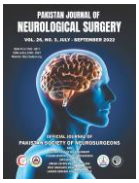

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Case Report

Primary CNS Lymphoma in an Immunocompetent Patient: An Unusual Case Illustrating the Usual Problems Facing Brain Tumour Management in a Lower-Middle-Income Country

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ABSTRACT

Primary central nervous system lymphoma (PCNSL) is a rare extra-nodal non-Hodgkin lymphoma (NHL). It primarily affects the immunocompromised but is rarely seen in immunocompetent individuals. The pitfalls in the healthcare system of lower-middle-income countries produce many obstacles, impeding timely diagnosis, timely treatment, and optimal quality of care. A 57-year-old immunocompetent, diabetic female presented with progressive generalised fatiguability, forgetfulness, and subtle behavioural changes for the last one and a half years. MRI revealed an area of gyri from dense post-contrast enhancement in the right posterior parietal region. Her symptoms kept aggravating with periods of partial remission as steroids were being administered. Reasons for delays in diagnosis and hence timely treatment include lack of primary care referral, conflicting neurosurgical opinion, and absence of multidisciplinary team management. A right posterior parietal parasagittal craniotomy was performed to excise the lesion. The patient was subsequently referred for adjuvant therapy. We use our patient's clinical journey to exemplify the structural barriers to providing optimal and timely care for brain tumour patients in a developing country. Primary CNS Lymphomas in immunocompetent patients are rare. Poor infrastructure and referral pathways contribute to delayed diagnosis. Lack of multi-disciplinary care owing to organisational issues is a major problem faced by brain tumour patients in a lower-middle-income country like ours. Brain tumour management requires a specialist multidisciplinary team approach to ensure timely diagnosis and optimal treatment.

Keywords: Primary CNS Lymphoma, Immunocompetent, Multidisciplinary cancer care.

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INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare extra-nodal non-Hodgkin lymphoma (NHL). It may occur in the brain, leptomeninges, eyes or spinal cord, usually without the evidence of systemic lymphoma.[1] It mostly presents in the immunocompromised and is rarely seen in immunocompetent individuals.

Here, we describe a 57-year-old immunocompetent female with a primary CNS lymphoma. We discuss her case as the sequel of management, in addition to the rarity of this case, exemplifies an important national issue that plagues cancer care and brain tumour management in Pakistan; that is poor healthcare infrastructures and the absence of a multidisciplinary team approach in the management of brain tumour patients which result in an inappropriate and delayed diagnosis and hinders timely and appropriate treatment initiation.

Case Presentation

Clinical Presentation

A healthy 57-year-old female with well-controlled diabetes and hypertension presented to her family physician in March 2021, with a progressive onset of slowing and forgetfulness, with subtle behavioural alterations over one and a half years that her immediate family noticed. There was an increased generalised weakness and early fatiguability. The patient then developed recurrent episodes of left-sided weakness with a subsequent fall on the floor. By August 2021, she was completely bedbound, which is when she came under our care.

Radiological Evaluation

In March 2021, a plain CT scan of the brain was ordered by her family physician, which revealed an area of hypodensity in the right posterior parietal region without mass effect (Figure 1a). The patient was treated as a stroke case by her family physician due to the sudden onset of left-sided weakness. The practitioner placed her on secondary prevention and rehabilitation for stroke but on further neurological deterioration, ordered an MRI brain.

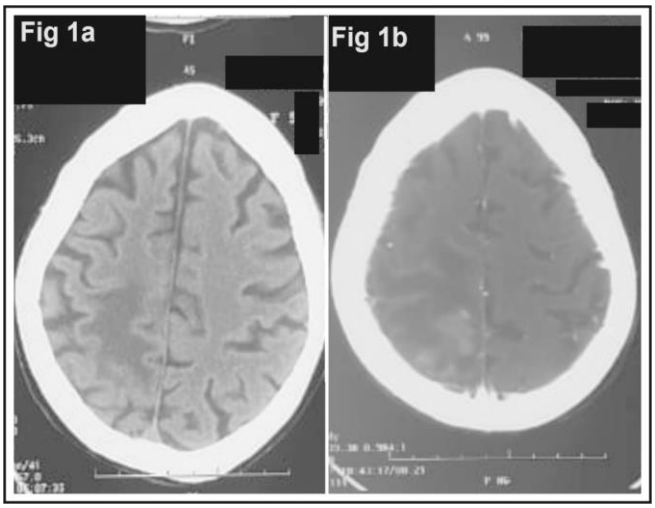

Figure 1: Left (1a): Shows the patient's first non-contrast CT, performed in March 2021, demonstrating right posterior parietal hypodensity without mass effect. **Right (1b):** Shows second contrast CT performed in June 2021 demonstrating the same lesion to contrast-enhancing with some nodularity (Scans added with patient's permission).

In April 2021, her first MRI brain with contrast was performed, revealing a contrast-enhancing gyri form lesion with mild diffusion restriction and surrounding oedema with some mass effect (Fig. 2a & 2b). In addition, there were some T_2 signal changes (Fig 2c&2d). As she did not improve with treatment and her weakness kept progressing, she consulted the senior author after one month (May 2021), who advised her on an MR spectroscopy. She obtained her MR Spectroscopy and second MRI in June 2021 from a laboratory different from those that performed her first MRI. There were no significant MR picture changes compared to her scan in April, except for the absence of diffusion restriction. Spectroscopy showed an increase in the choline level with a moderate decrease in NAA.

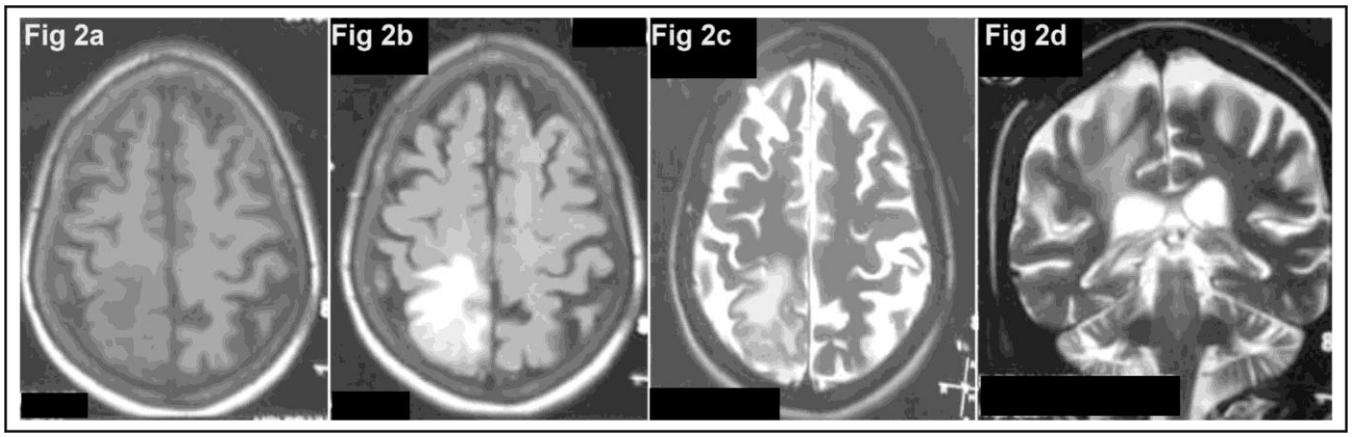

Figure 2: The first MRI scan performed in April 2021 revealed contrast-enhancing gyri form lesion with mild diffusion restriction and surrounding oedema with debateable mass effect and patchy T_2 changes. **From left; (2a):** Axial T_1, **(2b):** Axial T_1 contrast, **(2c):** Axial T_2, **(2d):** Coronal T_2. (Scans added with patient's permission).

Lymphoma was reported as the top differential diagnosis. She was advised a stereotactic biopsy by the senior author; however, she consulted another neurosurgeon who believed the MRI picture resembled a demyelinating disorder and that the enhancing lesion was most likely an MS plaque which was in keeping with her indolent neurological condition. The patient's husband bought the latter idea, and the family proceeded with steroid management under the care of our patients family physician. The patient showed a slight improvement in her power and alertness, and her family doctor ordered a second CT brain with contrast in June 2021 (Figure 1b). It revealed the initial lesion to be contrast-enhancing with some nodularity. However, her continuing conservative treatment with steroids did not show any further improvement and led to a relapsing weakness until she got bedridden. She left her family physician and self-referred to our care again. This time, she was bed bound with altered alertness and poor intake.

A repeat MRI brain in August 2021 was performed. T_1 contrast and T_2 weighted images (Figure 3a, 3b & 3c), revealed a right posterior parietal lobe, slightly lobulated gyri form mass-like lesion with involvement of the adjacent posterior right frontal lobe in the right parasagittal location. The lesion was isointense on T_1 and hyperintense on T_1 contrast, the latter radiological change being the most major noticeable change as her original MRI demonstrated minimal hyperintensity on T_1 contrast (Figure 2b). In addition, the lesion had nearly doubled in size, despite steroid therapy. T_2 weighted sequences demonstrated iso to slightly high signal with significant surrounding vasogenic oedema within the surrounding frontal, parietal, and occipital lobes (Figures 3b & 3c).

Our case shows peculiarity as despite being a lymphoma, her tumour doubled in size rather than shrinking on steroid therapy. Also, the course of the disease was rather indolent as the symptoms existed for more than 18 months before the presentation, which otherwise typically manifest in 3 to 5 months.

Surgery

The patient's GCS deteriorated from 15 to 12 after suddenly becoming hemiplegic therefore the attendants consented to excision with the hope to alleviate the mass effect. A right posterior parietal parasagittal craniotomy was performed to excise the lesion. The tumour could be further localised due to the discoloured overlying cortex. The lesion was situated in the subcortical white

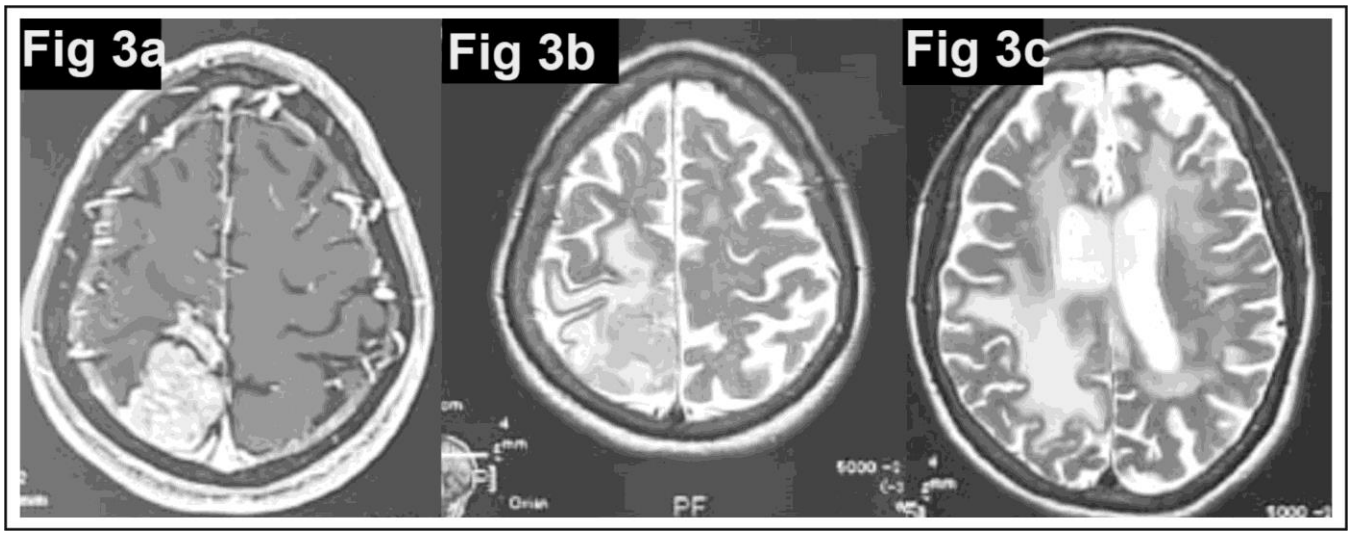

Figure 3: The third MRI scan was performed in August 2021. **From Left; (3a)**: Axial T_1 contrast, **(3b and 3c)**: Axial T_2. T_1 contrast **(3a):** Confirms lesion has doubled in size (relative to figure 2b) over 4 months. There is a poorly defined, slightly lobulated gyriform lesion in the right posterior parietal lobe with a mass effect involving the adjacent posterior right frontal lobe in the right parasagittal location. T_2 sequences demonstrate iso to high signal with surrounding vasogenic oedema within surrounding frontal, parietal, and occipital lobes. (Scans added with patient's permission).

matter, which was dissected circumferentially. It was adherent to the falx on the medial side from where it was detached. The lesion itself was greyish and had a grating sensation with fibrotic consistency.

Pathology and Molecular Cytogenetics

Histological examination of sections and levels reveals glial tissue infiltrated by atypical dis-cohesive lymphoid cells arranged in sheets showing pleomorphism, hyperchromatic nuclei and increased atypical mitosis (figure 4a).PAS stain revealed negative fungal organisms. Molecular genetics confirmed LCA, BCL12, and MUM-1 positivity, whilst BCL6 and CD 10 negativity (Figure 4b). The Ki-67 proliferative index was deemed high (80%) and CD 20 was positive. The diagnosis of primary CNS lymphoma was confirmed.

Prognosis and Adjuvant Therapy

The postoperative course was uneventful, and the patient made a full recovery and started speaking sentences with awareness of their surroundings with the improvement of power from grade 0 to grade 3 on her left side (MRC scale). The patient was referred to an oncologist at a separate institution for further treatment.

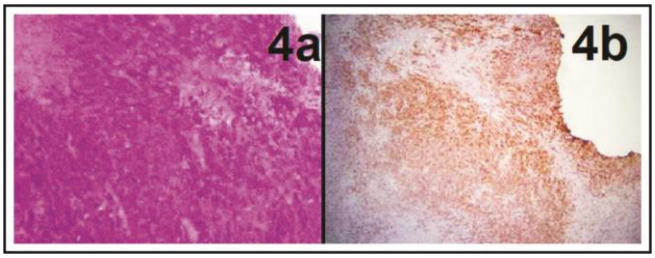

Figure 4: Left (4a): Shows Glial tissue infiltrated by atypical lymphoid cells arranged in sheets showing pleomorphism and **right (4b):** Shows LCA Positivity. (Figures added with patient's permission).

DISCUSSION

PCNSL, a rare subtype of extra-nodal lymphoma, usually involves the brain, leptomeninges, spinal cord or eye.[2] Immunodeficiency constitutes a major risk factor for lymphoma genesis, and the relative risk is correlated with both the level and

the type of immunosuppression.[3] PCNSL used to be very rare in the immunocompetent. However, over the last 30 years, its incidence in the immunocompetent has been increasing.[4,5] The median age of presentation is 55 years, whereas the median time from onset of symptoms to diagnosis is 3 – 5 months.[6] Cognitive decline, gait disturbances and behavioural changes are the most common presenting symptoms of PCNSL. Focal neurological deficits are also common.[7] Our patient presented with similar complaints, but the symptoms existed for more than one and a half years before diagnosis. The MRI of PCNSL in the immunocompetent usually does not show, haemorrhage, calcifications, necrosis, or ring enhancement.[2]

Stereotactic biopsy aids in confirming the definitive diagnosis. The use of steroids is avoided until the biopsy because they cause remission of the tumour, thus interfering with the biopsy results. The current gold standard for the treatment of PCNSL includes methotrexate-based chemotherapy. Recently, the advent of Bruton's tyrosine kinase inhibitor (BTKi) has made more treatment options available.[8] Unfortunately for our patient, the delay in diagnosis meant medical management was not initiated in time and the subsequent sudden neurological decline warranted urgent surgery to alleviate the mass effect.

Issues faced by Brain Tumour Patients in a Developing Country

Our case is a prime example of the pitfalls that exist in the healthcare system of a developing country due to a lack of communication among the professionals, no concrete referral pathways, and a general absence of a multidisciplinary team approach to managing cancers, including brain tumours.[9] Multidisciplinary care is defined as an integrated approach by medical and allied health care professionals to provide an individual treatment plan for a patient. Multidisciplinary teams (MDT) work by improving communication and coordination among healthcare professionals and its use in cancer care is endorsed worldwide.[9] MDT decisions not only lead to revisions to cancer diagnoses and better adherence to evidence-based guidelines but also enhance patient satisfaction.[10] Whereas neurosurgeons, oncologists, neurologists, radiologists, and nurse practitioners can decide as a team the optimal treatment and management, the absence of multidisciplinary care has jeopardised the care of cancer patients, particularly brain tumours, in most domains from timely diagnosis to timely execution of best treatment in the poor socioeconomic conditions of countries like Pakistan.[10]

Our patient received three MRI scans from three different laboratories from the onset of her symptoms to surgery, despite the availability of an MRI facility at the hospital where she was being treated. Her choice was shopping around for the cheapest option. As a result, formal comparisons by a qualified radiologist could not be made, and her treating neurosurgeons alone had to decide the evolution of the lesion, that too with only printed films, which is usually what patients are provided, that contain major cuts; this is less than ideal. Our patient also opted to receive her oncological treatment at a separate hospital due to her husband's employment privilege for that specific centre. This hindered the continuity of care between her surgeons and oncologists.

Whilst this report is of a single patient, the issues discussed are faced by neurosurgeons treating brain tumours in Pakistan far too often. Cancers require a comprehensive MDTand making sure such systems are in place avoids many of the issues our patients and many others face. There is a need for an infrastructure where family physicians can refer patients for complete and comprehensive care within a single institution by radiologists, neurologists and neurosurgeons, oncologists, and specialist cancer nurses.[10]

CONCLUSION

The pitfalls in the healthcare system infrastructures of lower-middle-income countries produce many obstacles to the quality care of patients. A multidisciplinary team approach is necessary to provide the best standard of care for brain tumour patients. There is an urgent need to refine healthcare infrastructures nationally to ensure such care is provided for every new brain tumour diagnosis.

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Additional Information

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AUTHORS CONTRIBUTIONS

Sr.#	Author's Full Name	Intellectual Contribution to Paper in Terms of:
1.	Mohammad Ashraf	Literature review and report writing.
2.	Minaam Farooq	Case supervision and report writing.
3.	Muhammad Ahmad Malik Syed Shahzad Hussain, & Naveed Ashraf	Literature review.
4.	Shazib Ali, Shehreen Iqbal	Data collection.