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Atypical presentation of very aggressive ALK-Negative Primary CNS Burkitt's Lymphoma in a Child: A Rare Case Report

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ABSTRACT

Primary central nervous system (CNS) lymphoma is exceptionally rare in paediatric populations, being particularly unusual when they present with abdominal symptoms. This case report describes a nine-year-old patient with atypical presentation of this aggressive malignancy. A nine-year-old child, born of a second-degree consanguineous marriage with low birth weight (1.5 kg), presented with a 10-day history of diffuse abdominal pain with vomitings. Physical examination revealed multiple congenital anomalies including bifid tongue, tongue tie, dermatological findings included café au lait spots (midline and left buttocks), hypopigmented patches suggestive of vitiligo on the left knee, and diffuse hyperpigmented dry skin. Subsequent evaluation led to the diagnosis of ALK-negative primary CNS Burkitt's lymphoma, a rare entity in paediatric patients.

This case highlights the importance of considering primary CNS Burkitt's lymphoma in the differential diagnosis of paediatric patients presenting with nonspecific symptoms and neurological findings, particularly in the context of congenital anomalies that might suggest underlying genetic predisposition. The atypical presentation underscores the need for heightened clinical suspicion and comprehensive diagnostic workup in similar cases very early and start the child on chemotherapy so that aggressive tumour can be treated.

Keywords: *primary CNS Burkitt's lymphoma, abdominal symptoms, aggressive tumour, ALK-negative lymphoma, congenital anomalies.*

1. INTRODUCTION

A very aggressive Burkitt's lymphoma that only affects the central nervous system (CNS), which includes the brain, spine, cerebrospinal fluid (CSF), and eyes, is called primary CNS Burkitt's lymphoma (PCNSL). Although it frequently responds favourably to chemotherapy and radiation therapy, in contrast to other brain tumours, its survival is typically lower than that of lymphomas outside the central nervous system.[1]

Based on the site of CNS involvement, patients with Primary CNSL experience focal neurologic deficits (56% to 70%), changes in mental status and behaviour (32% to 43%), headaches, nausea, vomiting, and papilledema (32% to 33%), and seizures (11% to 14%) over the course of weeks. A homogenously enhancing mass lesion is typically shown on imaging;

this is typically a single brain lesion (66%), with a supratentorial location (87%), and frontoparietal lobe involvement (39%). Eyes (15% to 25%), CSF (7% to 42%), 5-7, and the spinal cord are less commonly implicated. [2]

The most common B cell non-Hodgkin lymphoma (B-NHL) in adults is diffuse large B cell lymphoma (DLBCL), which accounts for 30–40% of all new diagnoses. It includes cases that develop de novo as well as cases that arise from the histologic transformation of different, less aggressive B-NHL types (such as follicular lymphoma and chronic lymphocytic leukaemia). Although good results are seen in patients treated by contemporary *R- COPADM* chemoimmunotherapy, 40% of cases do not achieve long-term remissions and will eventually succumb to their disease.[3]

2. CASE REPORT

Nine- year-old with grandmother as the informant presented with abdominal pain from 10 days. Pain was dull aching and diffuse which was not localised not localised to one area. It was increased after vomiting and resolved after rest. It was associated with vomiting which was non bilious and had food particles in the vomitus. Each vomitus was approximately 100 ml. It was non-projectile. Patient had head ache which was insidious in onset and gradually progressive. It was started after the admission in the hospital. Headache was holocranial and was intermittent. It was not aggravated by during work or school. It was consistently present. It was not associated with vomiting episodes.

Patient was the first child of a second degree consanguineous marriage who underwent home delivery with birth weight of 1.5 kg after normal vaginal delivery. Patient is immunised fully as per the NIA schedule. On examination, patient was weakly built and nourished with underweight for the age.

General Examination:

Head : normal shape, Anterior fontanelle and Posterior fontanelle Closed

Hair : Sparse, thin lustreless.

Face : old man like appearance.

Eyes : Normal.

Ear : Normal, Ear wax present.

Mouth : Bifid tongue and tongue tie.

Teeth : dental caries.

Neck : Hyperpigmented and thick skin.

Chest : Normal

Abdomen : Scaphoid and Umbilicus: Normal in shape and inverted

Extremities: Hypopigmented patches - ? Vitiligo changes over the left knee

: Rest normal

Nails : White nails

Skin : Café Au lait spots over the back – two,

Midline – 3x2 cm,

Left buttocks – 2x3 cm

Thick hyperpigmented dry skin diffusely over the entire body especially palms and soles

Systemic Examination:

CNS: Conscious, Coherent and oriented to time, place and person.

Left Facial palsy (Left Nasolabial Fold Obliteration)

Tone:	Right	Left
Upper limb	Normal	Normal
Lower limb	Normal	Normal
Power		
Upper Limb	5/5	5/5
Grip	**Weak**	Good
Lower Limb	5/5	5/5

Reflexes	+2	+2
Plantars	upgoing	down going

Gait was normal

Other systems: normal

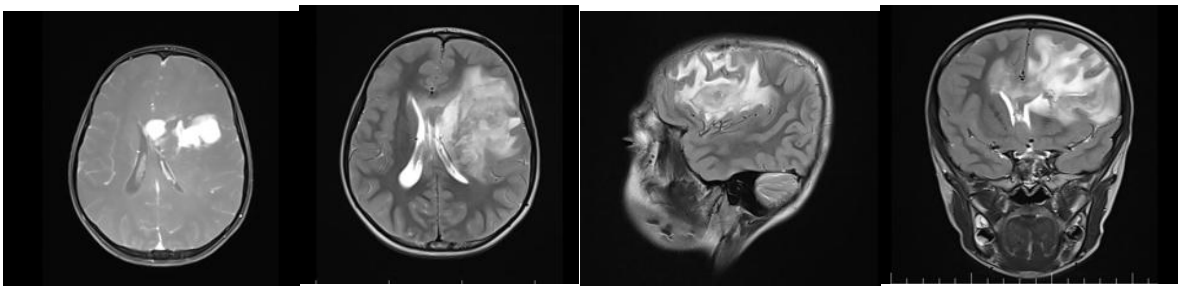
Investigations:

Routine blood investigations normal with No active infection.

Liver function test: low albumin

Pre-operative MRI Brain plain with contrast imaging

MRI brain s/o homogenously enhancing T2 and FLAIR hyperintense areas with diffusion restriction in the left centrum semi-ovale, left corona radiata, left frontal region, left thalamus, left ganglia-capsular region, midbrain on left side, body of the corpus callosum and crossing midline with significant vasogenic oedema on adjacent brain parenchyma.



MRI plain and contrast with left temporopaietal space occupying lesion which shows multi-focality and multi-centricity

Procedure:

Left temporal Burr hole with Biopsy of the Right Temporoparietal Space occupying lesion under Neuronavigation guidance on Jan 6th, 2025.

HPR report from NIMHANS:

s/o High Grade B-Cell Non Hodgkin Lymphoma; Left Fronto-parietal

OLIG2 – Highlights native glial cells

CD20 - Highlights sheets of atypical lymphoid cells

CD99 - Variable positivity

CD3 – Shows reactive pattern

ALK – Negative

MIB- 1 labelling index – 85-90%

Histopathology:

Figure-1:

A- Linear core biopsy showing increased cellularity at low power (H&E, 100x)

B- & C– High power view showing atypical lymphoid cells with large hyperchromatic nuclei.

C- prominent nucleoli and scant cytoplasm. These cells also show an angiocentric distribution (H&E, 200x).

D- D – Brisk mitotic activity in these cells (H&E, 400x)

Figure-2:

E – CD20 diffusely positive in the large atypical lymphoid cells (CD20 immunostain, 200x).

F – CD3 positive in the small lymphocytes in the parenchyma (CD3 immunostain, 200x)

G – OLIG2 highlights the native glial cells (200x).

H – Ki67 shows a proliferation index of 80%.

Histopathology:

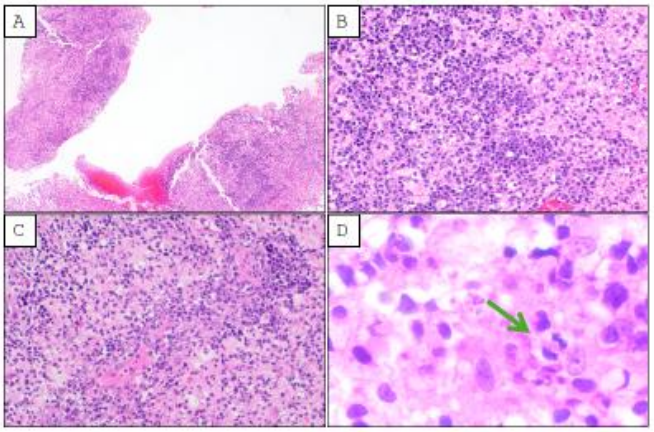


FIGURE A- Linear core biopsy showing increased cellularity at low power (H&E, 100x). B, C- High power view showing atypical lymphoid cells with large hyperchromatic nuclei, prominent nucleoli and scant cytoplasm. These cells also show an angiocentric distribution (H&E, 200x). D - Brisk mitotic activity in these cells (H&E, 400x)

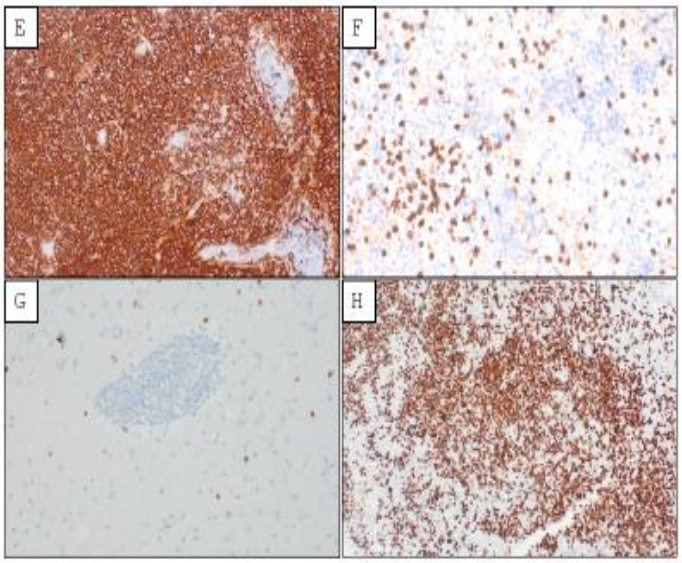
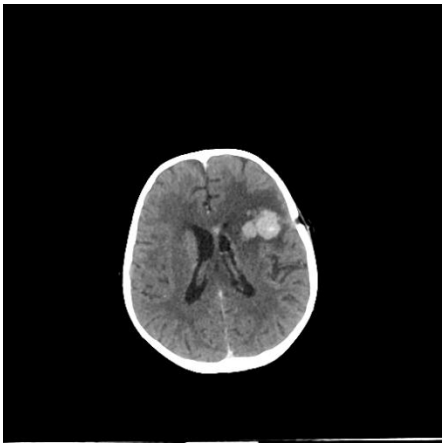


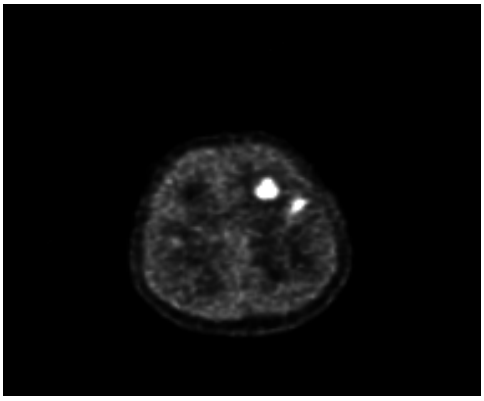
FIGURE. E - CD20 diffusely positive in the large atypical lymphoid cells (CD20 immunostain, 200x). F - CD3 positive in the small lymphocytes in the parenchyma (CD3 immunostain, 200x) G - OLIG2 highlights the native glial cells (200x). H - Ki67 shows a proliferation index of 80%.

Post-operative Imaging:

Post biopsy - Left temporoparietal space occupying lesion s/o Non-Hodgkin's lymphoma

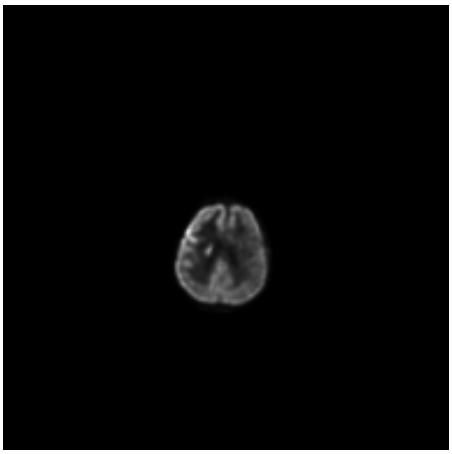


PETCT Whole Body – 28th January 2025



Left temporoparietal tumour uptake on PET CT

PETCT Whole Body – March 2025



No Uptake for the PECT CT done in March 2025

No residual or recurrence of lymphoma, as per PECT CT 2025

Chemotherapy:

Patient of height – 118 cm's and weight 17.8 kg was started on R - COPADM regimen which was the management for Burkitt's Lymphoma[13]

Induction, R- COPADM #1

- Cyclophosphamide (Cytoxan) 250 mg/m^2 IV twice per day on days 2 to 4 (total dose: 1500 mg/m^2)
- Vincristine (Oncovin) 1.4 mg/m^2 (maximum dose of 2 mg) IV once on day 1
- Doxorubicin (Adriamycin) 60 mg/m^2 IV once on day 2
- Methotrexate (MTX) 3000 mg/m^2 IV over 3 hours once on day 1

Glucocorticoid therapy:

- Prednisone (Sterapred) 60 mg/m^2/day IV or PO on days 1 to 6

Supportive therapy:

- Leucovorin (Folinic acid) 15 mg/m^2 every 6 hours on days 2 to 4

CNS therapy, prophylaxis (group B)

- Methotrexate (MTX) 15 mg IT once per day on days 2 & 6
- Hydrocortisone (Cortef) IT once per day on days 2 & 6 (admixed with MTX)

CNS therapy, treatment (group C)

- Methotrexate (MTX) 15 mg IT once per day on days 2, 4, 6
- Cytarabine (Ara-C) 40 mg IT once per day on days 2, 4, 6
- Hydrocortisone (Cortef) (dose not specified) IT once per day on days 2, 4, 6 (admixed with MTX & Ara-C)

One course As soon as the ANC was greater than 1500/μL and platelet count was greater than 100 x 10^9/L, patients proceeded to:

INDUCTION, R-COPADM#2:

Chemotherapy

- Cyclophosphamide (Cytoxan) 500 mg/m^2 IV twice per day on days 2 to 4 (total dose: 3000 mg/m^2)
- Vincristine (Oncovin) 1.4 mg/m^2 (maximum dose of 2 mg) IV once per day on days 1 & 6
- Doxorubicin (Adriamycin) 60 mg/m^2 IV once on day 2
- Methotrexate (MTX) 3000 mg/m^2 IV over 3 hours once on day 1

Glucocorticoid therapy

- Prednisone 60 mg/m^2/day IV or PO on days 1 to 6

Supportive therapy

- Leucovorin (Folinic acid) 15 mg/m^2 (route not specified) every 6 hours on days 2 to 4

CNS therapy, prophylaxis (group B)

- Methotrexate (MTX) 15 mg IT once per day on days 2 & 6
- Hydrocortisone (Cortef) (dose not specified) IT once per day on days 2 & 6 (admixed with MTX)

CNS therapy, treatment (group C)

- Methotrexate (MTX) 15 mg IT once per day on days 2, 4, 6
- Cytarabine (Ara-C) 40 mg IT once per day on days 2, 4, 6
- Hydrocortisone (Cortef) (dose not specified) IT once per day on days 2, 4, 6 (admixed with MTX & Ara-C)[13]

Addition of rituximab to a short intensive chemotherapy programme improves five year survival rate with Burkitt's leukaemia or lymphoma. After the chemotherapy patient was to be started on supportive therapy.

Consent has been taken from parents for the pictures of the patient

3. DISCUSSION

A number of distinctive characteristics set this case apart from other primary CNS Burkitt's lymphoma (PCNSBL) presentations. Instead of the more typical neurological symptoms linked to PCNSBL, the 9-year-old patient's primary presentation was gastrointestinal (vomiting and abdominal pain). The patient also had a number of congenital abnormalities, such as vitiligo alterations, café au lait spots, tongue tie, and bifid tongue, which could indicate a genetic predisposition or condition.

Histopathological analysis and immunohistochemistry confirmed the diagnosis of high-grade Burkitt's lymphoma. The tumour was highly aggressive, as evidenced by the remarkably high MIB-1 proliferation index (85–90%) and CD20 positive. The lesion's left fronto-parietal site was supported by the neurological findings of weak left grip and right facial palsy. It is quite uncommon for PCNSBL for gastrointestinal symptoms to be the primary presenting complaint.

PCNSBL is extremely uncommon in juvenile populations, making up less than 3% of all paediatric primary CNS tumours and roughly 1% of all paediatric non-Hodgkin lymphomas. Children who do experience PCNSL usually exhibit symptoms that are specifically related to the cerebral lesion, such as seizures, focal neurological impairments, or elevated intracranial pressure. There are a few possible explanations for our case's unusual presentation with a preponderance of gastrointestinal symptoms: (1) lymphoma-related paraneoplastic consequences; (2) brain autonomic centre invasion that impacts gastrointestinal function; and (3) potential co-occurring gastrointestinal pathology.

It is particularly significant because this patient has several congenital abnormalities. Although PCNSBL has been observed in immunodeficiency syndrome patients, there is little evidence in the literature to link it to cutaneous signs like café au lait spots and congenital abnormalities like bifid tongue[3]. These results could point to a genetic predisposition that predisposed the patient to malignancy and developmental abnormalities.

According to recent research by Mair et al.[15], children with specific genetic disorders are more likely to acquire primary CNS tumours, such as lymphomas, highlighting the involvement of genetic determinants in paediatric CNS malignancies.

Since ALK (Anaplastic Lymphoma Kinase) expression is generally linked to a subpopulation of lymphomas with unique clinical features and therapeutic responses, our patient's lymphoma's ALK-negative status is noteworthy. Oschlies et al.[16] found that paediatric patients with ALK-negative lymphomas frequently exhibit more aggressive features and may experience worse outcomes than those with ALK-positive lymphomas. This emphasises how crucial immunophenotypic characterisation is in directing therapeutic choices.

Our case was treated with the R-COPADM regimen, which combines traditional chemotherapy with rituximab. The results of Minard-Colin et al.[17], who showed notable enhancements in survival outcomes when rituximab was given to conventional chemotherapy regimens for children with high-risk B-cell non-Hodgkin lymphoma, lend support to this strategy. The absence of tumour uptake on follow-up PET-CT indicates a full response in our patient, which is consistent with the generally positive response rates seen in paediatric lymphomas treated with aggressive multimodal therapy.

The imaging features seen in our instance align with the results reported by Nabavizadeh et al.[18], who said that because of its high cellularity, PCNSBL usually manifests as uniformly enhanced lesions with noticeable limitation on diffusion-weighted imaging. The diffuse infiltrative pattern frequently observed in CNS lymphomas is typified by the multifocal character of the lesions in our patient, which involved the left centrum semi-ovale, corona radiata, frontal area, thalamus,

and corpus callosum.

According to Behzad-Behbahani et al.[19], who discovered that corpus callosum involvement is more frequent in CNS lymphomas than in other brain tumours and could be a diagnostic clue when interpreting neuroimaging, our patient's involvement is especially interesting. This distinctive distribution pattern is consistent with the midline crossing that we saw in our instance.

The tumor's anatomical distribution is reflected in our patient's neurological symptoms, which include grip weakness and left facial palsy. According to Hoang-Xuan et al.[20], neurological impairments in PCNSBL are correlated with the lesions' site and can develop quickly because the disease is infiltrative. The plasticity of the paediatric brain, which frequently makes up for lesions that would produce more severe abnormalities in adults, may be the reason for the relatively mild neurological results in our instance despite significant CNS involvement.

According to Dandapani et al.[21], managing PCNSL in paediatric patients poses particular difficulties. They stressed the significance of striking a balance between therapeutic effectiveness and long-term neurocognitive damage. As in our instance, using high-dose methotrexate as the mainstay of treatment has been linked to better results in paediatric PCNSBL and may lessen the need for cranial radiation, which entails a high risk of long-term cognitive sequelae in growing brains.

According to Perry et al.[22], supportive care interventions—such as the use of leucovorin rescue following methotrexate administration—are essential elements of treatment. These steps enable efficient disease control while reducing the toxicity of rigorous chemotherapy regimens. Our patient's capacity to endure the rigorous treatment regimen was probably aided by the comprehensive supportive care approach.

Our patient's tumor's high proliferation index (MIB-1 85–90%) is in line with research by Deckert et al.[23], which found that aggressive disease behaviour is associated with elevated proliferation indices, which are prevalent in PCNSL. But they also pointed out that, ironically, higher rates of proliferation might be linked to superior reactions to chemotherapeutic medicines that are active in the cell cycle, which could account for the full response our patient showed.

Despite the aggressive histological features and extensive CNS involvement, our case's excellent response to treatment is consistent with Gross et al.[24]'s findings that, when treated with similar regimens, paediatric patients with PCNSL frequently show better outcomes than adult patients. Disparities in tumour biology, host variables, and treatment tolerance could be the cause of this age-related prognostic advantage.

According to Korfel et al.[25], surveillance measures for PCNSL after therapy usually entail serial imaging examinations, with PET-CT emerging as a useful tool for evaluating treatment response and identifying early recurrence. Although the full metabolic response seen in our patient's follow-up PET-CT is encouraging, the possibility of a late relapse in high-grade lymphomas will require continued monitoring.

Holdhoff et al.[26] also out that late relapses can happen in PCNSL patients, with documented recurrence rates of up to 30–60% in long-term survivors, thus even though our patient had a full response to early therapy, long-term follow-up will be crucial. Optimising long-term results for this patient will require close observation and prompt action at the first indication of recurrence.

4. CONCLUSION

This case highlights an exceptionally rare presentation of primary CNS Burkitt's Lymphoma in a paediatric patient with predominant gastrointestinal symptoms and multiple congenital anomalies. The atypical clinical features underscore the importance of considering PCNSBL in the differential diagnosis of children with unusual neurological or systemic symptoms, particularly when accompanied by developmental anomalies that might suggest an underlying genetic predisposition. Further research is needed to elucidate potential associations between congenital anomalies and the development of PCNSBL in paediatric populations. Early diagnosis and treatment is the back bone for treatment of Burkitt's Lymphoma.

Conflict of Interest: None

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