

# Clinical, Radiological, and Pathological Features of Cerebral and Spinal Syphilitic Gumma: A Cross-Sectional Study

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**Background and Objectives:** Syphilitic gumma is rare and has atypical manifestations. Herein we report the clinical, imaging, and biological findings of a cross-sectional study of syphilis with gumma. Seven patients are described, offering promise in terms of early diagnosis and thereby enabling timely detection and treatment.

**Methods:** In this study, 397 neurosyphilis patients were consecutively from January 2021 to June 2024. We identified seven neurosyphilis patients with gumma. Their sociodemographic, clinical status, manifestations, neuroimaging, and laboratory manifestations were assessed.

**Results:** In the 397 neurosyphilis patients, seven had gumma — a frequency of 1.8%. Two of the seven (28.6%) were male. Their age ranged from 46 to 70 years, and the median symptom onset age was 56 years old. All patients experienced symptoms of unilateral limb weakness or numbness. Two patients displayed varying degrees of headache symptoms, three exhibited memory deterioration, and three manifested lightning pain. Enhanced MRI scans showed continuous nodule-like or partly high signal intensity of the brain or spine. The pathological sections of the intracranial syphilitic gumma displayed neuronal degeneration, proliferation of glial cells, and infiltration of lymphocytes. All serum samples showed decreased levels after therapy. The levels of WBCs and protein had reduced in all patients after therapy. All patients were followed up for 6 months to 1.5 years after therapy, and follow-up brain and enhanced spine MRI scans indicated part or complete remission after treatment.

**Conclusion:** In clinical practice, gumma should be considered for patients with intracranial lesions and positive serum syphilis antibodies. Timely and accurate diagnosis would enable patients with gumma to achieve a more favorable prognosis through active anti-syphilis treatment.

**Keywords:** neurosyphilis, gumma, enhanced MRI, cerebrospinal fluid

## Introduction

Syphilitic gumma was an extremely rare condition, especially in the context of modern medical advancements.<sup>1,2</sup> However, with the recurrence of syphilis in recent years, there has been an increase in case reports of syphilitic gumma. The global prevalence of syphilis ranges between 18 and 36 million cases with an incidence of 5.6–11 million new cases every year in adults according to WHO research.<sup>3</sup> Syphilitic gumma was often misdiagnosed as a central nervous system tumor, which requires clinicians to maintain high vigilance during diagnosis.<sup>4,5</sup> Accurate preoperative diagnosis of syphilitic gumma through routine magnetic resonance imaging (MRI) was challenging.<sup>6,7</sup> Additionally, syphilitic gumma rarely presented in multiple manifestations in the central nervous system and typically required serological and cerebrospinal fluid tests for confirmation, with good prognosis achieved through penicillin treatment.<sup>8</sup>



A diagnosis of syphilitic gumma requires a combination of various diagnostic tools and methods, especially when imaging results are inconclusive. Clinicians should consider the possibility of syphilitic gumma to avoid unnecessary surgical intervention and ensure that patients receive timely and appropriate treatment.

## Methods

### Participants

We conducted a retrospective review of patient records at Department of Neurology, Beijing Ditan Hospital from January 2021 to June 2024. This study was approved by the ethics committee of Beijing Ditan Hospital, Capital Medical University, Beijing, China (approval DTQH201607), and written informed consent was obtained from all participants and their immediate family members.

### Diagnostic Criteria

All neurosyphilis patients had positive serum toluidine red unheated serum test (TRUST), rapid plasma regain (RPR), and treponema pallidum particle agglutination (TPPA) results. All enrolled individuals met the European guidelines<sup>9</sup> and those of the US Centers for Disease Control.<sup>10</sup> The criteria included positive serologies and at any stage meeting to one of two conditions in the cerebrospinal fluid (CSF): (1) TRUST- or RPR-positive; (2) TPPA or fluorescent treponemal antibody absorption (FTA-ABS)-positive with elevated CSF leukocyte count (>5 cells/ $\mu$ L) and/or elevated CSF protein concentration (>45 mg/dL).<sup>11</sup> Patients were excluded if they had infections or tumors.

### Statistical Analyses

Statistical analyses were conducted using SPSS Statistics 25.0 (IBM Corporation, New York, USA). Continuous variables are shown as medians (minimum–maximum) and categorical variables as frequencies and percentages.

## Results

### Frequency of Gumma in Neurosyphilis Patients

In 397 neurosyphilis patients, seven (1.8%) had gumma from January 2021 to June 2024. Among these, four cases (57.1%) had intracranial syphilitic gumma, with the other three (42.9%) having spinal syphilitic gumma (Table 1).

**Table 1** Demographic information of neurosyphilis patients with gumma

	Patients	Median (range)
Male, n (%)	2 (28.6%)	
Female, n (%)	5 (71.4%)	
Age, years		56 (46–70)
Age of onset, years		54 (45–66)
Disease duration, months		23 (5–60)
Intracranial syphilitic gumma	4 (57.1%)	
Spinal syphilitic gumma	3 (42.9%)	
Anti-HIV positivity	0	
HBsAg positivity	0	
Anti-HCV positivity	0	
CD4 count <350 cells/mm <sup>3</sup>	0	

**Abbreviations:** HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

## Detailed Clinical Forms of Neurosyphilis Patients with Gumma

Demographic variables, including sex, age, age of onset, disease duration, etc., are described in Table 1. Of the seven neurosyphilis patients with gumma, two (28.6%) were male. Patients' age ranged from 46 to 70 years, and the median symptom onset age was 56 years. Median age of onset was 54 years, and disease duration was 23 months. All patients experienced symptoms of unilateral limb weakness or numbness, two patients displayed varying degrees of headache symptoms, three patients exhibited memory deterioration, and three patients manifested lightning pain (Table 2).

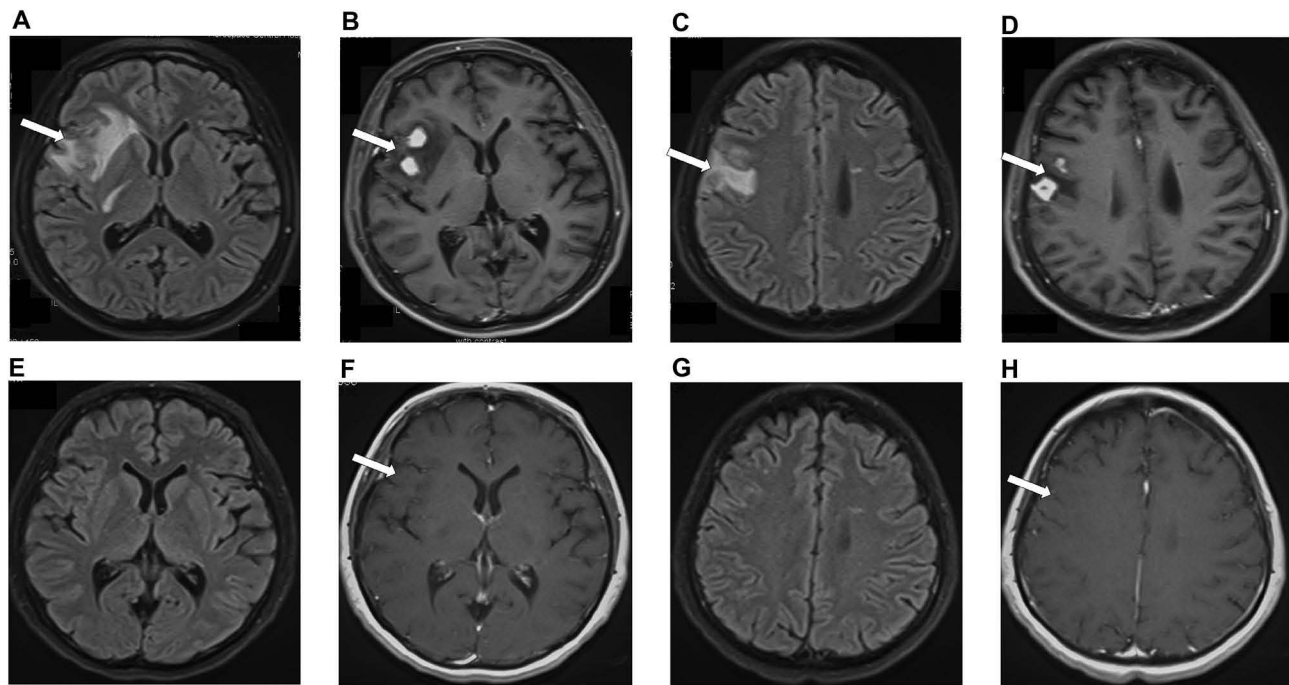
## MRI Features and Histopathology of Neurosyphilis Patients with Gumma

All patients had had MRI examinations performed after the confirmation of neurosyphilis. The following MRI sequences were included for the brain and spinal MRI examinations: axial T1-weighted imaging (T1WI), axial T2-weighted imaging (T2WI), fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and gadolinium-enhanced T1WI. Among the seven patients, four underwent enhanced MRI brain scans (Table 2), and their sagittal T1WI showed continuous nodule-like or partly high signal intensity (Figure 1). Three patients underwent enhanced cervical, thoracic, and lumbar spine MRI examinations (Table 2). In three patients, sagittal T1WI of the spinal cord showed nodule- or dotted-like enhancement of the cervical spine. Two of three patients had positive nodule- or dotted-like enhancement of the cervical and thoracic spine (Figure 2). Four neurosyphilis patients with intracranial syphilitic gumma had had surgical resections performed. Pathological sections displayed neuronal degeneration, proliferation of glial cells, and infiltration of lymphocytes (Figure 3).

**Table 2** Clinical features, MRI findings and histopathology of neurosyphilis patients with gumma

Case/age (years)/sex	Clinical symptoms	MRI Findings		Histopathology
		Lesion	Enhancement patterns	
1/48/F	Headache, weakness of limbs, memory deterioration	Temporal lobe, basal ganglia lacunar	Nodule-like	The pathological section showed partial brain tissue, characterized by neuronal degeneration and lymphocyte infiltration in small blood vessels, with the formation of basophilic bodies and vascular cannula and accompanied by the formation of vacuoles, nuclei of plasma cells, and the wide cytoplasm.
2/48/F	Headache, double vision, numbness	Pontine, frontal lobe, temporal lobe	Nodule-like	Glial cell proliferation, focal lymphocyte infiltration with perivascular lymphocyte intussusception.
3/51/M	Weakness of limbs, memory deterioration, psychological and behavior disorders, seizure	Temporal lobe, hippocampus, and thalamus	Partial enhancement	Mild proliferation of glial cells, neuronal degeneration, and infiltration of lymphocytes around amyloid-like small blood vessels in the interstitium.
4/62/F	Dizziness, weakness of limbs, memory deterioration	Frontal and temporal lobe	Nodule-like	Neuronal degeneration, glial and plasma cell proliferation.
5/54/M	Lightning pain, girdle sensation, numbness	Cervical and thoracic spine	Nodular and dotted-like	NA
6/70/F	Hypopsia, numbness, urinary incontinence, loss of balance, lightning pain	Cervical spine	Nodule-like	NA
7/46/F	Lightning pain, numbness	Cervical and thoracic spine	Nodule-like	NA

**Abbreviations:** F, female; M, male; NA, not applicable.



**Figure 1** Brain MRI scans of neurosyphilis patients with gumma showing nodule-like signal intensity. (A–C) Axial T2 fluid-attenuated inversion recovery (FLAIR) sequences showed high signal in frontal lobe (arrow). (B–D) Axial postgadolinium T1WI showing nodule-like enhancement (arrow). One year later, T2 FLAIR (E–G) showed no lesion recurrence, and nodule-like enhancement had decreased (F–H) (arrow).

## CSF Findings of Neurosyphilis Patients with Gumma

All seven patients had positive serum and CSF TPPA. Analysis of the serum and CSF is summarized in Table 3. Serum samples showed decreased levels of WBCs and protein in all these patients after therapy.

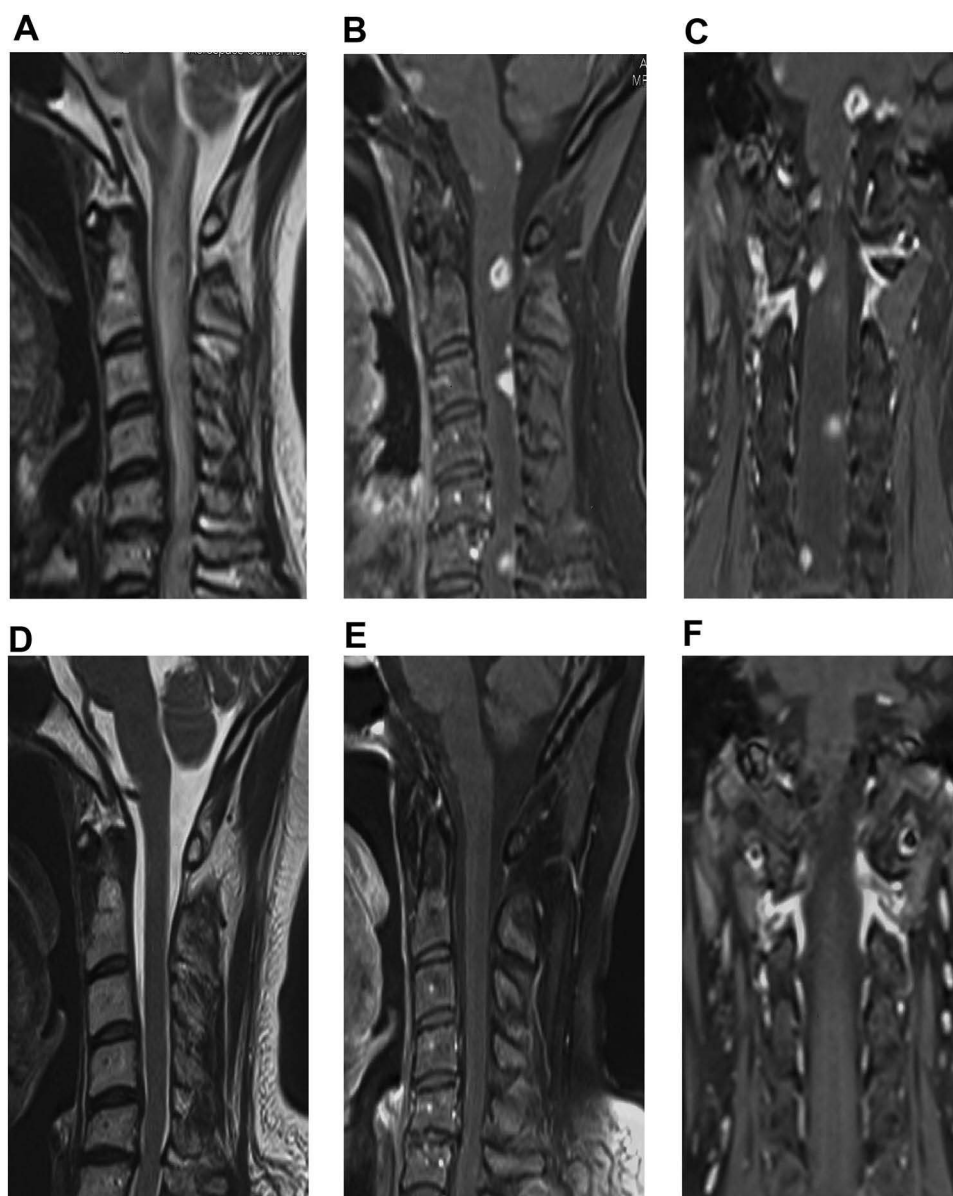
## Treatment Response and Outcomes of Neurosyphilis Patients with Gumma

The therapy plan comprised a total of 24,000,000 units of intravenously administered benzylpenicillin sodium for 10–14 days. In the next step, intramuscular injections of benzathine benzylpenicillin G were administered at a dosage of 2,400,000 U weekly three times (Table 4). All patients were followed up for 6 months to 1.5 years after therapy, and follow-up brain (Figures 1 and 4) and spine (Figure 2) enhanced MRI scans displayed part or complete remission after treatment.

## Discussion

### Frequency of Gumma

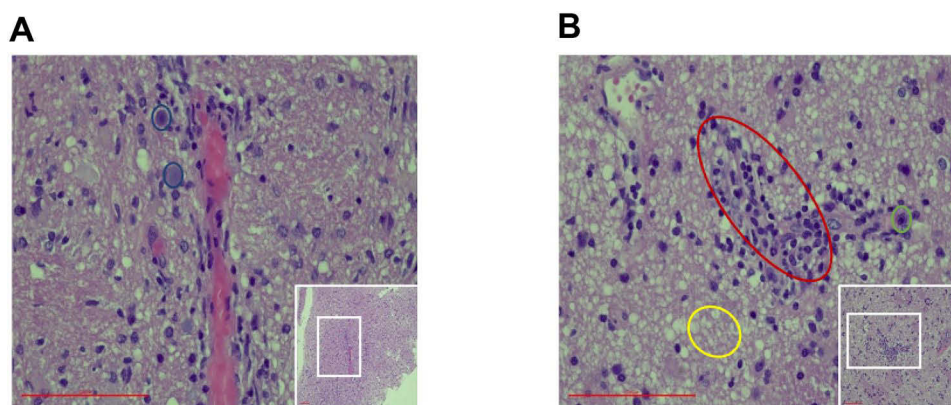
Cerebral syphilitic gumma occurs more than 10 years after contracting syphilis.<sup>12,13</sup> There have been few studies regarding the frequency or incidence of neurosyphilitic gumma.<sup>14</sup> In the 397 neurosyphilis patients recruited in this study, the frequency of gumma was 1.8%, higher than a previous study of gumma in intracranial tumors (0.2%).<sup>15</sup> The differences could be attributed to different subgroups of neurosyphilis patients instead of tumors. Drago et al found that gumma was rare, with 10 cases (3.5%) among a reviewed 286 reported cases of neurosyphilis.<sup>16</sup> Despite the presently low incidence of syphilitic gumma, it could be expected to increase in the future due to the high incidence of syphilis.<sup>17</sup> It is of significance to intervene in neurosyphilis and even broaden the focus to syphilis.



**Figure 2** Cervical spine MRI scan of neurosyphilis patients with gumma showing nodular or ring-like signal intensity in T1WI hyperintensity. **(A)** T2WI showed high signals in the cervical spine. **(B)** Sagittal T1-weighted images with fat suppression (T1WI FS) showed nodular or ring-like enhancement. **(C)** Coronal T1WI FS images showed nodule-like enhancement. **(D)** One year later, T2WI showed no lesion recurrence, and nodule-like enhancement had decreased in the cervical spine **(E and F)**.

## Clinical Forms, MRI Findings, and Histopathology of Neurosyphilis Patients with Gumma

In this study, 71.4% patients (five of seven) with gumma were female, a higher proportion than previous data.<sup>5,18</sup> These inconsistent results might be due to the small sample — we had only seven subjects. On the other hand, we speculated that female gumma patients were mostly infected by their male partners and had not been objectively or accurately assessed for a history of syphilis in some cases. These female neurosyphilis patients might postponed treatment such that they progressed to gumma. The number of patients coinfecting with syphilis and HIV has increased, due to destruction of the blood–brain barrier in the CNS and limitation of immune-cell movement.<sup>19,20</sup> Some studies have reported that HIV incidence increased to 20% a decade after syphilis diagnosis.<sup>21,22</sup> HIV-positive patients are more likely to have CNS gumma earlier than HIV-negative patients.<sup>23</sup> In this study, all enrolled gumma patients were HIV-negative, and their CD4



**Figure 3** Pathological characteristics of gumma (pathological sections enlarged version of white rectangular boxes). (A) Hematoxylin and eosin staining showing partial brain tissue characterized by neuronal degeneration and lymphocyte infiltration in small blood vessels, with the formation of basophilic bodies (blue circle) and vascular cannula (B, red circle), accompanied by (B) the formation of vacuoles (yellow circle), nuclei of plasma cells, and the wide cytoplasm (green circle). H&E;  $\times 200$  magnification.

count was  $>350$  cells/mm.<sup>3</sup> Accordingly, we should pay great attention to differences in susceptibility to gumma and CD4 count in HIV-negative patients and regular monitoring of HIV-positive patients.

The manifestations and signs of cerebral syphilitic gumma are aspecific and secondary to space occupation, size, and relationship to adjacent tissue.<sup>6,24</sup> These lesions can occur in different intracranial regions, such as the pituitary gland, cerebellum, and brain stem, etc.<sup>16,18,25</sup> These lesions occur most commonly found on the convex side of the brain and adhere to dura.<sup>16,25,26</sup> The distribution of lesions in our study predominantly involved the frontal and temporal lobe, similar to previous research.<sup>4,18</sup> In our research, the clinical presentations of patients were limb weakness, numbness, and memory deterioration, etc. Almost 28.6% (two of seven) patients had headache because of meningeal irritation. However, the clinical presentations of gumma were not distinctive features and were similar to other lesions of the nervous system, resulting in misdiagnosis. In clinical practice, we should pay careful attention to a history of unprotected sexual behavior, which significantly leads to diagnostic considerations for this disease.<sup>27</sup>

*T. pallidum* invades the central nervous system and causes a local inflammatory response of arteries or surrounding tissue at the cerebral dura mater or cerebral pia mater,<sup>6</sup> and is often misdiagnosed as tumors due to direct invasion into the parenchyma. Gumma lesions show low or isointensity on MRI T1WI and exhibit high signal intensity on MRI T2WI.<sup>27</sup> Most reported cases have shown ring enhancement and nodularity with a dural tail, which are associated with enhancement of the surrounding meninges<sup>4,24,26,28</sup> and areas of edema around the lesion. Some studies have reported that the margins of the lesion tended to form an obtuse angle with the surrounding meninges.<sup>28,29</sup> In our study, these lesions manifested with nodule- and dotted-like enhancement, mostly in the temporal and frontal lobes. As syphilitic gumma involves the meninges, it can cause meningeal thickening and fibrous tissue proliferation.<sup>30</sup> After treatment with penicillin G, the lesions in this study had reduced or disappeared on imaging (Figure 3).

**Table 3** Detailed biological data of neurosyphilis patients with gumma

Case/age (years)/sex	Blood TRUST <sup>a</sup>	TRUST <sup>b</sup>	CSF TRUST <sup>a</sup>	TRUST <sup>b</sup>	WBCs ( $\times 10^6/L$ ) <sup>a</sup>	WBCs ( $\times 10^6/L$ ) <sup>b</sup>	Protein (mg/dL) <sup>a</sup>	Protein (mg/dL) <sup>b</sup>
1/48/F	1:8	1:1	1:4	—	23	3	71.7	36.2
2/48/F	1:8	1:4	1:4	—	39	5	98.5	23.5
3/51/M	1:16	1:2	1:4	—	3	1	47.8	43.8
4/62/F	1:64	1:4	1:1	—	7	3	45.2	41.7
5/54/M	1:16	1:2	1:2	—	9	4	53.6	38.8
6/70/F	1:32	1:8	1:1	—	92	3	279.0	31.8
7/46/F	1:8	1:8	1:2	—	82	9	141.1	41.2

**Abbreviations:** F, female; M, male; <sup>a</sup>analysis at baseline; <sup>b</sup>repeat analysis after therapy.

**Table 4** Treatment and outcomes of neurosyphilis patients with gumma

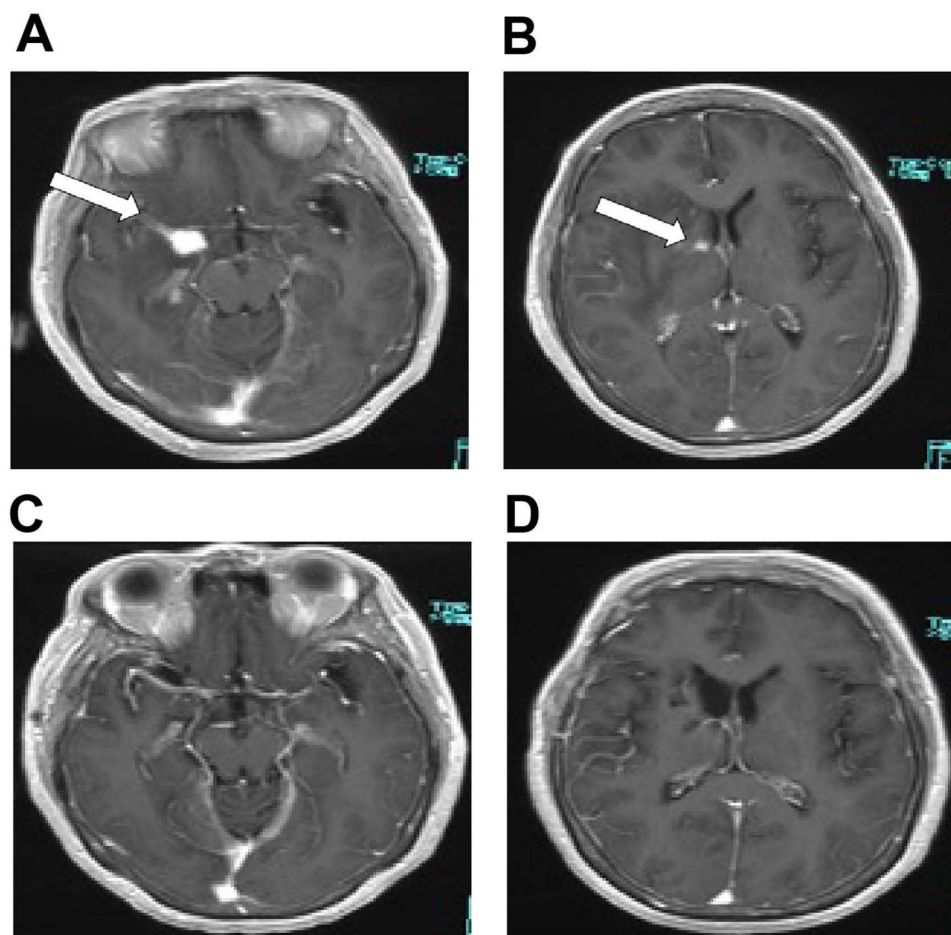
Case/age (years)/sex	Treatment	Outcome
1/48/F	Surgical resection and intravenous injections of penicillin G at a dosage of 24,000,000 U daily for 10–14 days, then IM benzathine penicillin G (2.4 million U QW) for 21 days, a total of 3 courses.	After 12 months: Headache and weakness of limb completely relieved; memory deterioration partially improved.
2/48/F	Surgical resection, doxycycline and intravenous injections of penicillin G at a dosage of 24,000,000 U daily for 10–14 days, then IM benzathine penicillin G (2.4 million U QW) for 21 days, a total of 2 courses.	After 12 months: Headache and double vision completely relieved; numbness partially improved.
3/51/M	Surgical resection and intravenous injections of penicillin G at a dosage of 24,000,000 U daily for 10–14 days, then IM benzathine penicillin G (2.4 million U QW) for 21 days, a total of 3 courses.	After 36 months: Seizure completely relieved; memory deterioration, psychological and behavior disorders partially improved.
4/62/F	Surgical resection and intravenous injections of penicillin G at a dosage of 24,000,000 U daily for 10–14 days, then IM benzathine penicillin G (2.4 million U QW) for 21 days, a total of 3 courses.	After 35 months: Dizziness and weakness of limbs completely relieved; memory deterioration partially improved.
5/54/M	Intravenous injections of penicillin G at a dosage of 24,000,000 U daily, for 10–14 days, then IM benzathine penicillin G (2.4 million U QW) for 21 days, a total of 2 courses.	After 12 months: completely relieved.
6/70/F	Intravenous injections of penicillin G at a dosage of 24,000,000 U daily for 10–14 days, then IM benzathine penicillin G (2.4 million U QW) for 21 days, a total of 5 courses.	After 36 months: Hypopsia, urinary incontinence, loss of balance, and lightning pain completely relieved; numbness partially improved.
7/46/F	Intravenous injections of penicillin G at a dosage of 24,000,000 U daily for 10–14 days, then IM benzathine penicillin G (2.4 million U QW) for 21 days, a total of 2 courses.	After 6 months: Lightning pain and numbness partially improved.

**Abbreviations:** F, female; M, male; IM, intramuscular; QW, quaque week.

However, these radiographic findings are similar to other intracranial space-occupying lesions, which remains a challenge in clinical practice.<sup>31,32</sup> Four cases in this cohort were misidentified as space-occupying lesions and underwent surgical resection. Histopathological staining was useful in the diagnosis of gumma.<sup>29</sup> In our study, the pathological characteristics exhibited proliferation of glial cells, neuronal degeneration, and infiltration of lymphocytes around small blood vessels, consistent with previous studies.<sup>29,33</sup> It was speculated that the mechanism might involve a hypersensitive reaction after *Treponema pallidum* entering the central nervous system that activated phagocytes to engulf vessels, resulting in inflammatory reactions and granulomatous lesions to the vessel, vascular collapse, and the development of obliterative arteritis or periarteritis.<sup>27,29</sup>

## Serological and CSF Analysis of Neurosyphilis with Gumma

In this study, we found that patients receiving penicillin G achieved higher serological responses and less treatment failure. Two of seven serum samples (28.6%) were male, and all patients had positive CSF TRUST results at baseline. During follow-up, our subjects received treatment with penicillin G. Four of seven serum samples (57.1%) achieved a fourfold decline, and all patients' CSF titers were negative with decreased CSF pleocytosis and protein concentrations. The main clinical features of our patients significantly improved, and the number of lesions on MRI findings was obviously reduced or vanished. Penicillin G is still the preferred therapy for neurosyphilis, as it might have potential synergistic effects by interfering with bacterial cell wall.<sup>34</sup> In the future, alternative drugs such as doxycycline, ceftriaxone, or erythromycin should be selected for patients who are allergic to penicillin.



**Figure 4** Brain MRI scans of neurosyphilis patients with gumma showing nodule-like signal intensity. Axial postgadolinium T1WI showing nodule-like enhancement in temporal horn and (A) basal ganglia (B) (arrow). Seven months later, nodule-like enhancement had decreased (C and D).

## Limitations

This investigation had limitations. Firstly, lumbar puncture was delayed in the elderly population, so the sample size was relatively insufficient. Secondly, the cross-sectional design hampered causal interpretation of our findings, and a prospective study is needed in the future. Thirdly, it was tough to unify the imaging parameters in our cases because of different field-strength MRI scanning. Furthermore, all our cases should have had high-field MRI performed to clarify the lesions.

## Conclusion

In this study, we focused patients with gumma, which is rare, atypical, and can be misdiagnosed as tumor. MRI may contribute to identifying these patients. The features of radiological findings in some cases were that the margins of the lesion tended to form an obtuse angle with ring or nodular enhancement. After correct diagnosis has been made, antisiphilitic treatment could be helpful to reverse the disease instead of surgical treatment.

## Data Sharing

The data are available from the first author upon reasonable request.

## Ethics Approval and Consent to Participate

This investigation's protocol was approved by the Ethics Review Board of Beijing Ditan Hospital, Capital Medical University. The procedures for this cross-sectional study were conducted in accordance with the Declaration of Helsinki on ethical principles for medical research involving human subjects.

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## Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no competing interests.

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