biopsy and penile muscle biopsy suggestive of ARMS. The final diagnosis was alveolar RMS with massive involvement of the bone marrow and the primary site in the perineal muscles.

5	Stall JN and Bailey NG 2012 [15]	17/F	History of left cheek Alveolar Rhabdomyosarcoma (ARMS), now presented with bruising, thrombocytopenia and anaemia	-	Bone marrow biopsy cells are CD45-, CD56+. Positive for IHC markers desmin and myogenin Flowcytometry showed CD45-, CD56+ Karyotype t (2;13) and interphase FISH confirmed rearrangement involving FOXO1 A diagnosis of metastatic ARMS was made.
6	Aida Y et al., 2015 [16]	29/F	Epistaxis, glabellar pain, headache, fever, malaise	MRI-contrasted mass infiltrating from the right nasal cavity to the ethmoid sinus FDG-PET showed high level of accumulation in the bone marrow, including the sternum extending from right nasal cavity to the ethmoid sinus	BMA- Myeloperoxidase (MPO) negative Flowcytometry- CD56 positive, CD45 and other myeloid, lymphoid antigens negative Biopsy from nasal cavity mass- morphology revealed ARMS Diagnosis of ARMS of nasal cavity with bone marrow metastasis was made.
7	Present study	12/M	Fever, cough, cold, loss of weight, loss of appetite, difficulty in breathing	CECT chest showed a large mediastinal mass encasing the airway and large vessels	BMA- Acute leukaemia with blasts 35% Flowcytometry- Suggestive of acute erythroid leukaemia/acute megakaryoblastic leukaemia USG guided biopsy from mediastinal mass- Rhabdomyosarcoma (RMS), tumour cells positive for IHC markers desmin and myogenin A final diagnosis of Rhabdomyosarcoma (RMS) with bone marrow metastasis was made.

[Table/Fig-11]: Comparison of the present case with previous studies [1,4,6,8,15,16].

CONCLUSION(S)

The authors reported a rare case of RMS with diffuse bone marrow involvement, without evidence of a primary tumour initially, which mimicked acute leukaemia. The presence of atypical blast-like cells, characterised by deeply basophilic cytoplasm, cytoplasmic vacuoles, cytoplasmic blebs and irregular cytoplasmic membranes, was similar to the morphology of proerythroblasts and megakaryoblasts. The limited markers used in flow cytometric analysis indicated that the tumour cells had a phenotype resembling acute erythroid or acute megakaryoblastic leukaemia. Additionally, the lack of a bone marrow biopsy to confirm the diagnosis with IHC was misleading. A later biopsy from the primary mediastinal tumour was subjected to histopathological examination, and with the help of IHC, a final conclusive diagnosis was made.

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