Journal of Community Hospital Internal Medicine Perspectives

Volume 13 | Issue 6 Article 5

2023

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Recommended Citation

Acharya, Indira; DeBoer, Scott R.; and Bhansali, Deepty (2023) "Acute presentation of primary CNS lymphoma mimicking Toxoplasma in HIV infection," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 13: Iss. 6, Article 5.
DOI: 10.55729/2000-9666.1251
Available at: https://scholarlycommons.gbmc.org/jchimp/vol13/iss6/5

CASE REPORT

Acute Presentation of Primary CNS Lymphoma Mimicking Toxoplasma in HIV Infection

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Abstract

Primary CNS lymphoma (PCNSL) accounts for up to 15% of non-Hodgkin lymphomas in HIV patients and is the second most common cause of space-occupying brain lesions in HIV patients after CNS toxoplasmosis. Differentiation of PCNL and CNS toxoplasmosis is crucial as PCNL carries a poor prognosis with survival time of 2−4 months without treatment but can be improved with prompt initiation of chemotherapy. These two entities often present clinically in a similar manner, and conventional imaging can also be a diagnostic challenge due to overlapping imaging characteristics. Thus, definitive diagnosis of PCNSL relies on histopathologic confirmation. Here, we present a case of intracranial lesion that presented acutely in the context of headache and left sided body weakness and was found to have PCNSL.

Keywords: Primary CNS lymphoma (PCNSL), Non-Hodgkin lymphomas, Space-occupying, Brain lesions, CNS toxoplasmosis, Chemotherapy, Histopathologic confirmation

1. Introduction

Primary CNS lymphoma is a malignant non-Hodgkin's B-cell lymphoma.[39] CNS toxoplasmosis is the most common focal brain lesion, followed by primary CNS lymphoma in HIV patients.[1] Primary CNS lymphoma is a malignant non-Hodgkin's B-cell lymphoma, hypothesized to occur due to the unsuppressed proliferation of lymphocytes in the context of overexpression of oncogenic protein triggered by Epstein Barr virus (EBV).[2,3,39] CNS toxoplasmosis is an opportunistic infection, common in HIV patients with a low CD4 count of fewer than 200 cells/microliter, and occurs mainly by consumption of infected food and water.[21,28]

The clinical features of PCNSL are often shared by CNS toxoplasmosis, ranging from headache and photophobia to focal neurological deficit and death.[6] Brain imaging is sometimes inconclusive for the confirmation of diagnosis, as hallmark imaging findings may not always be present.[20] Histopathological examination after brain lesion biopsy is required to avoid unnecessary delay in diagnosis.[4]

Focal brain lesions in HIV-positive patients should be treated empirically for toxoplasmosis until the diagnosis is confirmed via biopsy.[32] The mainstay of treatment of PCNSL is antiretroviral therapy along with chemotherapeutic agents containing a high dose of methotrexate.[38,39] Radiotherapy alone or in combination with chemotherapy has a limited role in treating PCNSL.[46]

2. Case presentation

A 51-year-old woman presented in the context of progressive frontal throbbing headache and left-sided upper and lower extremity weakness for 5 days. Her headache was severe, constant, 8/10 in intensity, and associated with photophobia, nausea, and several episodes of vomiting. Simultaneously, the patient also noticed some left-sided weakness in both the upper and lower extremities. Medical history was notable for HIV, epilepsy, mood disorder, and treated pulmonary tuberculosis. Her home medications included Biktarvy, divalproex sodium and sulfamethoxazole-trimethoprim.

Received 9 February 2023; revised 31 July 2023; accepted 3 August 2023.
Available online 4 November 2023

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https://doi.org/10.55729/2000-9666.1251

Upon presentation, she was noted to have sinus bradycardia (54 beats per minute) and associated hypotension (93/60 mm Hg) with an otherwise preserved respiratory rate and oxygen saturation. Physical examination was remarkable for excessive sensitivity of both eyes to bright light with the presence of eye cover on both eyes, decreased sensation to light touch in left extremities and decreased motor strength in left upper (2/5) and lower extremities (1/5).

Laboratory diagnostics demonstrated (Table 1) leukopenia, low absolute CD4 count (6 cells/UL) and CD4/CD8 and high HIV 1 viral load. Her computerized tomography (CT) of head without contrast (Fig. 1) showed right parietal lobe ill-defined mass with substantial surrounding vasogenic edema resulting in 7 mm leftward midline shift. MRI brain with contrast (Fig. 2) showed heterogeneously enhancing horseshoe-shaped intra-axial lesion within the right parietal lobe resulting in vasogenic edema and midline shift towards left by 5.5 mm at the septum pellucidum with partial involvement of posterior aspect of corpus callosum.

The differential diagnosis was CNS opportunistic infection, including toxoplasmosis and tuberculosis, primary CNS lymphoma, other CNS primary or secondary neoplasm, and less likely tumefactive demyelination. Given that cerebral toxoplasmosis is one of the most common opportunistic neurological infections in AIDS patients, our patient with the high HIV viral load, low CD4 count, non-adherence to antiretroviral therapy, acute onset of her symptoms along with significant photophobia and a history of rearing three cats in her home, toxoplasmosis was our leading diagnosis. But a single hypoattenuating lesion causing a pronounced mass effect in the brain was more in the favor of CNS neoplasm. CSF analysis may provide definitive diagnosis; however, lumbar puncture was not pursued in our patient given the mass effect and concern for herniation as a complication of lumbar puncture. Though her brain imaging was less concerning for brain abscess; she was started on a broad-spectrum antibiotic for coverage of possible intracranial infection. Her home sulfamethoxazole-trimethoprim was increased to therapeutic CNS dosing for empiric toxoplasmosis treatment. Later, her toxoplasma IgG and IgM antibodies, interferon-gamma release assay (IGRA), and cryptococcal antigen resulted as negative, making infectious etiology less likely.

Table 1. Laboratory diagnostics.

Parameters	Normal range	Laboratory values
WBC k/uL	4–108	2.9
Absolute CD4 count cells/uL	402–1612	6
CD4/CD8 ratio	1.01–2.81	0.03
HIV1 viral load copies/ml	<20	60711
Creatinine mg/dl	0.5–0.8	0.62
LDH units/L	120–246	204

Given the patient's radiographic finding and neurologic symptoms, surgical treatment comprising stereotactic right craniotomy for resection of left parietal mass was recommended. Intraoperatively the soft, friable, mottled, gray-colored intracranial mass was encountered about 1 cm beneath the cortex which was resected in piecemeal due to its friable texture and resected pieces were sent for histopathology and culture. The culture was negative for acid fast bacillus (AFB), fungi, or any other bacteria. The histopathology (Fig. 3) showed hypercellular brain tissue with atypical lymphoid proliferation showing angiocentricity and perivascular distributions. The background brain parenchyma demonstrated extensive necrosis and hemorrhage. The immunohistochemical stain showed that the tumor cells are positive for CD20, MUM1 and Bcl-2 with high (>90%) Ki-67 proliferation index. The morphology was suggestive of a HIV associated diffuse large B- cell lymphoma and the immunostaining panel supported the morphologic findings.

Postoperatively, patient was started on levetiracetam and steroids. Since the patient was not adherent with Biktarvy prior to admission, it was not restarted until after steroids to avoid immune reconstitution inflammatory syndrome (IRIS). Her PET imaging of the whole body showed asymmetrically reduced activity in superior right frontoparietal lobe likely secondary to postsurgical changes of right parietal craniotomy for mass resection with no evidence of fluro-deoxy- glucose (FDG) avid nodal or extra nodal disease in the body. On 11th postoperative day patient's strength in left upper and lower extremity gradually improved to her baseline. She commenced a bi-weekly regimen of combined chemotherapy, receiving an infusion of Methotrexate 3500 mg/m^2 along with Folinic acid 10 mg/m^2 and Rituximab 600 mg. She successfully completed the fifth cycle of this combined chemotherapy without encountering any complications. The treatment plan entails continuing with a total of 7 cycles. A follow-up CT scan of her head without contrast, conducted one month after the surgery demonstrated a stable appearance of the previous surgical site.

3. Discussion

The common differential for focal brain lesions in HIV patients includes opportunistic infections,

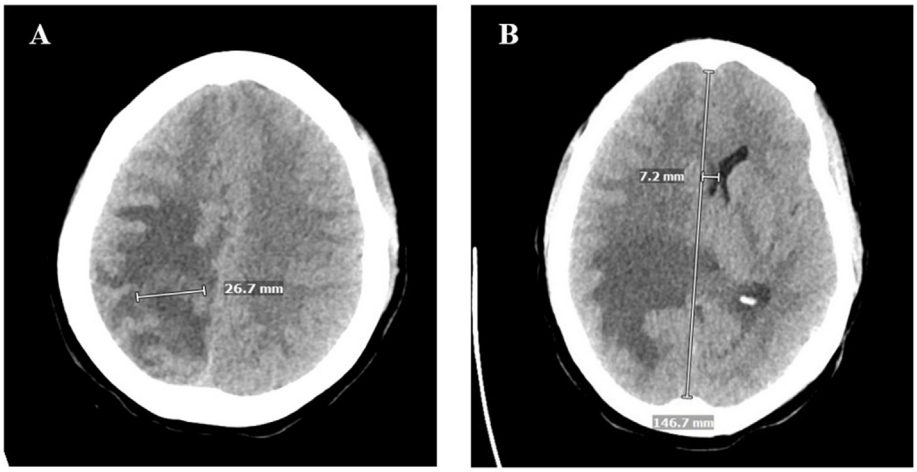

Fig. 1. A: Computerized tomographic (CT) imaging of head without contrast showing right parietal lobe ill-defined mass with substantial surrounding vasogenic edema. B: Computerized tomographic (CT) imaging of head without contrast showing 7 mm leftward midline shift at the level of the septum pellucidum.

neoplasms or cerebrovascular disease.[31] In developed countries, CNS toxoplasmosis (50%) is the most common HIV-associated focal brain lesion which is followed by primary CNS lymphoma (30%) and progressive multifocal leukoencephalopathy PML (20%).[1,32,33] Kaposi's sarcoma, herpes simplex, cryptococcosis, bacterial abscesses, CNS tuberculosis, candida albicans, and aspergillosis are reported in a minority of cases.[4,5] However, in developing countries, endemic infections are the principal cause of focal brain lesions in HIV patients.[31] In one study carried out on 32 HIV-infected South African patients, with focal brain lesions, except for one patient with PCNL and another

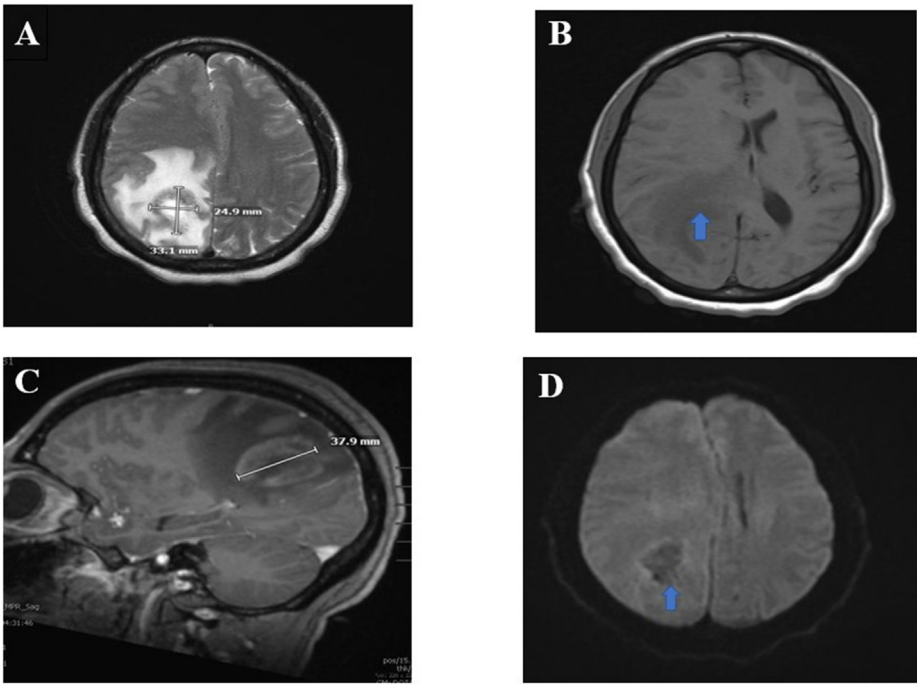

Fig. 2. Magnetic resonance imaging (MRI) brain showing right parietal lobe, intra-axial mass with vasogenic edema and midline shift. (A) T2 weighted: demonstrates hyperintense lesion within the right parietal lobe with vasogenic edema and midline shift. Partial involvement of the posterior aspect of the corpus callosum(B) T1 weighted, pre-contrast: demonstrates hypointense lesion (C) T1 weighted post-contrast: demonstrates enhancing lesion (D) Diffusion weighted imaging (DWI): demonstrates minimal diffusion restriction.

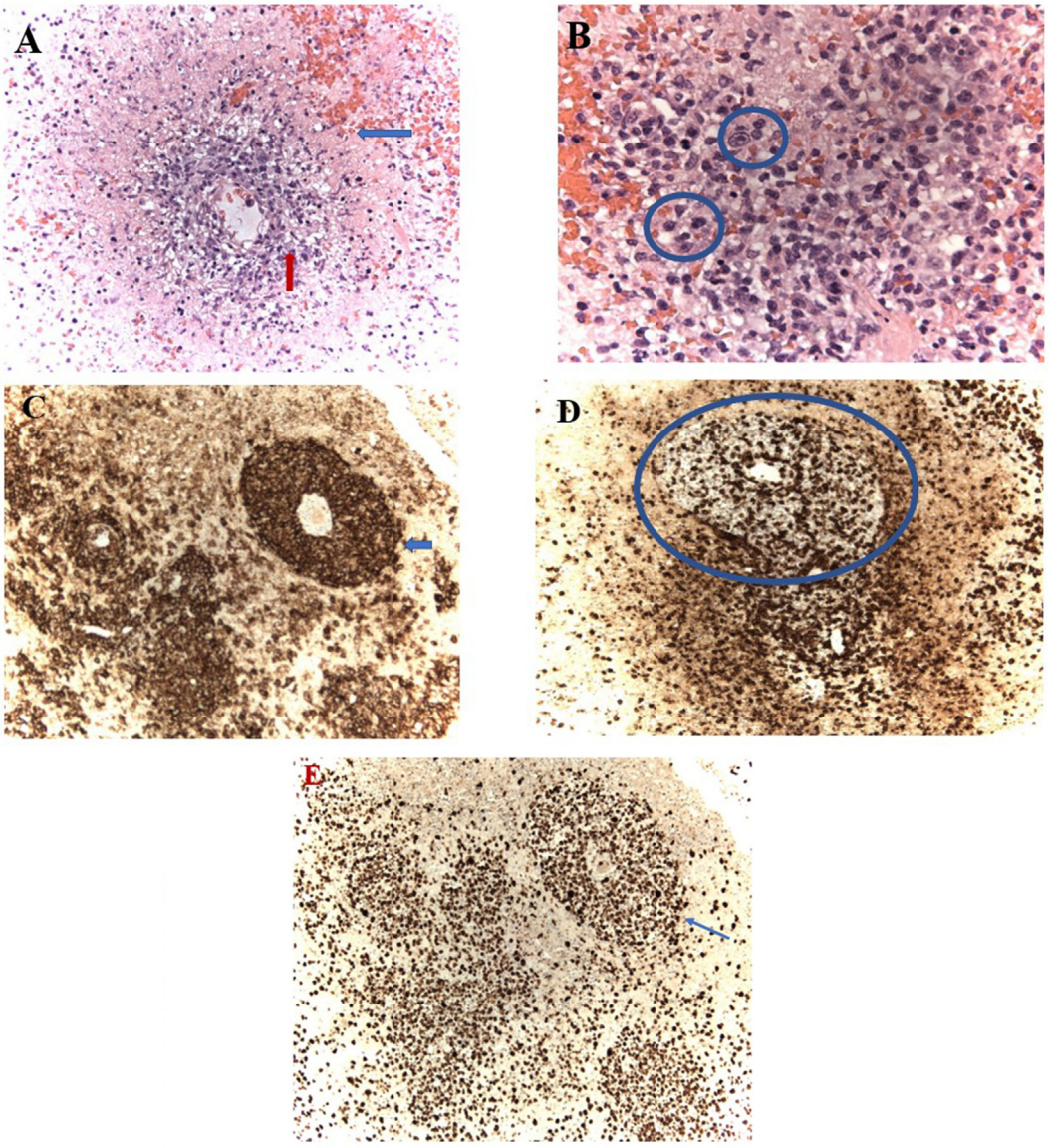

Fig. 3. Histopathology (A) H&E staining of brain biopsy in 20 X power demonstrates infiltrating lymphocytes in characteristic perivascular distribution "perivascular cuffing" perivascular cuffing (red arrowhead) and necrosis (blue arrowhead). (B) H & E staining of brain biopsy in 40X power demonstrates prominient nucleloi compatible with immunoblastic morphology (blue circle). (C) CD20 immunostaining of brain biopsy in 10X demonstrates predominant B lymphocytes in perivascular distribution (arrowhead). (D) CD3 immunostaining of brain biopsy in 10X demonstrates fewer T lymphocytes in perivascular cuff (blue circle). (E) Immunostaining of brain biopsy with Ki-67 in 10X demonstrates a high proliferation index in lymphocytes cells (arrowhead).

patient with PML, all the remaining patients were found to have infectious etiology causing brain lesions, of which TB was most common[31]).

The likelihood of PCNSL in HIV patients is 250 to 500-fold that of the average population in the USA.[4] It arises due to ineffective immunoregulation of EBV that precipitates expression of oncogenic protein with simultaneous loss of apoptosis and unregulated proliferation of lymphocytes.[7,8,34] The histological types are diffuse large cell, immunoblastic or small noncleaved cell lymphoma and are usually of B-cell phenotype.[41] Diffuse large B cell lymphoma (DLBCL) is the most common AIDS related lymphoma[41] and small noncleaved lymphoma usually occurs in patient with high CD4 count.[41] DLBCL accounts 30% of NHL without HIV infection and 45% of cases with HIV associated lymphoma[41] The common clinical presentations include fever, headache, seizures, focal neurologic deficits, cranial nerve palsies, visual disturbances, confusion, and psychomotor changes which are the features also shared by CNS toxoplasmosis.[9,11,12,35] In CT head,

PCNL appears as a hyperdense lesion, sometimes isodense, associated with edema and mass effect.[42]

Toxoplasma encephalitis is the most common opportunistic infection in HIV patients in developed countries and the most common cause of focal brain lesions and death.[13–16,20] It occurs by ingestion of contaminated water, food from oocysts excreted by cats, or improperly cooked infected meat,[21-23] and the nosocomial condition occurs through blood transfusion, organ transplants, and laboratory accidents.[25-27] CNS toxoplasmosis usually occurs when the CD4 cell count is < 200 cells/microliter, and the risk is most significant when CD4 count is less 50 cells/microliter.[28-30] In our case, the patient's CD4 count was six cells/microliter rendering her at the greatest risk for CNS toxoplasmosis. The hallmark CT finding seen in the majority of CNS toxoplasmosis is a hypodense lesion with ring enhancement and peri-lesional edema, however, 20% of lesions donot enhance with contrast, mimicking PCNSL.[17,20]

As per the American Academy of Neurology (AAN), a HIV-positive patient who presented with a focal brain lesion should be initially treated empirically for toxoplasmosis and should undergo a brain biopsy if there is no clinical or radiological improvement in 2 weeks.[32] One study emphasizes the importance of initial treatment with medication specific to the infections that are endemic to the population especially in developing countries, as noninfectious etiologies are uncommon.[31] Because of overlapping clinical and radiological features of PCNL and CNS toxoplasmosis, histopathological confirmation of the diagnosis is pivotal.[4] However, histopathological examination requires an invasive neurosurgical procedure associated with significant morbidity, patients are often reluctant to perform biopsy resulting in unnecessary delay in diagnosis and treatment.[4] The common histopathological finding in PCNSL is demyelination and infiltrating lymphocytes in characteristic perivascular distribution which also called as perivascular cuffing.[18,19,48]

Treatment of PCNSL includes various combinations of chemotherapy regimens alone or along with radiotherapy.[36] Unlike other intracranial tumors, surgical resection has a limited role in PCNSL, given the diffuse and infiltrative nature of the lesion.[43] Various retrospective studies have shown the worse outcome of cytoreductive methods without any clear survival benefit.[37,44,45] The cornerstone of treatment is a combination of antiretroviral therapy (ART) and a chemotherapeutic regimen containing high-dose methotrexate.[38,39] The other option is ARTin combination with whole-brain radiotherapy.[44] However, in one randomized phase III study on 320 patients with recently diagnosed PCNSL, who were followed up for a median of 81.2 months, it was found that whole-brain therapy did not significantly increase survival compared to methotrexate-based chemotherapy.[46] Antiviral agents like Zidovudine or Ganciclovir directed against EBV may help improve survival, but this needs further study.[47] In our case, once the PCNSL was confirmed through parietal lesion biopsy, patient was started on methotrexate based chemotherapeutic regimen.

HIV-related PCNSL has a very poor prognosis, with a median survival of 2–4 months without treatment.[10,24] The 5-year survival is 30% after chemotherapeutic treatment,[36] with a median survival of approximately 1.5 years.[10] Consideration of infection prophylaxis and antiretroviral therapy also plays an important role for a better prognosis.[40] The poor determinants of prognosis are age >60 years, WHO performance status worse than grade 2, tumor number, cerebrospinal fluid dissemination, high LDH level, low CD4 count, and presence of B symptoms.[36,38,41] Good response to treatment is usually seen in a patient with higher CD4 counts; however, there is no similar correlation with HIV viral load.[31] Patients with low Ki-67 expression (<49%) are found to have remarkably worse progression-free (PFS) and overall (OS) survival, independent of other clinical risk factors.[49,50] In our case younger age of the patient, single focal lesion, low LDH level, absence of B symptoms and high K:67 proliferation (>90%) index were indicative of good prognosis though her low CD4 count was not in favor of it.

4. Conclusion

PCNL is an extremely fatal condition with poor prognosis if left untreated. Its timely differentiation from other common causes of intracranial lesions and definitive diagnosis is empirical as its appropriate treatment can improve long-term survival.

Conflict of interest

There is no conflict of interest.

References

1. Dina TS. Primary central nervous system lymphoma versus toxoplasmosis in AIDS. *Radiology*. 1991 Jun;179(3):823–828.
2. Karia SJ, McArdle DJT. AIDS-related primary CNS lymphoma. *Lancet*. 2017;389:2238.
3. Moulignier A, Lamirel C, Picard H, et al. Long-term AIDS-related PCNSL outcomes with HD-MTX and combined antiretroviral therapy. *Neurology*. 2017;89:796–804.
4. Marcus C, Feizi P, Hogg J, et al. Imaging in differentiating cerebral toxoplasmosis and primary CNS lymphoma with

special focus on FDG PET/CT. *AJR Am J Roentgenol*. 2021 Jan 1; 216(1):157−164.
5. Mamidi A, DeSimone JA, Pomerantz RJ. Central nervous system infections in individuals with HIV-1 infection. *J Neurovirol*. 2002;8:158−167 9.
6. Price RW. Neurological complications of HIV infection. *Lancet*. 1996;348:445−452, 10. Porter SB, Sande MA.
7. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. *N Engl J Med*. 1992;327: 1643−1648.
8. National Comprehensive Cancer Network website. *Cancer in people living with HIV*. Version 2; 2019. www.nccn.org. Accessed August 18, 2020. Updated February 12, 2020.
9. Utsuki S, Oka H, Abe K, et al. Primary central nervous system lymphoma in acquired immune deficiency syndrome mimicking toxoplasmosis. *Brain Tumor Pathol*. 2011;28:83−87.
10. Brandsma D, Bromberg JEC. Primary CNS lymphoma in HIV infection. *Handb Clin Neurol*. 2018;152:177−186.
11. Post MJ, Chan JC, Hensley GT, Hoffman TA, Moskowitz LB, Lippmann S. Toxoplasma encephalitis in Haitian adults with acquired immunodeficiency syndrome: a clinical-pathologic-CT correlation. *AJR*. 1983;140:861−868, 17.
12. Navia BA, Petito CK, Gold JW, Cho ES, Jordan BD, Price RW. Cerebral toxoplasmosis complicating the acquired immune deficiency syndrome: clinical and neuropathological findings in 27 patients. *Ann Neurol*. 1986;19:224−238.
13. Lee YY, Bruner JM, Van Tassel P, Libshitz HI. Primary central nervous system lymphoma: CT and pathologic correlation. *AJR*. 1986;147:747−752.
14. Brandsma D, Bromberg JE. Primary CNS lymphoma in HIV infection. *Handb Clin Neurol*. 2018 Jan 1;152:177−186.
15. Berger JR. Mass lesions of the brain in AIDS: the dilemmas of distinguishing toxoplasmosis from primary CNS lymphoma. *AJNR Am J Neuroradiol*. 2003 Apr;24(4):554−555. PMID: 12695179; PMCID: PMC8148702.
16. Ciricillo SF, Rosenblum ML. Use of CT and MR imaging to distinguish intracranial lesions and to define the need for biopsy in AIDS patients. *J Neurosurg*. 1990;73:720−724.
17. Ciricillo SF, Rosenblum ML. Use of CT and MR imaging to distinguish intracranial lesions and to define the need for biopsy in AIDS patients. *J Neurosurg*. 1990;73:720−724.
18. Kupfer MC, Zee CS, Colletti PM, Boswell WD, Rhodes RTI. MRI evaluation of AIDS-related encephalopathy: toxoplasmosis versus lymphoma. *Magn Reson Imag*. 1990;8:5lâ€"5.
19. Lorberboym M, Estok L, Machac J, et al. Rapid differential diagnosis of cerebral toxoplasmosis and primary central nervous system lymphoma by thallium-201 SPECT. *J Nucl Med*. 1996 Jul 1;37(7):1150−1154.
20. Basavaraju A. Toxoplasmosis in HIV infection: an overview. *Tropical parasitology*. 2016 Jul;6(2):129.
21. Baril L, Ancelle T, Goulet V, Thulliez P, Tirard-Fleury V, Carme B. Risk factors for Toxoplasma infection in pregnancy: a case-control study in France. *Scand J Infect Dis*. 1999;31:305−309.
22. Kapperud G, Jenum PA, Stray-Pedersen B, Melby KK, Eskild A, Eng J. Risk factors for *Toxoplasma gondii* infection in pregnancy. Results of a prospective case-control study in Norway. *Am J Epidemiol*. 1996;144:405−412.
23. Cook AJ, Gilbert RE, Buffolano W, et al. Sources of toxoplasma infection in pregnant women: European multicentre case-control study.*BMJ*. 2000 Jul 15;321(7254):142−147. https://doi.org/10.1136//bmj.321.7254.142.
24. European research network on congenital toxoplasmosis. *BMJ*. 2000;321:142−147.
25. Rabaud C, May T, Amiel C, et al. Extracerebral toxoplasmosis in patients infected with HIV. A French National Survey. *Medicine (Baltim)*. 1994;73:306−314.
26. Kimball AC, Kean BH, Kellner A. The risk of transmitting toxoplasmosis by blood transfusion. *Transfusion*. 1965;5:447−451.
27. Segall L, Moal MC, Doucet L, Kergoat N, Bourbigot B. Toxoplasmosis-associated hemophagocytic syndrome in renal transplantation. *Transpl Int*. 2006;19:78−80.
28. Rawal BD. Laboratory infection with toxoplasma. *J Clin Pathol*. 1959;12:59−61.
29. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H. Centers for disease control and prevention (CDC); national institutes of health; HIV medicine association of the infectious diseases society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the national institutes of health, and the HIV medicine association of the infectious diseases society of America. *MMWR Recomm Rep (Morb Mortal Wkly Rep)*. 2009;58:1−207.
30. Leport C, Chêne G, Morlat P, et al. Pyrimethamine for primary prophylaxis of toxoplasmic encephalitis in patients with human immunodeficiency virus infection: a double-blind, randomized trial. ANRS 005-ACTG 154 Group Members. Agence Nationale de Recherche sur le SIDA. AIDS Clinical Trial Group. *J Infect Dis*. 1996;173:91−97.
31. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS. Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. *JAMA*. 1984;252:913−917.
32. Modi M, Mochan A, Modi G. Management of HIV-associated focal brain lesions in developing countries. *QJM*. 2004 Jul 1; 97(7):413−421.
33. Quality Standards Subcommittee of the American Academy of Neurology. Evaluation and management of intracranial mass lesions in AIDS. *Neurology*. 1998;50:21−26.
34. Sadler M, Brink NS, Gazzard BG. Management of intracerebral lesions in patients with HIV: a retrospective study with discussion of diagnostic problems. *Q J Med*. 1998;91:205−217.
35. Khanna R, Burrows SR, Moss DJ. Immune regulation in Epstein-Barr virus-associated diseases. *Microbiol Rev*. 1995 Sep;59(3):387−405.
36. Lim T, Kim SJ, Kim K, et al. Primary CNS lymphoma other than DLBCL: a descriptive analysis of clinical features and treatment outcomes. *Ann Hematol*. 2011 Dec;90(12):1391−1398.
37. Shibamoto Y, Ogino H, Suzuki G, et al. Primary central nervous system lymphoma in Japan: changes in clinical features, treatment, and prognosis during 1985-2004. *Neuro Oncol*. 2008 Aug 1;10(4):560−568.
38. Batchelor T, Loeffler JS. Primary CNS lymphoma. *J Clin Oncol*. 2006;24(8):1281−1288. https://doi.org/10.1200/JCO.2005.04.8819.
39. Shenkier TN, Voss N, Chhanabhai M, et al. The treatment of primary central nervous system lymphoma in 122 immunocompetent patients: a population-based study of successively treated cohorts from the British Colombia Cancer Agency. *Cancer*. 2005;103:1008−1017.
40. Schlegel U, Schmidt-Wolf IG, Deckert M. Primary CNS lymphoma: clinical presentation, pathological classification, molecular pathogenesis and treatment. *J Neurol Sci*. 2000 Dec 1;181(1−2):1−2.
41. Sparano JA. Clinical aspects and management of AIDS-related lymphoma. *Eur J Cancer*. 2001 Jul 1;37(10):1296−1305.
42. Schommers P, Hentrich M, Hoffmann C, et al. Survival of AIDS-related diffuse large B-cell lymphoma, Burkitt lymphoma, and plasmablastic lymphoma in the German HIV Lymphoma Cohort. *Br J Haematol*. 2015 Mar;168(6): 806−810.
43. Amin-Hanjani S, Harsh GR. Tumors: cerebral metastases and lymphoma. *Neurosurgery*. 2005:281−297. Springer, London.
44. Labak CM, Holdhoff M, Bettegowda C, et al. Surgical resection for primary central nervous system lymphoma: a systematic review. *World Neurosurg*. 2019 Jun 1;126:e1436−e1448.
45. Berry MP, Simpson WJ. Radiation therapy in the management of primary malignant lymphoma of the brain. *Int J Radiat Oncol Biol Phys*. 1981 Jan 1;7(1):55−59.
46. Ferreri AJ, Reni M, Villa E. Therapeutic management of primary central nervous system lymphoma: lessons from prospective trials. *Ann Oncol*. 2000 Aug 1;11(8):927−937.
47. Korfel A, Thiel E, Martus P, et al. Randomized phase III study of whole-brain radiotherapy for primary CNS lymphoma. *Neurology*. 2015 Mar 24;84(12):1242−1248.
48. Bossolasco S, Falk KI, Ponzoni M, et al. Ganciclovir is associated with low or undetectable Epstein-Barr virus DNA load in cerebrospinal fluid of patients with HIV-related primary

central nervous system lymphoma. *Clin Infect Dis*. 2006 Feb 15;42(4):e21–e25.
49. Alderson L, Fetell MR, Sisti M, Hochberg F, Cohen M, Louis DN. Sentinel lesions of primary CNS lymphoma. *J Neurol Neurosurg Psychiatr*. 1996 Jan 1;60(1):102–105.
50. Hasselblom S, Ridell B, Sigurdardottir M, Hansson U, Nilsson-Ehle H, Andersson PO. Low rather than high Ki-67 protein expression is an adverse prognostic factor in diffuse large B-cell lymphoma. *Leuk Lymphoma*. 2008 Jan 1;49(8): 1501–1509.