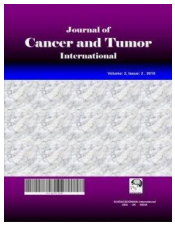

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Case Report of Primary Lymphoma of the Central Nervous System in an Immunocompetent 10-Year Old Boy

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Authors' contributions

This work was carried out in collaboration between all authors. Authors YTIA and PEI designed the study and wrote the first draft of the manuscript. Authors OPO, CA and ECO managed the literature searches. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Primary central nervous system lymphoma (PCNSL) is a very rare and aggressive form of B-cell non- Hodgkin's lymphoma. It originates but is restricted to the central nervous system (CNS) at the time of diagnosis. Patients typically present with focal neurologic deficits, cranial neuropathies and features of raised intracranial pressure (RICP). Systemic involvement is uncommon in documented cases of PCNSL.

We report a 10-year-old boy who presented with a headache, neck pain and early morning projectile vomiting of eight weeks duration. He developed abnormal behaviours, gait and visual disturbance and lapsed into unconsciousness two days before presentation. He had cranial neuropathies, dilated pupils, papilloedema but had no lymphadenopathy, systemic involvement and no meningeal irritation. There was no background immunosuppression. A diagnosis of suspected cerebral astrocytoma with RICP was made. CNS tuberculosis was also considered. The

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computerised tomography scan showed multiple homogenous contrast-enhancing lesions with mild peri-lesional oedema in the frontal lobes, left thalamus with effacement of the sulci and Sylvian fissures. All the ventricles appeared normal. He had leucocytosis of 31.9 x 103/uL with neutrophilia. Cerebrospinal fluid analysis revealed elevated protein and lymphocytic infiltrate. Screening for tuberculosis and human immunodeficiency virus (HIV) were negative. A definitive diagnosis of PCNSL was then made. He had intra-thecal steroids and chemotherapy before he succumbed to the illness. Histology at autopsy confirmed the diagnosis of PCNSL. Though rare in children, PCNSL should be considered in any child who presents with features of characteristic mass lesions in the brain with RICP.

Keywords: Primary central nervous system lymphoma; PCNSL; non- Hodgkin's lymphoma.

1. INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is predominantly a form of extra-nodal non-Hodgkin's lymphoma of B-cell origin that arises within and is restricted to the central nervous system (CNS) at the time of diagnosis [1–3]. It is a very rare tumour accounting for about 1% of tumours in immunocompetent patients to 6% in immunocompromised individuals [4]. Although, congenital and acquired immunodeficiency state such as ataxia telangiectasia, acquired immunodeficiency syndrome (AIDS) and others have been known predisposing factors for PCNSL, the incidence is increasing among immunocompetent patients [1,3,5–7]. It typically presents as a brain tumour but may involve the leptomeninges, eyes, spinal cord or any combination of these sites [4].

Little is known about the pathogenesis of PCNSL [1]. It has been postulated that PCNSL may originate from systemic B-cells trafficking in and out of the CNS that have been trapped in the CNS. It is also hypothesized that PCNSL may result from metastasis of occult systemic lymphoma eradicated by an intact immune system but escaping within the immune sanctuary of the CNS [3]. Diagnosing PCNSL is based primarily on imaging studies and histology. It has a characteristic appearance of multiple homogenously enhancing lesions, sometimes periventricular on both brain CT scan and MRI [4,5]. Basically, all but 5% of PCNSL are diffuse large B cell lymphoma on histology [1,4]. Primary CNS lymphoma is a radiosensitive and chemo-sensitive tumour. Surgery may be difficult because of the deep-seated and multiple nature of a tumour, hence, surgery is usually reserved for diagnostic biopsy if possible [2,5].

Because of the rarity of this tumour in children, there is no established, efficacy-proven treatment for paediatric PCNSL to the authors' knowledge. Documented information regarding treatment are been extrapolated from the results of adult studies [8]. Hence, we report the challenges of management of the first known child with PCNSL who presented to our facility.

2. CASE REPORT

The patient was A. Z, a 10-year-old previously healthy boy referred to our facility with a diagnosis of suspected complicated meningitis with raised intracranial pressure to rule out a CNS a tumour. He was in an apparent good state of health until eight weeks prior to presentation when he developed headache, neck pain and early morning projectile vomiting. Headache was frontal in location and was throbbing, aggravated by noise and transiently relieved by vomiting. The neck pain was sharp, located on the sides with the associated inability to bend the neck or turn the head from side to side. The pain was not radiating to any other part of the body and there were no known relieving factors. Vomiting was projectile, non-bilious, occurring in the mornings on waking. He had about three episodes per day.

He was taken to a private facility where he was admitted and treated with intravenous ceftriaxone for suspected bacterial meningitis for two weeks. He was discharged following treatment, although, he had not returned to his pre-morbid state of health and symptoms were still present. He subsequently developed abnormal behaviours, decreasing visual power, gait disturbance, lethargy and lapsed into unconsciousness two days prior to presentation. Prior to the onset of symptoms, he was a quiet, easy going boy, with complete immunisation history, normal motor development and had good academic records. He was not a recipient of organ transplant and was not on any immunosuppressive medications. He was the fourth of six children in a non-consanguineous, monogamous marriage. His father was a 54-year-old farmer with a primary level of education

and mother was a 48 year old farmer with a primary level of education.

At presentation, he was a well-grown school-aged child with no peripheral lymph node enlargement; he was afebrile, not pale and well hydrated. Central nervous system examination revealed an unconscious child with intermittent lucid interval when he makes incomprehensible words. He had cranial nerve II and VII palsies bilaterally. Both pupils were dilated and sluggishly reactive to light (worse on left eye), with no light perception in both eyes. There was papilloedema with dilated and tortuous retinal vessels. The tone and deep tendon reflexes were reduced globally and power was at least grade 2. There was neck stiffness but Kernig's sign was negative. His pulse rate was 88 beats in a minute and blood pressure was 100/60mmHg. Examination of the other systems was normal. With review of the history and examination findings, a tentative diagnosis of primary CNS tumour possibly cerebral astrocytoma and CNS tuberculosis was made.

Cranial computerized tomography scan showed multiple varying sized homogeneously enhancing lesions with mild peri-lesional oedema in the frontal lobes, left thalamus and area of the pons. There was effacement of the sulci and sylvian fissures. Both lateral ventricles, third and fourth ventricles appeared normal with no significant shift in midline structures. Abdomino-pelvic ultrasound scan was normal with no detected mass lesion or abnormality in abdomino- pelvic organs. Blood investigation showed leucocytosis of 31.9 x 10^3/uL with segmented neutrophil predominance (22.7 x 10^3/uL) and thrombocytopaenia, platelet count was 94 x 10^3/uL. Haematocrit was 38.7%, erythrocyte sedimentation rate was 82mm/hr, serum uric acid, liver function tests and electrolytes were normal. His HIV status determined by ELISA technique was negative. Screening for Epstein Barr virus was not done because screening facility was unavailable. Based on the radiologic findings, a diagnosis of suspected PCNSL was made. Other diagnostic considerations were other primary CNS tumours such as cerebral astrocytoma until biopsy can be done for histologic diagnosis.

Raised intracranial pressure (ICP) was managed pharmacologically with mannitol 1 g/kg six hourly, dexamethasone 0.15 mg/kg/dose six hourly and acetazolamide 10 mg/kg/dose eight hourly. Ophthalmology review showed evidence of bilateral visual loss and papilloedema with no ocular mass lesion. Neuro-surgical review noted that raised ICP should be managed pharmacologically and with elective ventilation as surgical intervention will be challenging in this case with normal ventricles and multiple intracranial lesions with diffuse brain swelling. By the sixth day on admission, raised ICP had been controlled and lumbar puncture was performed with a small bore needle. Cerebrospinal fluid was clear and not under pressure. Cerebrospinal fluid (CSF) was sent for cytology and biochemistry. Intra-thecal methotrexate 12 mg stat and dexamethasone 2 mg/m^2 was given during this procedure. Cerebrospinal fluid protein was elevated at 104 mg/dl and cytology revealed clear coloured fluid with moderate lymphocytic infiltrate in a background of fibrin. Cranial irradiation was also considered, but the facility was faulty at the time and parents could not afford to move patient to the next available centre outside the State.

His condition remained apparently the same until the eighth day on admission when he developed fever, deteriorating consciousness, isolated systolic hypertension and had two seizures. A consideration of worsening raised ICP with suspected cerebral herniation was made. Pharmacologic management of raised ICP was continued, dose of dexamethasone was increased to 0.5 mg/kg/dose six hourly, intravenous ceftriaxone 100 mg/kg/day 12hourly was continued and oral carbamazepine 10mg/kg/dose 12 hourly via NG tube was added to his treatment. He was reviewed for intensive care admission; however, he had an apnoeic episode following a brief episode of irregular breathing and subsequently developed a cardiac arrest. He succumbed to the illness on the 9th day on admission.

Autopsy was done and showed a pale, enlarged brain weighing 1800 g (normal weight is 1200 g – 1600 g) sagging on its axis with asymmetric cerebral hemisphere, displacing the sagittal fissure to the right. The sulci were narrow and the gyri flattened globally. There were prominent meningeal vessels and marked cerebellar tonsillar grooving with herniation of the cerebellum into the foramen magnum. There was uncal herniation with prominence of the rectus gyri. Serial coronal sections of the cerebral hemisphere showed shiny wet surface with good grey-white matter differentiation and white matter expansion. There was asymmetry and relative effacement of the lateral ventricles. There were poorly delineated friable granular cream-yellow lesions in both cerebral hemispheres. There

were two bilateral masses in deep white matter of the frontal lobe rostral to the genu of the corpus callosum measuring 2x2x1 cm on the left and 2.5x2x1.5 cm on the right. There was also a lesion in the superficial white matter of the left cerebral hemisphere just deep to the superior frontal gyrus measuring (1x1x0.5 cm). Another lesion was in the left thalamic region extending from the thalamus into the posterior limb of the internal capsule and globus pallidus measuring 2x2.5x3 cm. There were no lesion in the cerebellum and brain stem. Sections taken for histology showed a malignant neoplastic lesion composed of proliferating small to medium sized atypical lymphocytes with hyperchromatic nuclei, prominent nucleoli and occasional mitosis. These cells are diffusely infiltrating the brain parenchyma with obvious angiocentricity of the tumour cells and involvement of the Virchow robin space. Histologic features are in keeping with primary CNS lymphoma. Immunocytochemistry facility was not available.

3. DISCUSSION

Primary central nervous system lymphoma (PCNSL) accounts for 1% - 6% of all brain tumours and approximately 1% of all non-Hodgkin's lymphoma [4]. It is known to occur with high frequencies in patients with congenital (such as ataxia telangiectasia) and acquired immunodeficiency states (such as AIDS). Primary CNS lymphoma is an AIDS-defining illness associated with low CD4 cell count (<50 cells/L) and Epstein Barr virus (EBV) [3,4,6]. However, incidence is increasing among immunocompetent patients and most reported cases are in immunocompetent individuals [4,6]. The incidence of PCNSL in western countries is 5 per 1,000,000 persons per year. Incidence in developing countries is largely unknown. However, overall incidence in blacks in Surveillance, Epidemiology and End Result (SEER) programme data from 1992 to 2002 is 1.10 per 100,000 per year [6]. In children, not much is known about PCNSL. The exact incidence of paediatric PCNSL is unknown but it is thought to be lower than the incidence in adults. In SEER programme, 1% of all reported PCNSL cases were in children younger than 19 years. There is a slight male preponderance with a male to female ratio of 2:1 and a median age of 14 years at diagnosis [6]. In a population-based non-Hodgkin's lymphoma Berlin-Frankfurt-Muenster (NHL-BFM) study of 3740 paediatric or adolescent patients registered between 1990 and 2011, 17 patients with PCNSL were identified: 12 (70.6%) were immunocompetent and 5 (29.4%) immunocompromised with a median age of 13.3 years [7]. The patient described was a ten year old boy with no evidence of immunodeficiency. This buttresses the male preponderance and the fact that increasingly, immunocompetent children are being reported with this condition.

The pathogenesis of PCNSL is largely unknown [1]. Several hypotheses have been put forth. One of such hypothesis is that PCNSL results from metastasis from an occult systemic lymphoma and this typically occurs late in the course of the disease [1]. This hypothesis is disproved by that fact that most CNS involvement in systemic lymphoma typically involves the meninges and only affects the brain parenchymal in 1% of cases. Similarly, examination findings, investigations and autopsies in patients documented to have PCNSL usually reveal no systemic focus of malignancy. Even, in some reports where systemic tumours have been documented, it was found that the CNS and systemic tumours were two distinctly different tumours histologically. A second postulation is that PCNSL results from trapped systemic B-cells trafficking through the central nervous system. However, the mechanism of tumour development in these trapped lymphocytes is not clear [1,3].

Primary CNS lymphoma occurs mainly in the brain in 95% of cases with widespread dissemination within the brain as seen in the index case [4–6]. It can also affect the leptomeninges, eyes, spinal cord. Only about 12-18% of patients with PCNSL will have involvement of the eyes. In most patients, meningeal involvement is limited to adjacent parenchymal lesions [4]. About one third of patients with PCNSL will have malignant cells in the CSF and another third will have suspicious lymphocytes in the CSF as seen in this particular case [5,7,8]. Sixty percent of PCNSL involve the supra-tentorial space and parenchyma of the cerebral hemispheres in diffuse or discrete multifocal pattern. Specific locations include frontal lobe (20-43%), temporal lobe (8%), parietal lobe (7%) and occipital lobe (3%). Other sites include basal ganglia/ periventricular regions (13-20%), corpus callosum (5%), posterior fossa (13%) and spinal cord (1-2%) [4,5].

The index patient with PCNSL presented with neurologic deficits, visual disturbance, cranial nerve neuropathies and raised intracranial pressure [4,6,7,9]. Documented clinical

presentations of PCNSL include focal neurological symptoms in 70% of cases and evidence of raised intracranial pressure in 33% of cases. Symptoms of increased intracranial pressure include headache (53%), nausea (53%), and vomiting (47%) as documented in this case. Behavioural and neuropsychiatric symptoms may occur in 43% of patients. Cranial neuropathies occur in 59% of cases. Usually, median interval from onset of symptoms to diagnosis is about 8 weeks (range is 2-20 weeks) [7] which is as seen in this case. Ocular disease may antedate intracranial lesions in 15-20% of cases. Other symptoms include motor and sensory focal deficits, headaches, nausea, vomiting and uveitis, ataxia and symptoms of cranial nerve disorders [6,7]. Patients are often treated for meningitis/encephalitis and non-response to this anti-infective treatment usually results in the consideration of tumour before biopsy and diagnosis of PCNSL, which is the situation in this case [7].

For malignant disorders, histology is the gold standard for definitive diagnosis. There are several challenges with obtaining tissue for histology in cases of PCNSL. First, the deep seated, multiple nature of the tumour may preclude biopsies for diagnosis. Secondly, the presence of intractable raised intracranial pressure may also make it difficult to carry out surgical procedures for biopsy. Finally, it is a highly radio- and chemo-sensitive tumour with characteristic CT scan and magnetic resonance imaging (MRI) features. Thus, in patients that surgical intervention for biopsy is difficult; diagnosis is hinged on the characteristic neuro-imaging features of PCNSL. Cranial CT scan lesions of PCNSL are multiple homogenously contrast enhancing lesion with peri-lesional oedema as seen in the index patient. In non-AIDS patient, it is usually a solitary homogenous enhancing lesion. Ring enhancement of lesion occurs in less than 13% of cases and this may make it difficult for differentiating the lesions from an abscess. Most often, the lesion is deep seated (peri-ventricular) or superficial (in contact with the meninges) in location. On imaging, frontal lobe lesion is reported in 20% - 43% of patients whereas basal ganglia are affected in 13% - 20% of cases [4,5]. Peri-lesional oedema is usually present but less prominent than that seen in metastasis [4]. Systemic involvement is so rare that extensive staging is not recommended and some authors only recommend careful clinical assessment, testing for human immunodeficiency virus, chest x-ray, CSF analysis and ocular slit-lamp examination [10]. In cases where lesions are superficial, biopsies are advised for histology and definitive diagnosis. However, in deep seated tumours, it may be difficult to access the lesions for biopsy, hence; diagnosis is dependent on neuro-imaging. Most PCNSL are of B-cell origin [10]. In the NHL-BFM study 11 (64.7%) of 17 patients with PCNSL has mature aggressive B-cell lymphoma [7]. In immunocompetent patient, all but 5% of PCNSL are diffuse large B cell lymphoma [10]. Cerebrospinal fluid (CSF) analysis can also provide diagnostic information in PCNSL. Biochemical abnormalities such as elevated CSF protein and low glucose have been documented in PCNSL. However, in up to 33-55% of cases, CSF protein may be normal [11]. In the index case, CSF protein was elevated and cytology had moderate lymphocytic infiltrate. Cytology examines morphologic features of the cells in the CSF and has low sensitivity of 2%–32% [11]. Flow cytometry determines the immunophenotype of the lymphocytes in the CSF and it is possible to identify atypical lymphoid cells as “neoplastic” as in lymphoma or “reactive” due to inflammation [11]. Thus, CSF flow cytometry is a useful adjunct to CSF cytology and has been shown to increase the ability to detect CNS involvement in high-risk individuals. In this case, facility for immunophenotyping was not available and thus not much premium could be placed on the CSF analysis result of the patient.

PCNSL is a highly radio- and chemo-sensitive tumour [2]. The use of chemotherapy alone or in combination with whole brain radiotherapy (WBRT) is common especially in adults [1]. Surgery is reserved for stereotactic brain biopsy [2,5,6]. There is no established treatment protocol for paediatric PCNSL [8]. Glucocorticoids typically induce a rapid improvement in symptoms (as seen in the initial response of this patient), and imaging responses in at least 40% of patients [4,5]. Steroid therapy, however, can also increase the risk of a non-diagnostic result from brain biopsy. From the NHL-BFM data study, the use of NHL-BFM protocols for systemic lymphoma is associated with low relapse rate and is being advocated [6,7]. Other phase II studies show that the addition of high-dose methotrexate as part of the initial therapeutic regimen results in improved outcome, although, the optimal dose of methotrexate has not been defined [1,3,9,12,13]. Cranial irradiation is another modality of treatment where it is available. However,

radiotherapy is fraught with a lot of complications such as hypopituitarism that discourage its use in children. Radiotherapy was not available in the facility when this patient was being managed. The NHL-BFM study suggested that PCNSL can be successfully treated without cranial irradiation [6–8].

Prognosis of childhood and adolescent PCNSL is poor but appears to be better than what is found in most adult series [6,8]. Early diagnosis and treatment is crucial for survival in both immunocompetent and immunocompromised individuals [4]. Death results from toxicity of therapy or complications of underlying disease such as raised ICP as seen in this reported case. The International PCNSL Collaborative Group (IPCG) cohort study found a two-year disease progression-free survival of 61% and the 3-year overall survival of 82% [6,7].

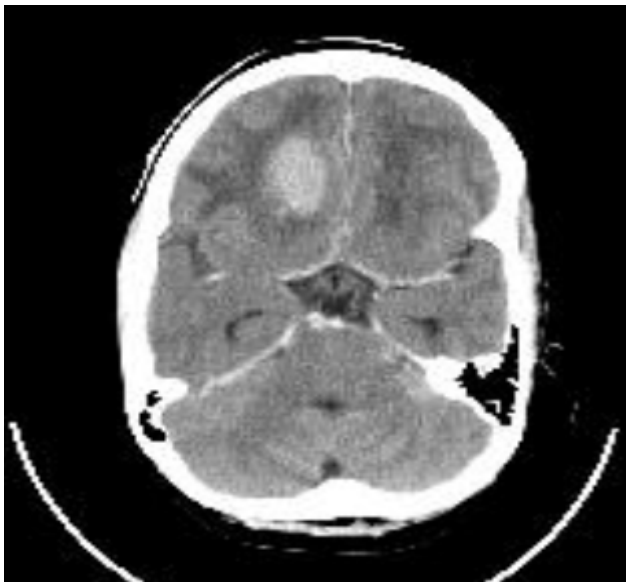

Fig. 1. Homogeneously enhancing lesions with peri-lesional oedema in the frontal lobe

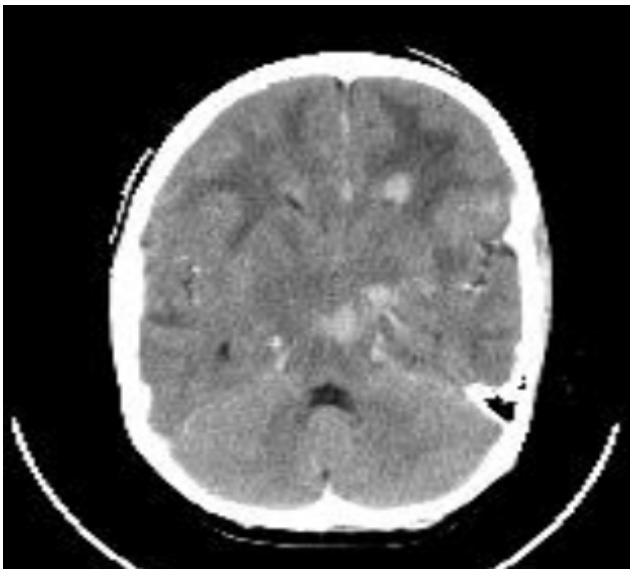

Fig. 2. Homogeneously enhancing lesions with peri-lesional oedema in the frontal lobes, left thalamus with effacement of the sulci and sylvian fissures

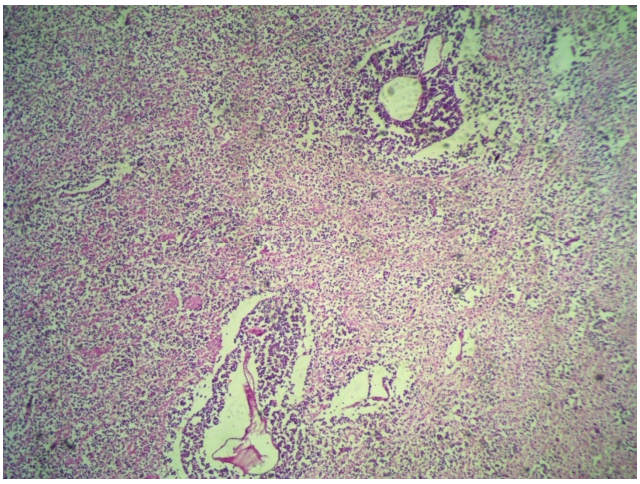

Fig. 3. Malignant neoplastic lesion composed of proliferating small to medium sized atypical lymphocytes with hyperchromatic nuclei, prominent nucleoli, occasional mitosis and angiocentricity of the tumour cells (x40 magnification)

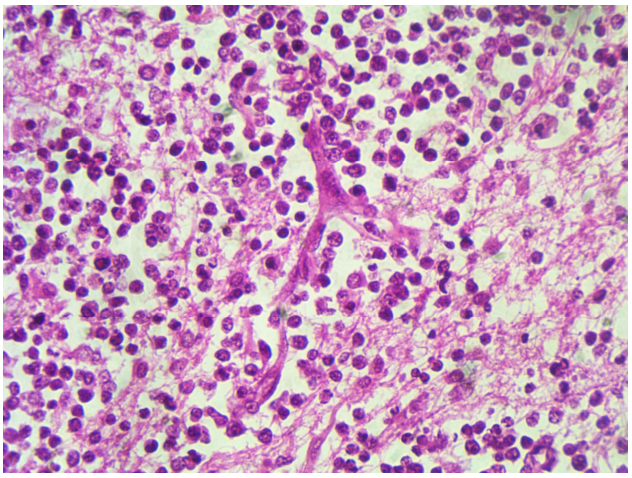

Fig. 4. Higher magnification of slide showing small to medium sized atypical lymphocytes with hyperchromatic nuclei, prominent nucleoli (x100 magnification)

4. CONCLUSION

Primary CNS lymphoma is rare and may occur in immunocompetent children. A presumptive diagnosis may be obtained from imaging studies and cytology, but confirmation is only through histopathology. Early diagnosis and prompt treatment with chemotherapy may increase survival rates, however, there are no standard protocols for management of PCNSL in children.

CONSENT

As per international standard or university standard, the patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical permission has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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