CASE REPORT

Primary intracranial leiomyosarcoma among patients with AIDS in the era of new chemotherapeutic and biological agents

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SUMMARY

Primary intracranial leiomyosarcoma (PIL) is a rare non-infectious aetiology of focal mass lesions among HIV-infected individuals. With only 16 published cases worldwide, information on its pathophysiology, risk factors, clinical course and management options is limited. We report two cases of PIL in HIV-infected Filipino men who presented with 1–3 months history of persistent headache, progressing in severity. Both had cranial MRI revealing intracranial mass diagnosed as leiomyosarcoma by excision biopsy and immunohistochemical staining. Both patients underwent adjuvant cranial radiotherapy and chemotherapy. Biologics were initiated in one patient. Both patients were alive with evidence of the disease.

BACKGROUND

Despite the availability of highly active antiretroviral therapy (ART), intracranial lesions that are considered AIDS-defining illnesses remain common in low/middle-income nations.[1 2] The complex interaction of HIV and the host immune system diversifies the differential diagnoses when confronted with a patient with HIV presenting with an intracranial lesion.[3 4] Primary intracranial leiomyosarcoma (PIL) is a rare malignant neoplasm of smooth muscle origin that has only been reported among 16 patients with HIV.[5–10] The extremely low incidence of PIL makes its diagnosis and management challenging. We report the first two cases of HIV-associated PIL in the Philippines and documented the dilemma encountered throughout their management to contribute to the better understanding of this rare malignancy.

CASE PRESENTATION

Case 1

A 29-year-old man with no known chronic medical illness presented with 1-month history of intermittent frontal headache. The patient initially thought the headache as 'migraine attacks' and self-medicated with ibuprofen with partial relief. The worsening severity of headache and the development of periorbital numbness and slurred speech prompted admission to a tertiary hospital.

Case 2

A 36-year-old man with known HIV presented with a 3-month history of intermittent nape pain and temporal headache. At the time of presentation, his cluster of differentiation 4 (CD4) count was 144 cells/mm^3 and was on ART regimen of efavirenz 600 mg/lamivudine 300 mg/tenofovir 300 mg tablet.

The patient was diagnosed with HIV infection 2 years prior to the occurrence of headache. He also received 6-month treatment for pulmonary tuberculosis (TB) on initial HIV diagnosis. Persistence of headache prompted consult to a neurologist.

INVESTIGATIONS

Case 1

On admission, a contrast-enhanced cranial CT scan showed a non-homogeneous slightly hyperdense ovoid mass at the left parietal lobe measuring 3.36×2.64×2.0 cm (figure 1). The patient was managed as a case of brain abscess with intravenous ceftriaxone and metronidazole.

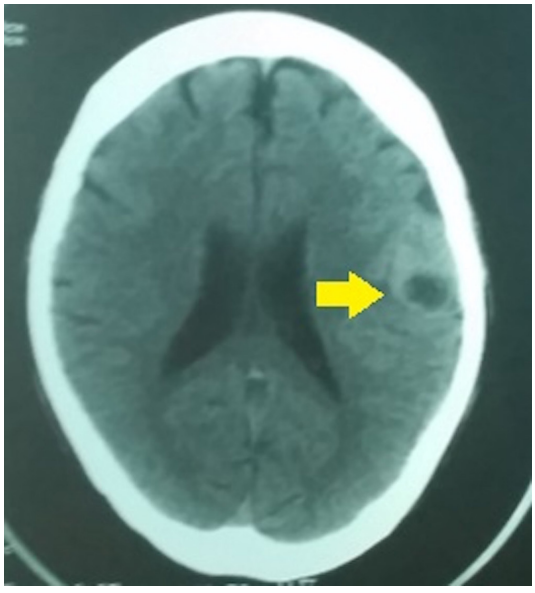

Figure 1 A contrast-enhanced cranial CT scan showing an enhancement of the hyperdense mass in the left frontoparietal region measuring 3.36×2.64×2.0 cm with areas of central necrosis (as pointed by an arrow).

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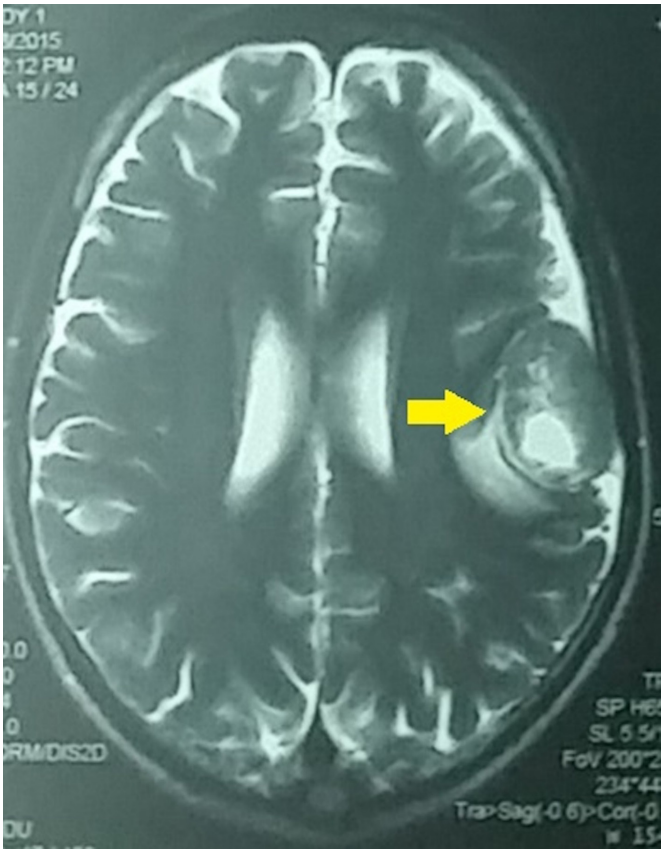

Figure 2 Cranial MRI with gadolinium showing a well-defined, extra-axial, heterogeneously enhancing solid mass in the left parietal area with central necrosis measuring 3.4×2.6×3.7 cm (as pointed by an arrow).

Cotrimoxazole 800/160 mg tablet two tablets every 8 hours were empirically started to cover for cerebral toxoplasmosis. Medical decompression with mannitol was also initiated. Admission laboratory results were unremarkable except for leucopenia (3.9 g/L, 60% lymphocytes) and slightly elevated serum lactate dehydrogenase (235 μ/L). On the 7th day of antibiotic treatment, cranial MRI showed no change in the size of the parietal mass (figure 2); hence, excision biopsy was performed. Histopathology showed spindle-like cells in fascicles. There is marked cytological atypia with more than 10 mitotic figures per 10 high power field (hpf) (figure 3). Immunohistochemistry staining demonstrated that the tissue was markedly positive for smooth muscle antigen (SMA) but

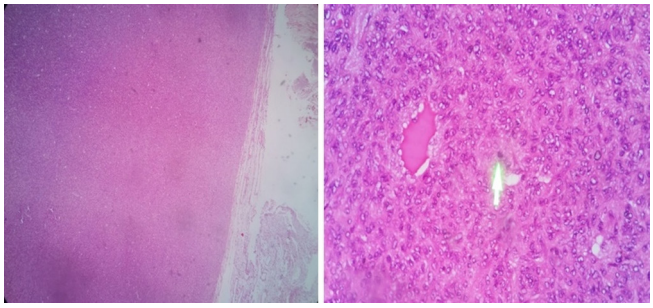

Figure 3 H&E stain of the left parietal mass showing a well-defined, eosinophilic staining tissue with interspersed blood vessels. Green arrow pointing to an area of a mitotically active nucleus.

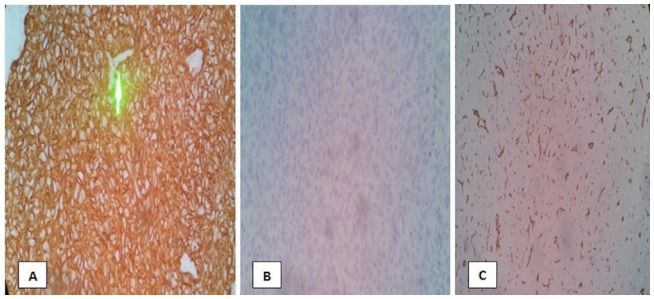

Figure 4 Immunohistochemistry staining of the left parietal mass revealed the following: (A) smooth muscle antigen—positive tumour cells (B) epithelial membrane antigen—negative tumour cells and (C) CD34 stain—negative tumour cells. Green arrow pointing to an area of tumor's vascular supply.

negative for epithelial membrane antigen (EMA) and CD34 (figure 4). Abdominal and chest CT scan with contrast did not show other lesions or possible sites of malignancy. A diagnosis of PIL was made. HIV infection was confirmed by western blot. CD4 count was 7 cells/mm^3. Serum toxoplasma IgG was negative. Cotrimoxazole dose was reduced to prophylaxis dosage (one 800/160 mg tablet once daily). Due to financial constraints experienced by the patient, tissue in situ hybridisation for Epstein-Barr virus (EBV)-encoded RNA was not performed. The limited funds were allocated for treatment.

Case 2

On admission, neurological and physical examination were unremarkable except for an enlarged bilateral neck mass. Cranial CT scan revealed a 2.0×1.7×1.6 cm hyperdense focus on the left occipital lobe and a 1.2×1.1×0.9 cm in the right uncal region (figure 5). Biopsy of the neck masses and the occipital mass was pursued. Histopathology of the neck mass tissue showed Langhans giant cells. Molecular testing

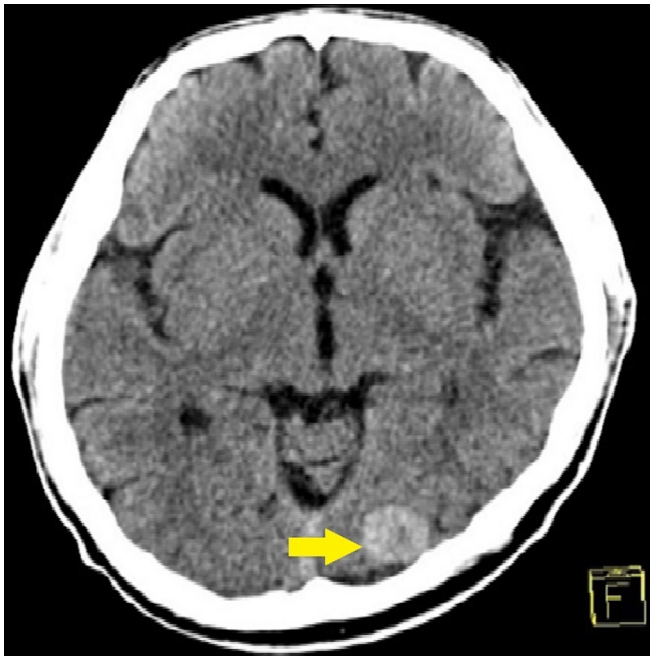

Figure 5 A contrast-enhanced cranial CT scan showing a 2.0×1.7×1.6 cm hyperdense focus on the left occipital lobe (as pointed by an arrow).

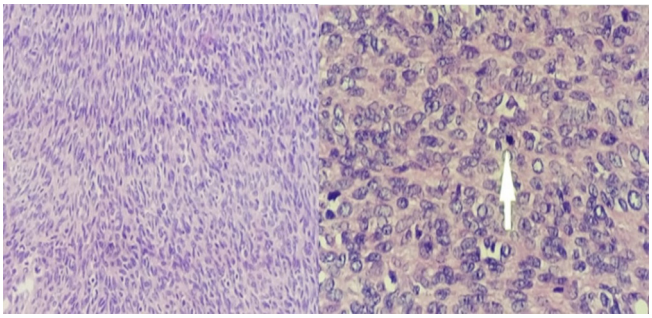

Figure 6 H&E stain demonstrating interlacing fascicles of spindle cells with mild to moderate pleiomorphism. Arrow pointing to a mitotically active cell nucleus.

with GeneXpert revealed rifampicin-resistant *Mycobacterium tuberculosis* (MTB). However, mycobacterial culture failed to isolate MTB. The patient was started on TB treatment (rifampicin 150 mg/isoniazid 75 mg/pyrazinamide 400 mg/ethambutol 275 mg fixed-dose combination tablet) plus levofloxacin 750 mg tablet. Excision biopsy of the left occipital mass showed interlacing fascicles of spindle-like cells with moderate pleiomorphism. Abnormal mitosis was noted with more than 10 mitotic figures per 10 hpf (figure 6). Immunohistochemistry results were consistent with leiomyosarcoma (positive for SMA, caldesmon and vimentin, and negative for s100, EMA, CD56 and CD31) (figure 7).

Two months after discharge, the patient experienced bilateral knee and ankle pain with associated lower extremity cramping. Neuropathic pain was considered. Electromyography and nerve conduction studies of all extremities were unremarkable but small muscle fibre disease cannot be ruled out. Abdominal and chest CT scan showed lytic foci in the 9th to 10th thoracic and 1st to 3rd lumbar vertebral bodies. Bone scintigraphy scan revealed a mildly increased osteoblastic activity in the right lambdoid suture and occipital bone. There are no metastatic foci noted in the thoracic and lumbar vertebral bodies (figure 8). Other workups included a negative serum toxoplasma IgG (0 UI/mL) and an elevated EBV IgG (5.37) and IgM (0.49). EBV-encoded RNA in situ hybridisation of the excised occipital mass was not done. The high cost of the test prevented us in documenting tissue EBV infection.

DIFFERENTIAL DIAGNOSIS

In areas with high burden of infectious diseases, opportunistic infections should always be considered as aetiologies of focal brain mass lesions. Bacterial brain abscess, TB and toxoplasmosis are common in patients with AIDS.[11] Immune reconstitution inflammatory syndrome (IRIS), a paradoxical worsening or unmasking of an inadequately treated opportunistic infection, can also present as brain mass lesions. One of the most

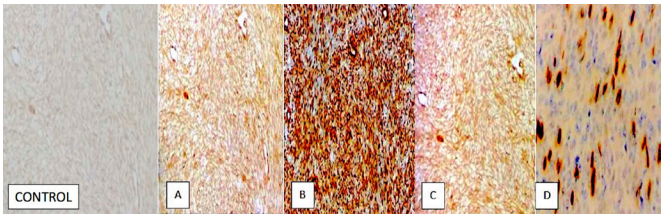

Figure 7 Immunohistochemical stains showing: (A) vimentin, (B) caldesmon, (C) smooth muscle antigen—positive in majority of the tumour cells, (D) desmin—focal, strong positive.

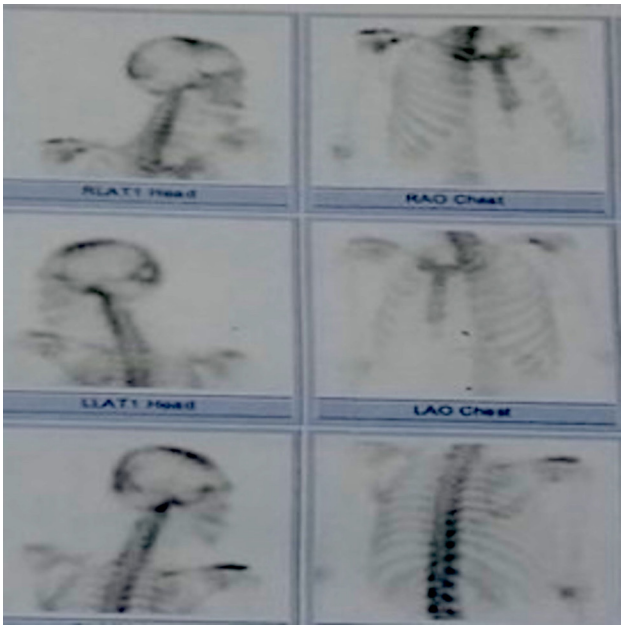

Figure 8 Bone scintigraphy revealed a mildly increased osteoblastic activity in the right lambdoid suture and occipital bone.

common non-infectious aetiologies include primary central nervous system lymphoma (PCNSL), a known AIDS-defining condition.[11] Other CNS masses include round cell neoplasms such as gliomas that may have spindle-like cell morphology similar to leiomyosarcoma, therefore, immunohistochemical stains are needed for differentiation.

TREATMENT

Case 1

The patient underwent adjuvant cranial radiotherapy with daily dose of 200 cGy for 30 days (total dose of 6000 cGy). Temozolomide 120 mg (75 mg/m^2 body surface area, BSA) was given 1 hour before radiotherapy. Temozolomide was maintained for the next 3 months together with nimotuzumab 200 mg intravenous every 14 days for six cycles. Nimotuzumab was shifted to cyclophosphamide intravenous (1 mg/m^2 BSA) after new brain lesions developed.

Case 2

Adjuvant whole brain radiotherapy using partial boost (100 cGy/dose for 12 days; total dose of 2400 cGy) was started. On discovery of the metastatic thoracic foci, radiotherapy of

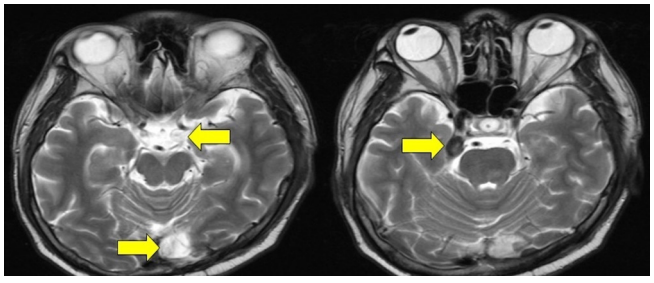

Figure 9 Cranial MRI showing increase in the size of the masses in the left occipital and middle aspect of the right middle cranial fossa. A new lesion was seen in the middle aspect of the left middle cranial fossa in the left parasellar region measuring 0.7×0.5×0.6 cm (as pointed by an arrow).

Table 1 Profile of all cases of primary intracranial leiomyosarcoma among HIV-infected population

Author	Age/sex	Location	CD4 count (cells/mm^3)	Time from HIV diagnosis (years)	ART	EBV	Treatment	Outcome (months)
Litofsky *et al*[32]	50/M	Occipital	27	6	NR	EBER-1 (+)	CR	NED 8 mos
Bejjani *et al*[39]	38/M	Lateral sphenoid	NR	0	NR	EBV LMP (–)	CR	NED 12 mos
Brown *et al*[25]	34/F	Pontine cistern	177	2	–	EBER-1 (+)	PR+Rx	AWD 12 mos
Blumentha *et al*[5]	43/M	Cavernous sinus	23	12	NR	EBER (+) EBV LMP (–)	Ch, Bx/excision	AWD 24 mos
Ritter *et al*[40]	5/F	Cavernous sinus	NR	4	NR	EBNA 2 (+)	PR	NR
Citow *et al*[41]	31/F	Parasellar	NR	0.5	NR	EBV IHC (+)	PR	NR
Lerdlum *et al*[27]	NR	NR	20–160	NR	NR	NR	Sx+Rx	NR
Zevallos-Giampietri *et al*[26]	29/M	Parasellar	NR	3	+	EBER (+) EBV LMP (–)	PR+Rx	AWD 6 mos
Suankratay *et al*[36]	43/F	Multifocal	26	4	+	EBER-1 (+)	CR+Rx	DOC 4 mos
	49/F	Multifocal	26	4	+	EBER-1 (+)	PR+Rx	AWD 10 mos
	34/F	Tentorium cerebelli	7	5	+	EBER-1 (+)	CR+Rx	NED 8 mos
	31/F	Multifocal	3	1	–	EBER-1 (+)	PR+Rx	AWD 5 mos
	35/M	Multifocal	20	0	+	EBER-1 (+)	CR+Rx	AWD 4 mos
Gupta *et al*[31]	17/F	Paracentral	22	14	–	EBER (+)	Bx+Rx+Ch	AWD 15 mos
Sivendran *et al*[8]	43/M	Frontal	14	NR	+	EBER (+)	CR	NED 20 mos
Muengtawee pongsa[10]	33/M	Cavernous sinus	NR	1.5	NR	NR	PR	NR
Francisco *et al* (2017)	29/M	Multifocal	7	0	+	NA	CR+Rx+Ch	AWD 23 mos
Francisco *et al* (2017)	36/M	Multifocal	144	1	+	NA	CR+Rx+Ch	AWD 27 mos

AWD, alive with disease; Bx, biopsy; Ch, chemotherapy; CR, complete resection; DOC, dead of other causes; DOD, dead of disease; EBER, Epstein-Barr Early RNA; EBNA, EBV nuclear antigen; EBV, Epstein-Barr virus; F, female; M, male; mos, months; NA, not applicable; NED, No evidence of disease; NR, not reported; PR, partial resection; Rx, radiotherapy; Sx, unspecified surgery.

the thoracic spine (T6–T11) was instituted (daily dose of 300 cGy for 10 days; total dose of 3000 cGy). The radiotherapy of the spine was discontinued after ruling out vertebral foci on bone scintigraphy. Medications for pain included pregabalin 75 mg tablet, carbamazepine 200 mg tablet and morphine 15 mg tablet.

OUTCOME AND FOLLOW-UP

Case 1

Three months after initial presentation, the patient had worsening headache, blurring of vision, complete ophthalmoplegia and ptosis of the left eye. Cranial MRI revealed new lesions at the left occipital and middle aspect of the right middle cranial fossa. Another lesion was seen in the middle aspect of the left middle cranial fossa measuring 0.7×0.5×0.6 cm (figure 9), which compresses the cavernous segment of the abducens, oculomotor and trochlear nerve.

The patient remained on ART and prophylactic medications for opportunistic infections. Repeat CD4 count was 34 cells/mm^3. Stereotactic radiosurgery of the new brain lesions was performed with continuation of cyclophosphamide treatment. One month after stereotactic radiosurgery, the patient improved with resolution of ophthalmoplegia and ptosis.

Case 2

Five months after the initial headache presentation, the patient developed bilateral lower extremity weakness and preferential gaze to the right. Follow-up cranial MRI showed new heterogeneous enhancing mass located in the proximal body of the corpus callosum, measuring 2.3×4.4×3.8 cm in its widest dimensions. Smaller lesions were also noted in the right distal body of the corpus callosum and the dorsal left aspect of the pons. Chemotherapy with etoposide (100 mg/m^2 BSA) and cisplatin (20 mg/m^2 BSA) was started. Cyclophosphamide (1 mg/m^2 BSA) was given 21 days after the initial chemotherapy.

DISCUSSION

In developed countries, PCNSL and cerebral toxoplasmosis account for most focal brain lesions.[11] In resource-limited settings, other infectious aetiologies remain common and should be considered. Depending on the level of immunosuppression, infectious agents may have varying presentations on imaging and can mimic a neoplasm.[12–14] Single-photon emission CT or positron emission tomography scan is the recommended screening imaging of choice for intracranial masses,[15] but the high cost of these tests limited the management of our patients. Empiric antibiotics for the first patient and anti-TB medications for the second patient were started while waiting for final histological diagnosis. TB IRIS of the CNS was also considered due to the concomitant TB adenitis in the second case.

Diagnosis of leiomyosarcoma requires histological confirmation. Leiomyosarcoma and its benign counterpart, leiomyoma are both positive for actin and desmin stains.[5–10 16] However, the presence of cellular atypia, coagulative necrosis and high mitotic index (10 or more mitosis per 10 hpf) favour a diagnosis of leiomyosarcoma.[17] Most cases of leiomyosarcomas are metastatic from other primary sites.[18] Our patients were diagnosed with PIL when no other primary sites were identified on whole-body imaging. PIL represents 0.1% of all intracranial tumours and its exact pathogenesis is poorly understood.[19 20] Some authors believe that immunosuppression is a prerequisite for its occurrence.[19 20] However, PIL has also been reported among immunocompetent individuals.[21–23]

We identified 16 published cases of PIL among HIV-infected individuals and compared our patients with the existing literature (table 1). From the 18 cases, mean age at

diagnosis was 34±11 years with no sex predilection. Most cases presented with single mass lesion (61%), while the rest were multifocal. The mean CD4 count on PIL diagnosis was 40±52 cells/mm^3. The time from initial HIV diagnosis to brain lesion discovery was a mean of 3.5±4 years. It can be hypothesised that chronic HIV infection is necessary to induce neoplastic changes. Although the diagnosis of HIV in our first patient was only made on current hospitalisation, it is likely that he has been chronically infected with HIV given the low CD4 count.

The association of PIL with EBV has been documented in multiple studies.[24–26] In our review, majority (93%) of patients had positive tissue EBV-encoded RNA using in situ hybridisation. We hypothesise that the ability of HIV and EBV to infect a wide array of cells and induce latency have synergistic action in tumourigenesis. On the other hand, some published cases did not report documentation of EBV infection in the tumour cells.[10 27] Similarly, the cases that we present are also limited by the lack of documentation of EBV tissue infection. In situ hybridisation remains the method of choice in detecting EBV in tissue sections.[28 29] The utility of serum EBV antibodies remains controversial. In resource-limited setting, EBV in situ hybridisation is not readily available in most centres and its high cost makes this test underused. Though the documentation of EBV–PIL association strengthens the role of EBV in tumourigenesis, however, it has limited clinical utility.

There are no standard guidelines for the management of PIL among HIV-infected patients.[30] Of the 18 patients reported, including our two cases, 94% (n=17) underwent surgical intervention. Adjuvant radiotherapy was instituted in 61% (n=11). Systemic chemotherapy was started in 22% (n=4), two of whom had unresected tumour. Chemotherapy alone was initiated in one patient due to the central location of the lesion.[5] In our case series, chemotherapy was started as adjunctive treatment following surgery and radiotherapy. Chemotherapy remains controversial due to poor blood–brain barrier permeability.[31 32] Temozolomide, an alkylating agent, was used in the first patient due to good brain penetration and acceptable safety profile.[33] It has modest activity in unresectable soft-tissue sarcomas with 8% tumour response rate making it a plausible agent against PIL.[9 33] One patient in our series was given nimotuzumab, an epidermal growth factor receptor (EGFR) monoclonal antibody. Soft-tissue sarcomas like leiomyosarcoma express EGFR,[34] wherein its blockade can decrease chemoresistance and inactivation of tumour survival pathways. Bevacizumab, a vascular endothelial growth factor receptor monoclonal antibody, has similarly been used in other reports.[23] Robust evidence on monoclonal antibody effectiveness against PIL is lacking.[23 35] Multimodality approach is applied making surgical resection and radiotherapy as mainstay of treatment.[30 31 36] Almost half of the PIL patients were on ART (44%). Immune reconstitution through ART initiation may theoretically improve patient outcomes, but there is limited evidence on the utility of ART in PIL progression, recurrence or cure.[37 38]

The prognosis of PIL is poor with the longest reported survival at 32 months after diagnosis.[29] Review of published cases with a reported mean duration of follow-up of 12 months showed that most patients were alive with the disease (n=9). No radiological evidence of the disease (NED) was reported in four patients with median duration of 10 months. NED cases had complete resection of unifocal tumour. On the other hand, long-term prognosis remains unknown.

Patient's perspective

I am very happy that despite the rarity of my condition, my doctors were able to diagnose me promptly. In this time of new diagnostic tests and medications, I remain hopeful that my health will improve continuously. I am now living a symptom free life and I am now enjoying life to its fullest. I hope that many doctors will learn from my case and be able to help other patients with the same condition.

Learning points

- The diagnostic work-up of an HIV-infected patient presenting with headache should include a comprehensive history taking, physical examination and appropriate laboratory and imaging tests.
- Primary intracranial leiomyosarcoma (PIL) is an extremely rare non-infectious mass lesion that has emerged among chronically infected HIV patients with very low CD4 count.
- The spectrum of differential diagnoses for chronically infected HIV patients presenting with headache and focal mass lesions should be expanded to infectious and non-infectious aetiologies.
- The diagnosis of PIL is made after excluding other possible primary sites of malignancy through whole-body imaging.
- There are no standard guidelines in the management of PIL, but a multimodal approach using surgery, chemotherapy and radiotherapy seem to be the most effective approach.

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Contributors CNF took part in patient data acquisition, involved in the planning and design of the report, writing of the manuscript, review of related literature, analysis of data and approval of the final manuscript. MA was involved in patient data acquisition, planning in the concept of the report, analysis of data, review of related literature, editing the manuscript and approval of the final manuscript. EMS was involved in patient data acquisition, analysis of data and approval of final manuscript. VMdVA was involved in patient data acquisition, planning and design of the report and approval of the final manuscript.

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