International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Research Article

NEUROSYPHILIS PRESENTING AS A BRAIN MASS: A DIAGNOSTIC PITFALL MIMICKING INFLAMMATORY PSEUDOLYMPHOMA - A CASE REPORT

Bibek Khatiwada[1], Yi Yang[1], Saral Sharma[1] and Guifang Yang[1*]

[1]Department of Pathology, Zhongnan Hospital of Wuhan University; No.169, Donghu Road, Wuchang District, Wuhan City, Hubei Province

ABSTRACT

Neurosyphilis is a distinct pathological manifestation of syphilis, recognized for its potential to cause inflammatory pseudotumors. Pathological studies on neurosyphilis are currently scarce, emphasizing the need to explore clinical diagnostic experiences to prevent misdiagnosis and unnecessary surgical interventions. This article presents three cases of neurosyphilis initially suspected to be metastatic or primary brain tumors. Diagnosis was confirmed through pathological examination following surgical resection, revealing morphological characteristics typical of peripheral soft tissue syphilis in the first and second stages. Treponema pallidum was detected in all cases, and microbial genetic testing further confirmed the diagnosis in one instance. Following standardized anti-syphilis treatment, all patients achieved full recovery and resumed normal lives. By reviewing these rare cases, this article aims to summarize the morphological characteristics and share our diagnostic experience, enhancing the understanding of neurosyphilis to avoid unnecessary surgeries.

Keywords: neurosyphilis, inflammatory pseudotumor, T.Pallidum,case report

INTRODUCTION

With the incidence of primary and secondary syphilis rising annually in China, there were 22 cases per 100,000 people in 2008 [1]. Neurosyphilis is now less common than it was before the introduction of penicillin. However, in a recent series, 3.5 percentage of patients with clinical or ophthalmologic signs of syphilis were found to have neurosyphilis based on cerebrospinal fluid (CSF) analysis. The incidence of neurosyphilis in various studies has been estimated to range from 0.47 to 2.1 cases per 100,000 people [2]. In certain studies, up to half of the patients with early-stage syphilis have been found to be co-infected with the human immunodeficiency virus (HIV) [3], and neurosyphilis is estimated to occur in twice as many persons with coinfection as persons without HIV infection [4]. While most knowledge about neurosyphilis originates from the pre-penicillin era, clinical descriptions from 1970 to 1984 closely resemble those documented between 1930 and 1940.[5][6]. However, patients with HIV coinfection may have earlier development of neurologic features than people without HIV infection, as well as incomplete responses to treatment [7][8]. Early neurosyphilis is usually characterized by asymptomatic meningitis, evidenced only by a cellular reaction in the CSF. However, it can be symptomatic with headache, meningismus, cranial nerve palsies, and blindness or deafness. Late symptomatic neurosyphilis, which develops decades after the primary infection, has been reported in 10 to 20 percentage of cases, according to data obtained before the introduction of penicillin; the rates may be lower now [4][9]. Studies have reported that neurosyphilis can cause the infiltration of lym- phocytes and plasma cells [10][11], cerebrovascular disease [12][13], and gum swelling[14].

However, pseudomatosis caused by neurosyphilis has not been reported. This paper discusses three cases where brain lesions were surgically removed due to masses identified in clinical and imaging diagnoses. All cases were pathologically confirmed as neurosyphilis. This highlights the importance of refining diagnostic approaches to neurosyphilis to prevent misdiagnosis and avoid unnecessary treatments.

CASE PRESENTATION

Case 1: The first patient, a 57-year-old male, was admitted to the hospital with a one- month history of intermittent headaches. He exhibited no primary anogenital ulcers, mucosal lesions, peculiar rashes, or alopecia. His medical history included hyperten- sion, diabetes, and gout, all managed with medication. Head CT and MRI revealed a space-occupying lesion (SOL) in the left temporoparietal occipital lobe, accompanied by significant surrounding edema Fig. 1 Although glioma was considered, metastasis could not be ruled out. Histopathological examination of the surgical specimen revealed thickened cerebral vascular walls, localized lumen stenosis and occlusion, perivascular cellulose deposition, lymphocyte and plasma cell infiltration, and localized microab- scess formation. Immunohistochemical analysis showed T. pallidum (+), CMV (-), EBER (-), HHV-8 (-), CD68

(histiocytes +), CD138 (+), CD20 (B cells +), and CD3(T cells +). These findings were consistent with the morphological characteristics of peripheral soft tissue syphilis in the first and second stages. Postoperative follow-up showed that the patient underwent anti-inflammatory treatment(details not available), recovered well, and did not experience a recurrence.

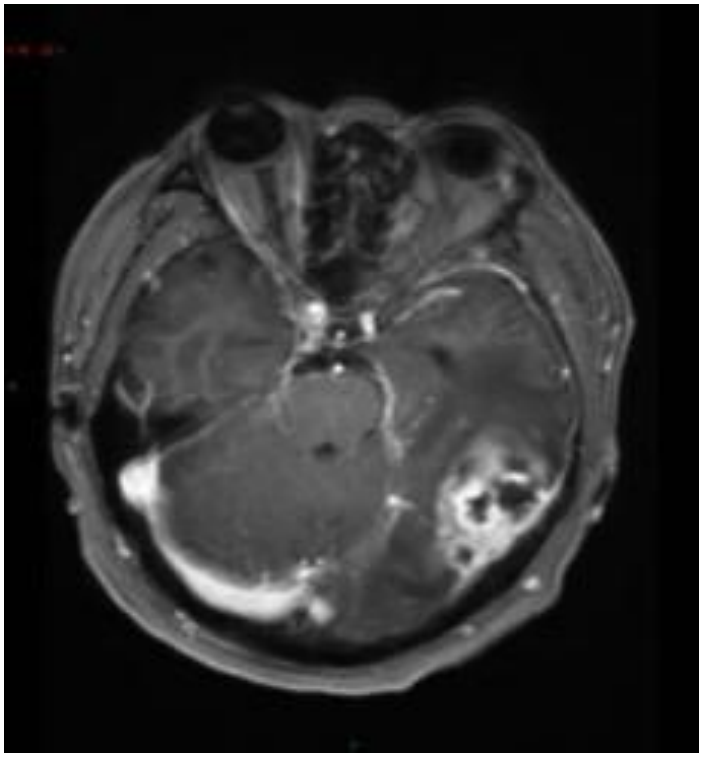

Figure 1: Brain MRI showing a space-occupying lesion (SOL) in the left temporoparietal occipital lobe, accompanied by significant surrounding edema

Case 2: The second patient, a 54-year-old female, was admitted following the discovery of a space-occupying lesion (SOL) in the left frontal lobe, identified two months earlier. She exhibited no primary anogenital ulcers, mucosal lesions, peculiar rashes, or alopecia. Her medical history included hypertension and diabetes, managed with medication. Two months prior, after a fall, an MRI revealed a left frontal lobe mass with surrounding edema, initially considered a possible metastasis, which did not improve with conservative treatment Fig.2. PET/CT showed an equal to slightly high-intensity shadow in the left frontal lobe, with abnormal metabolic increase, peripheral edema, and decreased metabolism, suggesting a possible malignant neo- plastic lesion. Upon admission, the patient tested serologically positive for HIV and syphilis. Post-surgery, histopathological examination of the mass revealed infiltra- tion by mononuclear macrophages, plasma cells, and lymphocytes, interstitial edema, granulomatous inflammation in necrotic brain tissue, and vascular lesions. Immunohistochemical analysis showed T. pallidum (+), GFAP (-), HHV-8 (-), CMV (-), EBER (-), CD68 (histiocytes +), and CD38 (plasmocytes +). These findings corresponded to the morphological characteristics of the third stage of peripheral soft tissue syphilis. Standardize anti-syphilis treatment was performed (Ampicillin, 1.2

million units, three intramuscular injections every other week) during postoperative follow-up, and no recurrence occurred.

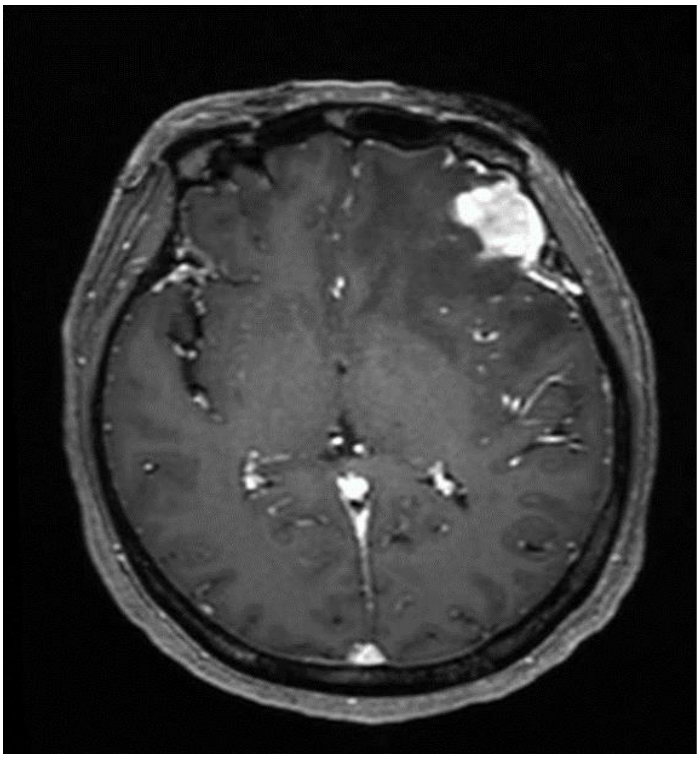

Figure 2: Brain MRI showing a left frontal lobe mass with surrounding edema

Case 3: A 71-year-old male patient was admitted to the hospital due to bilateral lower limb weakness for four days, which had worsened over the past half-day. He had no significant past medical history. Blood tests revealed a positive Rapid Plasma Reagin (RPR) for syphilis. Brain MRI showed nodules in the bilateral frontal and parietal 3 lobes with surrounding edema, suggesting the possibility of metastasis and recom- mending correlation with the clinical history Fig 3. Gross examination of the right parietal lobe lesion revealed an irregular mass of grayish-yellow to gray-brown tissue measuring 4 × 1.5 × 0.9 cm. Pathological analysis under low magnification showed chronic purulent inflammation with abscess formation, local degeneration, and necrotic tissue. High magnification revealed extensive infiltration of lymphocytes, plasma cells, and neutrophils, with pronounced inflammatory cell infiltration in the vascular walls, narrowing of some vascular lumens, and swollen endothelial cells. Amyloid bodies were noted around the vascular walls. Immunohistochemical analysis showed T. pallidum (+), CD3 (T cells +), CD30 (-), CD21 (-), CD138 (plasmocytes +), EBER (-), and Sil- ver stain (-). Metagenomic microbial detection confirmed the presence of Treponema pallidum (syphilis spirochete) Fig 4. The pathological diagnosis was syphilitic menin-gitis, displaying the morphological characteristics of peripheral soft tissue syphilis in the first and second stages.(Ampicillin, 1.2 million units, three intramuscular injections every other week) during postoperative follow-up, and no recurrence occurred.

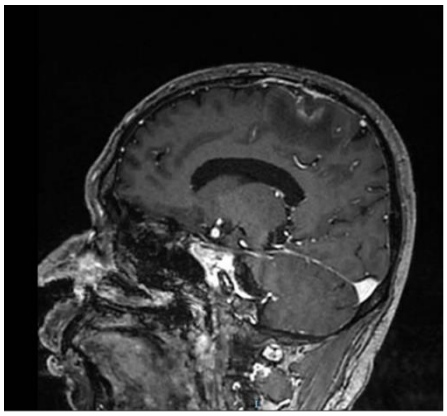

Figure 3: Brain MRI showing nodules in the bilateral frontal and parietal lobes with surrounding edema

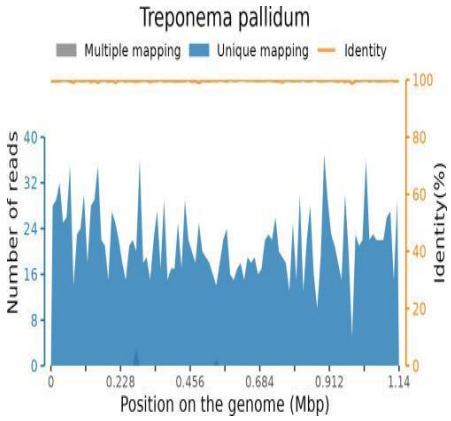

Figure 4: Metagenomic microbial detection confirming the presence of Treponema pal- lidum (syphilis spirochete)

MATERIALS AND METHODS

Existing hematoxylin and eosin–stained slides were reviewed on each case for parenchymal inflammatory changes (including degree, location, and cell types), vascular lesions, and granulomas. Immunohistochemical(IHC) staining for Treponema antigen, GFAP, CMV, EBER, HHV-8, CD68, CD138, CD20, and CD3 were used to perform on 3 cases under local laboratory conditions at the time of primary case workup, all of which were the auxiliary product from DAKO (ready-to-use, DAKO). The stain on each case was reviewed and reported as positive or negative based on whether any organisms were observed.

RESULTS

Histological findings:

The first case's histopathological features of the surgical specimen showed local microabscess

formation Fig 5, infiltration of lymphocytes and plasma cells Fig 6 , thickening of the cerebral vascular wall, local lumen stenosis and occlusion, perivas- cular cellulose deposition Fig 7. The second case's histopathological features showed infiltration of mononuclear macrophages, plasma cells, and lymphocytes Fig 8, inter- stitial edema, and granulomatous inflammation in necrotic brain tissue (Fig. 1 H and I). The third case's histopathological features showed chronic purulent inflammation with Fig 9, Fig 10 abscess formation was, with local degeneration and necrotic tis- sue under low magnification Fig 11 ; under high magnification, a large number of lymphocytes, plasma cells, and neutrophils were visible, with extensive inflammatory cell infiltration in the vascular walls, narrowing of some vascular lumens, and swollen endothelial cells Fig 13, Fig 14. Amyloid bodies were observed around the vascular walls Fig 13. Treponema IHC was positive Fig 14.

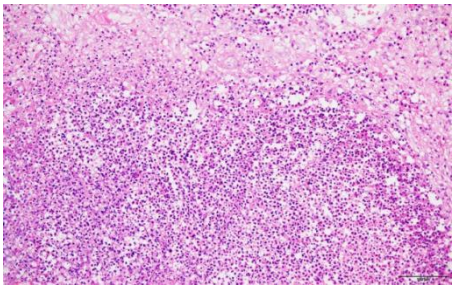

Figure 5

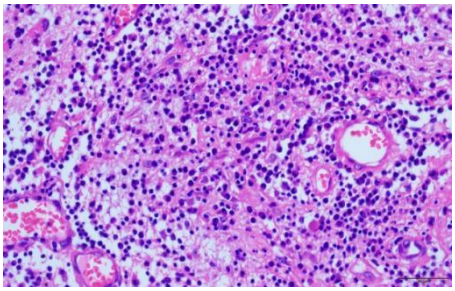

Figure 6

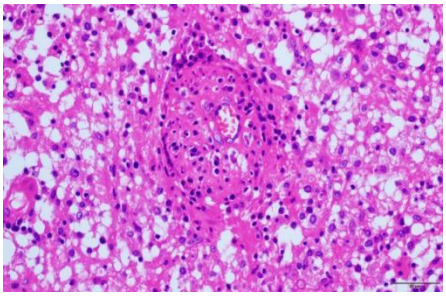

Figure 7

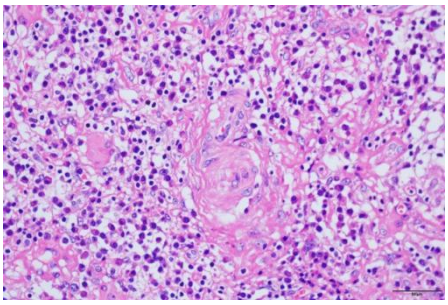

Figure 8

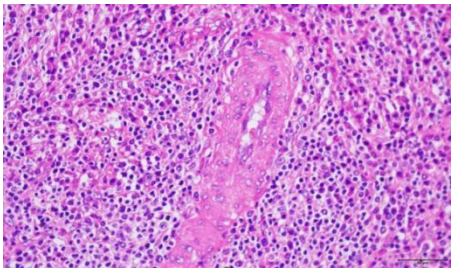

Figure 9

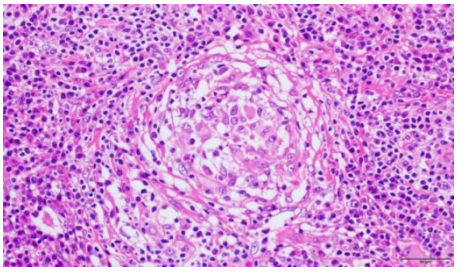

Figure 10

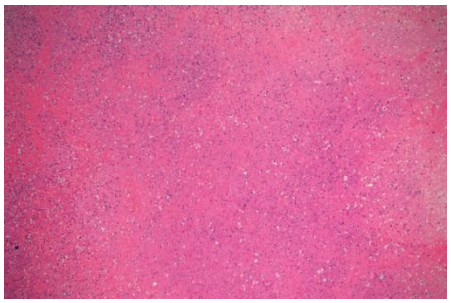

Figure 11

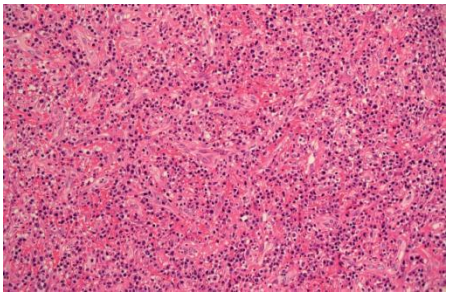

Figure 12

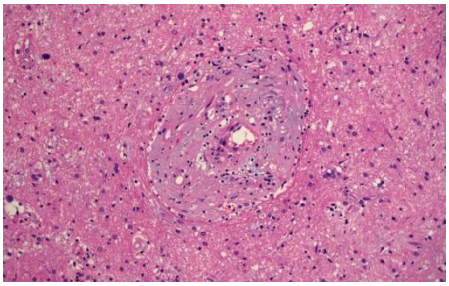

Figure 13

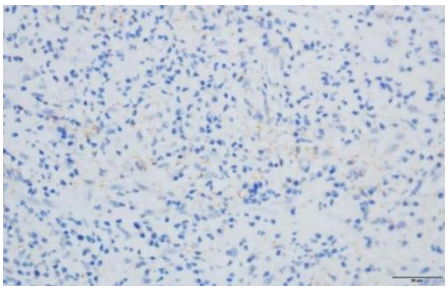

Figure 14

DISCUSSION

Secondary syphilis can have a wide and varied clinical presentation. The laboratory diagnosis of neurosyphilis is based on abnormal results of serum and CSF serologic tests and elevations in the CSF white-cell count and protein level [1]. However, these findings are neither sensitive nor specific, and a prior history of syphilis is not always known. They have no proper benchmarks. Serum and CSF serologic tests for neurosyphilis are classified as nontreponemal (tests using Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR] techniques) or treponemal (tests using fluorescent treponemal-antibody absorption [FTA-ABS] and related techniques)[15].

Estimates of serologic sensitivity and specificity depend on the choice of controls, the prevalence and stage of syphilis, and the accuracy of laboratory and clinical diagnoses used as a reference. Neurosyphilis is usually accompanied by CSF pleocytosis, which declines over decades, and mildly elevated protein levels [16]. The most common pattern in our series was the thickening of the cerebral vascular wall, local lumen stenosis and occlusion, perivascular cellulose deposition, and infiltration of lymphocytes and plasma cells Fig 7 Fig 9 Fig 13. Microabscess appeared in 1 case and gummatous swelling in the other, which respectively was primary syphilis and tertiary syphilis [17][18][19]. Cerebral vascular lesions have been linked with neurosyphilis in previous reports; some cases in prior large series had infiltration of lymphocytes and plasma cells [20] with partially combined HIV [21]. Microabscess formation and granulomatous inflammation in necrotic brain tissue can mimic brain mass as the first symptom. Case 1

and Case 3 showed images of brain abscesses, which are equivalent to Stage I/II syphilis Fig 5, Fig 8,Fig 11 ; Case 2 showed images of granulomas, which are equivalent to Stage III syphilis Fig 10. Three cases in our Imaging data findings mimicked possible malignant neoplastic lesions, but metastasis was not excluded. In this paper, 3 cases of brain lesions were removed by surgical resection due to mass in clinical and imaging studies and were pathologically diagnosed as neurosyphilis. Three patients showed noticeable effects on penicillin treatment and no disease progression. For patients with serological syphilis antibody positive, it is necessary to be alert to the possibility of brain inflammatory pseudotumor-like changes caused by neurosyphilis. Moreover, it is feasible to screen cerebrospinal fluid syphilis combined with penicillin therapy to avoid unnecessary surgical treatment. IHC for Treponemal organisms could be considered the gold standard for diagnosing neurosyphilis. IHC is helpful when positive but does not rule out the possibility of syphilis when negative. All three patients showed positive results for Treponema pallidum Fig 14 postoperatively, with Case 1 and Case 3 showing weakly positive results; further microbial metagenomic detection using high-throughput sequencing (NGS) identified Treponema pallidum. Similarly, reported cases of hepatic syphilis in the literature included positive cases [22][23] and negative cases [22][24][25] for spirochetes. Currently, reports on the pathoogy of neurosyphilis are relatively rare, with only one case reported [26]. The three patients exhibited a large amount of chronic inflammatory cell infiltration, with extensive lymphocytic infiltration. CD38 and CD138 showed positivity for plasma cells Fig 6 , Fig 13. CD3, CD20, and CD68 demonstrated scattered infiltration of T cells, B cells, and histiocytic cells, respectively. No clear atypia was observed in the cells, suggesting a low likelihood of lymphoma. Our series underscores that secondary syphilis should be included in the differential diagnosis in a wide variety of encephalopathy patterns, including local lumen stenosis and occlusion, granulomatous inflammation in necrotic brain tissue, and local microabscess formation. Takashi etc.[26] showed that mass formation may be caused by concomitant EBV reactivation in neurosyphilis. We also conducted relevant tests including CMV (Cytomegalovirus), EBV (Epstein-Barr Virus), HHV8 (Human Herpesvirus 8), and special staining-silver staining, to rule out more common viral and fungal infections. Postoperatively, the patients received standardized anti-syphilis treatment, recovered well and there was no recurrence during follow-up.

CONCLUSION

For patients with serological syphilis antibody positive, it is necessary to be alert to the possibility of brain inflammatory pseudotumor-like changes caused by neurosyphilis. Neurosyphilis histomorphology of the central nervous system caused by the change and other soft tissue morphological changes of syphilis is roughly similar, including parenchymal wall thickening, luminal stenosis, occlusion, and perivascular visible cel- lulose deposition and plasma cell infiltrates, and visible micro abscess formation, the formation of the brain tissue necrosis and syphilitic gumma. Furthermore,

when treat- ing patients with mass lesions of the central nervous system, it is important to check their medical history and perform laboratory screening for infectious diseases to avoid overlooking syphilis infections. For patients with brain lesions and serological-positive peripheral syphilis, it is feasible to screen cerebrospinal fluid syphilis combined with penicillin therapy to avoid unnecessary surgical treatment.

REFERENCES

1. I. M. Daey Ouwens *et al.*, "Neurosyphilis in the mixed urban-rural community of the Netherlands," *Acta Neuropsychiatr.*, vol. 26, no. 3, pp. 186–192, 2014, doi: 10.1017/NEU.2013.53.
2. M. Á. Conde-Sendín, R. Amela-Peris, Y. Aladro-Benito, and A. Angel-Moreno Maroto, "Current clinical spectrum of neurosyphilis in immunocompetent patients," *Eur. Neurol.*, vol. 52, no. 1, pp. 29–35, 2004, doi: 10.1159/000079391.
3. J. D. Tucker and M. S. Cohen, "China's syphilis epidemic: epidemiology, proximate determinants of spread, and control responses.," *Curr. Opin. Infect. Dis.*, vol. 24, no. 1, pp. 50–55, Feb. 2011, doi: 10.1097/QCO.0b013e32834204bf.
4. A. De Voux, S. Kidd, and E. A. Torrone, "Reported Cases of Neurosyphilis Among Early Syphilis Cases-United States, 2009 to 2015," *Sex. Transm. Dis.*, vol. 45, no. 1, pp. 39–41, Jan. 2018, doi: 10.1097/OLQ.0000000000000687.
5. E. C. Wolters, "Neurosyphilis: a changing diagnostic problem?," *Eur. Neurol.*, vol. 26, no. 1, pp. 23–28, 1987, doi: 10.1159/000116306.
6. M. Timmermans and J. Carr, "Neurosyphilis in the modern era," *J. Neurol. Neurosurg. Psychiatry*, vol. 75, no. 12, pp. 1727–1730, Dec. 2004, doi: 10.1136/JNNP.2004.031922.
7. D. R. Johns, M. Tierney, and D. Felsenstein, "Alteration in the natural history of neurosyphilis by concurrent infection with the human immunodeficiency virus," *N. Engl. J. Med.*, vol. 316, no. 25, pp. 1569–1572, Jun. 1987, doi: 10.1056/NEJM198706183162503.
8. R. T. Rolfs *et al.*, "A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group," *N. Engl. J. Med.*, vol. 337, no. 5, pp. 307–314, Jul. 1997, doi: 10.1056/NEJM199707313370504.
9. T. GJESTLAND, "The Oslo study of untreated syphilis; an epidemiologic investigation of the natural course of the syphilitic infection based upon a re-study of the Boeck-Bruusgaard material," *Acta Derm. Venereol. Suppl. (Stockh).*, vol. 35, no. Suppl 34, 1955, doi: 10.2340/00015555343368.
10. H. Tiwana and A. Ahmed, "Neurosyphilis: mighty imitator forays with benign presentation and unique neuroimaging findings," *Sex. Health*, vol. 15, no. 4, pp. 358–360, 2018, doi: 10.1071/SH17088.
11. J. J. B. Garcia, J. L. Coralde, M. A. C. Bagnas, and K. J. O. Khu, "Isolated Cranial Nerve VI Palsy and Neurosyphilis: A Case Report and Review of Related Literature," *IDCases*, vol. 27, Jan. 2022, doi: 10.1016/J.IDCR.2022.E01377.
12. C. Li, S. Wang, G. Tang, L. Liu, and G. Chen, "Neuroimaging findings of cerebral syphilitic gumma," *Exp.*

Ther. Med., vol. 18, no. 6, Oct. 2019, doi: 10.3892/ETM.2019.8089.

13. R. Inui *et al.*, "Serial Radiological Findings in Meningovascular Neurosyphilis Presenting as Acute Ischemic Stroke: A Case Report," *J. Stroke Cerebrovasc. Dis.*, vol. 30, no. 11, Nov. 2021, doi: 10.1016/J.JSTROKECEREBROVASDIS.2021.106087.
14. C. M. Marra, "Neurosyphilis," *Continuum (Minneap. Minn).*, vol. 21, no. 6 Neuroinfectious Disease, pp. 1714–1728, Dec. 2015, doi: 10.1212/CON.0000000000000250.
15. A. H. Ropper, "Neurosyphilis," *N. Engl. J. Med.*, vol. 381, no. 14, pp. 1358–1363, Oct. 2019, doi: 10.1056/NEJMRA1906228.
16. A. H. Ropper, "Neurosyphilis," *N. Engl. J. Med.*, vol. 381, no. 14, pp. 1358–1363, Oct. 2019, doi: 10.1056/NEJMRA1906228.
17. J. R. Berger and D. Dean, "Neurosyphilis," *Handb. Clin. Neurol.*, vol. 121, pp. 1461–1472, 2014, doi: 10.1016/B978-0-7020-4088-7.00098-5.
18. C. Rowe, N. Buckley, B. Chhetri, and S. Paudel, "Neurosyphilis: A Monkey Among Men," *J. community Hosp. Intern. Med. Perspect.*, vol. 12, no. 3, pp. 57–60, May 2022, doi: 10.55729/2000-9666.1055.
19. S. Pujari *et al.*, "Neurosyphilis, A True Chameleon of Neurology," *Ann. Indian Acad. Neurol.*, vol. 24, no. 4, pp. 566–572, Jul. 2021, doi: 10.4103/AIAN.AIAN_28_21.
20. L. G. Yi *et al.*, "Clonal cutaneous and neurosyphilis: A pitfall in pseudolymphoma diagnosis," *J. Cutan. Pathol.*, vol. 49, no. 3, pp. 288–292, Mar. 2022, doi: 10.1111/CUP.14153.
21. A. Tomkins, S. Ahmad, D. E. Cousins, C. M. Thng, F. J. Vilar, and S. P. Higgins, "Screening for asymptomatic neurosyphilis in HIV patients after treatment of early syphilis: an observational study," *Sex. Transm. Infect.*, vol. 94, no. 5, pp. 337–339, Aug. 2018, doi: 10.1136/SEXTRANS-2016-052938.
22. C. E. Hagen, M. Kamionek, D. S. McKinsey, and J. Misdraji, "Syphilis presenting as inflammatory tumors of the liver in HIV-positive homosexual men," *Am. J. Surg. Pathol.*, vol. 38, no. 12, pp. 1636–1643, 2014, doi: 10.1097/PAS.0000000000000264.
23. J. Serigado, E. Lewis, and G. Kim, "Rectal bleeding caused by a syphilitic inflammatory mass," *BMJ Case Rep.*, vol. 12, no. 1, Jan. 2019, doi: 10.1136/BCR-2018-226595.
24. J. O. Lo, R. A. Harrison, and A. J. Hunter, "Syphilitic hepatitis resulting in fulminant hepatic failure requiring liver transplantation," *J. Infect.*, vol. 54, no. 3, Mar. 2007, doi: 10.1016/J.JINF.2006.07.005.
25. R. Palacios *et al.*, "Liver involvement in HIV-infected patients with early syphilis," *Int. J. STD AIDS*, vol. 24, no. 1, pp. 31–33, Jan. 2013, doi: 10.1177/0956462412472316.
26. T. Hibiya *et al.*, "Epstein-Barr virus-positive monoclonal lymphoplasmacytic proliferation associated with neurosyphilis in an immunocompetent patient: A case report," *Neuropathology*, vol. 44, no. 2, pp. 104–108, Apr. 2024, doi: 10.1111/NEUP.12934.