Pearls & Oy-sters: Primary CNS Burkitt Lymphoma in Pregnancy

Management Challenges of a Rare Entity

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Pearls

- Primary CNS lymphoma (PCNSL), albeit rare in pregnancy, needs to be considered in the differential diagnosis of neurologic deficits with multifocal brain lesions.
- The hormonal and immune changes in pregnancy can influence the dynamics of disease activity in both lymphoproliferative and CNS inflammatory disorders.
- Diffusion-weighted imaging (DWI) provides useful clues to diagnosis of PCNSL.
- Corticosteroids provide dramatic clinical and radiologic improvement in nearly 40% of PCNSL cases; poststeroid brain biopsies can be misdiagnosed as sentinel demyelination.
- Early diagnosis of PCNSL in pregnancy potentially translates into good outcomes.

Oy-sters

- Diagnosis of CNS lymphoma in pregnancy is often delayed as cases tend to masquerade as CNS inflammatory disorders.
- Inflammatory disorders like neuromyelitis optica spectrum disorder (NMOSD), acute disseminated encephalomyelitis (ADEM), neuro-Behçet, and neurosarcoid can have onset and worsening in pregnancy.
- Multimodality imaging including PET are contraindicated in pregnancy posing limitations in diagnosis.

A 25-year-old primigravida, who conceived using in vitro fertilization, presented at 22 weeks of gestation with unsteadiness of gait and right-sided weakness of 3 days duration. There was no significant medical history. Clinical examination revealed gaze-evoked nystagmus, right upper motor neuron facial palsy, and right-sided weakness (Medical Research Council grade 4 in upper and lower limb). There was no lymphadenopathy, organomegaly, or palpable mass lesions anywhere in the body. MRI of the brain showed multifocal, T2, and fluid-attenuated inversion recovery (FLAIR) hyperintense signal changes involving the left cerebral peduncle, midbrain, left internal capsule, dorsal pons, cerebellar peduncles, and left frontal periventricular region (figure, A). There was intermediate high signal on DWI in the left basal ganglia and posterior limb of internal capsule (figure, B). The high signal on DWI was not accompanied by significantly low apparent diffusion coefficient (ADC) values (ADC $\sim$ 900) (figure, C). Postcontrast imaging was not completed, citing concerns related with pregnancy.

NMOSD, ADEM, neuro-Behçet, histiocytosis, atypical infections, and lymphoma were considered in the differential diagnosis. CSF analysis revealed 2 cells/ μ L, glucose 62 mg%, and protein 75 mg %. CSF cultures, viral multiplex PCR including Epstein-Barr virus, cytology, and oligoclonal bands were negative. HIV ELISA was negative. Serum anti-aquaporin 4 and anti-myelin oligodendrocyte glycoprotein autoantibodies were negative. None of the brain lesions were amenable for a biopsy.

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Fluid-attenuated inversion recovery (FLAIR) signal changes in left internal capsule, cerebral peduncle (A) with high signal on diffusion-weighted imaging (DWI) (B) without significant low apparent diffusion coefficient (ADC) changes (C). Serial scan postpartum day 5 shows partial resolution in FLAIR (D) with reduction in high DWI signal (E) and subtle enhancement (F). Repeat scan 3 weeks later shows remarkable increase in FLAIR (G), mild high signal on DWI (H), very low ADC (I), and nodular enhancement (J). (K) PET shows subcortical and midbrain hypermetabolism. (L) Histopathologic sections show sheets of atypical lymphoid cells with high mitotic activity and prominent basophilic nuclei (hematoxylin & eosin, ×200).

There was dramatic improvement in the patient's symptoms following treatment with methylprednisolone. She was discharged on a tapering schedule of weekly pulse of methylprednisolone considering the possibility of a CNS inflammatory disease (in view of the acute presentation) with advice to follow-up closely.

There was no interim worsening. At 29 weeks of gestation, the patient underwent an emergency caesarean section in view of fetal distress. MRI performed on postpartum day 5 showed partial resolution of the FLAIR and DWI changes with subtle enhancement in the left cerebral peduncle and internal capsule (figure, D–F). Serum lactate dehydrogenase was 448 U/L (normal 225–460 U/L) and uric acid was 3.1 mg/dL (normal 2.5–7.5 mg/dL). Whole-body PET showed evidence of left subcortical hypermetabolism (standardized uptake value 15.39), without any involvement elsewhere (figure, K). Brain biopsy was planned considering the possibility of a neoplastic disorder.

Three weeks later, the patient was noted to have hypersomnolence, seizures, and progressive right-sided weakness

(Medical Research Council grade 3 in upper and lower limb). MRI revealed a remarkable increase in the extent of the parenchymal signal abnormalities, more areas of diffusion high signal, this time accompanied by lower ADC values (500) and nodular enhancing lesions involving the left cerebral peduncle and left internal capsule (figure, G–J). There was involvement of hypothalamus and left temporal lobe.

The patient underwent a craniotomy and left temporal lobe biopsy. Histopathology revealed nervous tissue diffusely infiltrated by atypical lymphoid cells arranged in an angiocentric pattern and composed of medium-sized round to oval pleomorphic nuclei, clumped chromatin, 2–4 basophilic nucleoli, and scanty amphophilic to basophilic cytoplasm (I L). Scattered tingible body macrophages were present, imparting a “starry sky” pattern. The tumor cells showed strong and homogenous staining for CD20, CD10, BCL-6, and c-MYC, and were negative for MUM-1 and BCL-2. The MIB-1 labeling index was 95%–100%. The overall features were consistent with a high-grade non-Hodgkin lymphoma: Burkitt lymphoma (BL). Testing for aberrations in the C-MYC gene

was not performed. The patient was started on systemic chemotherapy containing high-dose methotrexate and cytosine. She died of multidrug-resistant gram-negative sepsis in the ensuing neutropenic phase.

Discussion

This report highlights diagnostic and management challenges when confronted with multifocal brain lesions in pregnancy. PCNSL should be considered in the list of differential diagnosis. PCNSL could masquerade as CNS inflammatory disorders with features including steroid responsiveness often leading to a delay in diagnosis. The hormonal changes during pregnancy, which could have influenced the natural history of the lymphoma, as noted by the dramatic deterioration during the postpartum period in this case, also merit discussion.

PCNSL in Pregnancy

PCNSL accounts for approximately 0.5%–5% of all primary brain tumors.¹ There is lack of data regarding incidence of PCNSL in pregnancy considering the rarity of the disease. The common locations are cerebral hemisphere, basal ganglia, thalamus, and corpus callosum. BL is an aggressive, rare form with high growth fraction, mortality, and relapse rate.² The molecular hallmark of BL is the translocation of MYC at band 8q24 to the IGH region on chromosome 14q32, t(8;14) q (24;32). In pregnancy, BL involvement by breast infiltrations and ovarian lesions have been documented.^{2,3} Primary CNS BL comprises 4%–5% of PCNSL and occurrence in pregnancy has not been reported.

Choice of Appropriate Diagnostic Neuroimaging Modalities in Pregnancy

The choice of diagnostic imaging study in pregnancy is based on the provisional neurologic diagnosis, its severity, and the diagnostic utility and risks of the available modalities. CT and PET are often avoided considering fetal exposure to radiation. MRI is safer, although gadolinium-based contrast can cross placenta and hence is better avoided in early gestation. In clinical practice, postgadolinium MRI is advocated depending on the need for the study with respect to the health of the mother.

Diffusion restriction with low ADC due to high cellularity has been reported to be useful in differentiating PCNSL from inflammatory demyelination and gliomas. Inflammatory demyelinating lesions tend to have heterogeneity of ADC values with myelin destruction and vasogenic edema (increased ADC) and inflammatory infiltrates in periphery (reduced ADC).⁴ Fluorodeoxyglucose PET could show areas of abnormal uptake (standard uptake values between 14 and 22) in PCNSL. However, these could be less useful in diagnosis of lymphomatosis cerebri.⁴ Delayed acquisition techniques and combining methionine PET could be better strategies for definitive diagnosis.⁴

Corticosteroid Response

Nearly 40% of patients with PCNSL respond dramatically to corticosteroids, both clinically and radiologically.^{4,5} Corticosteroids can mask changes in DWI sequences. Biopsies can be false-negative in nearly 50% of cases as steroids could disrupt

lymphoma B cells. In addition, activated T cells could be spared from steroid-induced apoptosis, leading to erroneous reporting of demyelination on brain biopsies. This could be one of the factors contributing to reports of sentinel demyelination preceding diagnosis of PCNSL.⁵ The diagnosis of PCNSL could be delayed by months or years by use of corticosteroids.

Management of Lymphoma in Pregnancy

BL in pregnancy has been associated with fulminant outcomes. This could be attributable to delayed diagnosis, poor natural history, or compromised therapy. Termination of pregnancy irrespective of trimester is usually advised considering the need for intensive regimens.⁶ In indolent lymphomas, a strategy of observation until delivery could suffice in the majority. In late pregnancy with other aggressive lymphomas, treatment with intensified chemotherapy regimens has been advocated.⁶ Single agents like corticosteroids and rituximab during pregnancy could be used in lesser aggressive forms of PCNSL as a bridge to definitive treatment until delivery. These regimes are limited by poor CNS penetration of these agents. In PCNSL, the recommended therapy includes a combination of high-dose methotrexate with cytosine, both of which have excellent CNS penetration.⁷ The risks of maternal and fetal immunosuppression need to be discussed in detail. The goal of treatment would be to provide optimal treatment to the mother without impairing fetal growth. There is also an increased risk of pre-eclampsia, preterm births, and caesarean section.

Influence of Pregnancy on Inflammatory and Lymphoproliferative Disorders

In pregnancy, there is a transition from a T helper 1 (Th1) to a T helper type 2 (Th2) environment. Levels of estrogens and progesterone reach their peak in the third trimester and fall after delivery. Estrogens also induce cytokine changes consistent with a Th1 to Th2 shift.⁸ CNS inflammatory disorders could ameliorate, deteriorate, or remain stable during pregnancy.⁸ Multiple sclerosis (mainly Th1-mediated) tends to remit in pregnancy and could have relapses in the postpartum period. Conversely, this shift to Th2-mediated immunity could result in antigenic stimulation and worsening of NMOSD and ADEM.⁹ NMOSD could have onset in pregnancy or have relapses during pregnancy and the postpartum period.⁹ There have been cases of ADEM with onset and worsening in pregnancy requiring plasmapheresis and termination of pregnancy.

In contrast, pregnancy and exogenous hormonal supplements (low-dose estrogen) have been shown to reduce lymphomagenesis and reduce risk for developing diffuse large-cell lymphoma.¹⁰ There could be a protective effect against tumor growth in early pregnancy, which could be less prominent during late pregnancy, and this protective effect ceases after delivery.⁴

A high index of suspicion is required for early diagnosis of CNS lymphoproliferative disorders in the setting of pregnancy. Challenges include the limitations of imaging modalities in pregnancy and potentially nonamenable sites of biopsy, which often lead to delayed diagnosis.

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Name	Location	Contribution
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Ajith Sivadasan, DM	Christian Medical College, Vellore, India	Designed and conceptualised study, analysed the data, drafted and revised the manuscript for intellectual content
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