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When stroke is not stroke: cryptococcal meningitis presenting as progressive cerebral infarction in a patient with rheumatoid arthritis – a case report and literature review

Yihui Qiu
Guangdong Provincial People's Hospital
Tengyun Ma
Guangdong Provincial People's Hospital
Lijuan Wang
Guangdong Provincial People's Hospital
Jiehao Zhao
jiehao_zhao@163.com

Guangdong Provincial People's Hospital

Case Report

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Abstract

Background

Cryptococcal meningitis (CM) is a prevalent fungal infection of the central nervous system, particularly in immunocompromised hosts. Cerebral infarction, a well-recognized yet underappreciated severe complication, occurs in approximately 13% of CM cases, with a notably higher incidence observed in non-HIV populations than in those with HIV infection. Due to its frequently nonspecific clinical features, diagnosis and treatment are often delayed. Herein, we report a case of CM in which multiple cerebral infarctions constituted the predominant clinical manifestation, aiming to enhance clinicians' recognition of this atypical presentation.

Case presentation

A 66-year-old male with a history of rheumatoid arthritis(RA) presented with dizziness and headache initially diagnosed as "cerebral infarction" at another hospital. Despite standard secondary stroke prevention, his condition progressively worsened to gait instability, bilateral limb weakness, and neuropsychiatric abnormalities. Brain magnetic resonance imaging revealed newly developed infarctions in the bilateral basal ganglia, temporo-occipital lobes, and pons with meningeal enhancement. Cerebrospinal fluid analysis detected Cryptococcus neoformans by culture, next-generation sequencing, and positive cryptococcal antigen. The patient showed clinical improvement following antifungal therapy with amphotericin B, flucytosine, and fluconazole, though treatment was complicated by nephrotoxicity requiring regimen adjustment.

Conclusion

This case highlights that CM should be considered in immunocompromised patients presenting with cryptogenic multiple deep cerebral infarctions, particularly those involving the basal ganglia and posterior circulation with concomitant meningeal enhancement. Early cerebrospinal fluid examination is crucial for timely diagnosis and intervention.

Introduction

Cryptococcal meningitis (CM) is the most common fungal infection of the central nervous system (CNS), caused predominantly by Cryptococcus neoformans or Cryptococcus gattii[1]. While CM typically affects immunocompromised individuals, including those with HIV infection, organ transplantation, or corticosteroid therapy, it can also occur in apparently immunocompetent hosts[2]. The clinical presentation of CM is often nonspecific, with headache, fever, and altered mental status being the most common manifestations[1].

Cerebral infarction is a well-recognized but underappreciated severe complication of CM, occurring in approximately 13% of patients[3]. Mishra et al. demonstrated that compared to patients without infarcts,

those CM with infarcts had a 50% higher incidence of poor outcomes and double the mortality. Interestingly, the incidence of CM-associated infarction is higher in non-HIV populations compared to HIV-infected individuals (78% vs. 22% in one series)[3].

The non-specificity of clinical symptoms frequently poses a significant diagnostic challenge, consequently delaying therapeutic intervention and contributing to increased mortality. Herein, we report a case of CM presenting with progressive multiple cerebral infarctions in a patient with rheumatoid arthritis(RA) and suspected long-term use of corticosteroid-containing health supplements. This case highlights the diagnostic challenges when fungal infection mimics atherosclerotic stroke and underscores the importance of considering opportunistic infections in immunocompromised patients with cryptogenic cerebral infarction.

Case Report

Clinical Presentation

A 66-year-old man was admitted to our hospital on December 4, 2024, with a 3-month history of dizziness and a 10-day history of worsening symptoms with left-sided limb weakness.

In September 2024, the patient experienced sudden onset dizziness with rotational vertigo, accompanied by right frontal electric shock-like pain and nausea. Each episode lasted approximately 20 minutes and resolved spontaneously. Subsequently, he developed persistent head heaviness with intermittent right frontal drilling pain lasting several minutes. On October 21, 2024, he experienced another similar episode. Brain magnetic resonance imaging (MRI) at a primary hospital revealed multiple ischemic foci in the bilateral basal ganglia, temporal, and parietal lobes (Fig. 1a-c). Magnetic resonance angiography (MRA) showed no abnormalities. He was started on secondary stroke prevention with clopidogrel and atorvastatin, along with neurotrophic therapy, but his dizziness and headache persisted.

On November 6, 2024, he acutely developed gait instability with right-sided limb weakness. Diffusion weighted imaging (DWI) demonstrated an acute infarction involving the left posterior limb of the internal capsule. (Fig. 2a1-a3). Despite continued secondary prevention and rehabilitation, his right-sided weakness progressed. Follow-up DWI revealed enlargement of the left basal ganglia infarction with extension into the putamen and corona radiata, along with a new infarct in the insular lobe. (Fig. 2b1-b3). Accordingly, aspirin was added to his antiplatelet regimen.

On November 27, 2024, family members noted new-onset left-sided limb weakness that rendered him unable to walk, accompanied by mutism, paranoia (believing cameras were watching him), and refusal to eat, though he still recognized family members. Consequently, he was referred to our hospital. Throughout his illness, the patient remained afebrile. He exhibited poor appetite, weight loss (exact amount unspecified), and normal bowel and bladder function.

Medical History

The patient had a long-standing history of RA. Family members reported that he had been taking self-prescribed "health supplements" (powder form) for pain relief, which were suspected to contain corticosteroids. He had no history of hypertension, diabetes mellitus, or hyperlipidemia, and denied smoking or alcohol consumption. His father had a history of cerebral infarction.

Physical Examination

On admission, vital signs revealed a temperature of 37.6°C. Neurological examination showed an alert but apathetic patient with impaired comprehension, judgment, calculation, and orientation. Pupils were equal and reactive to light without gaze palsy. Cranial nerve examination revealed left nasolabial fold flattening, preserved gag reflex, and choking with swallowing. Motor examination demonstrated bilateral upper extremity weakness (grade 4/5), right lower extremity weakness (grade 3/5), and left lower extremity weakness (grade 2/5). Left Babinski sign was present. Nuchal rigidity was noted, while Kernig and Brudzinski signs were negative. The remainder of the examination was limited by poor cooperation.

Laboratory Findings

Laboratory investigations revealed: white blood cell count 10.3 × 10^9/L (elevated), hemoglobin 87 g/L (decreased), platelet count 292 × 10^9/L, neutrophil ratio 0.787 (elevated), D-dimer 2790 ng/mL (elevated), erythrocyte sedimentation rate 91 mm/h (elevated), interleukin-6 24.0 pg/mL (elevated), C-reactive protein 33.44 mg/L (elevated), and procalcitonin 0.050 ng/mL (elevated). Whole blood T-SPOT.TB was positive (antigen well spot count 12, exceeding the positive threshold of 11). Rheumatoid factor was markedly elevated at 672.8 IU/mL, and anti-cyclic citrullinated peptide antibody was > 500 U/mL (both elevated). Liver and renal function tests, cardiac enzymes, coagulation parameters, tumor markers, HIV, and syphilis serology were unremarkable.

Cerebrospinal fluid (CSF) analysis showed: opening pressure 200 mmH_2O (elevated), white blood cell count 92 × 10^6/L (elevated) with 65% lymphocytes, glucose 1.30 mmol/L (decreased; simultaneous blood glucose 6.29 mmol/L), chloride 112.7 mmol/L (simultaneous blood chloride 96.0 mmol/L), and protein 1970 mg/L (elevated). CSF PCR for Mycobacterium tuberculosis was negative, while cryptococcal antigen was positive, and both culture and next-generation sequencing confirmed Cryptococcus neoformans (sequence count 718, 99% confidence).

Neuroimaging

MRI of the brain demonstrated disease progression. DWI revealed new areas of restricted diffusion involving the right putamen, right corona radiata, right pons, and left temporal lobe. Additionally, the pre-existing infarct in the left basal ganglia and corona radiata had further enlarged, with extension into the

genu of the internal capsule (Fig. 2c1-c3). With the right putamen as the region of interest, magnetic resonance spectroscopy (MRS) showed a decreased N-acetylaspartate (NAA) peak, an elevated lactate (Lac) peak with an inverted doublet, and a normal choline (Cho) peak, with NAA/Cr and Cho/Cr ratios of 1.28 and 1.03, respectively (Fig. 3). These findings were consistent with the progression of acute cerebral infarction. Contrast-enhanced T1-weighted imaging revealed meningeal enhancement(Fig. 4a-d). MR angiography (MRA) and MR venography (MRV) were unremarkable (Fig. 4e-f).

Additional Investigations

Chest computed tomography showed fibrotic lesions in the left upper lobe and mild bronchiectasis with chronic inflammation in both lower lobes. Wrist ultrasound revealed synovial thickening with bone erosion, consistent with RA.

Diagnosis and Treatment

The patient was diagnosed with: (1) CM with multiple cerebral infarctions; and (2) Rheumatoid arthritis.

Antifungal therapy was initiated with amphotericin B (0.5 mg/kg/day), flucytosine (100 mg/kg/day), and fluconazole (400 mg/day). After three weeks of treatment, the patient developed elevated serum creatinine, prompting discontinuation of amphotericin B and adjustment of fluconazole to 600 mg/day. Follow-up CSF analysis on January 26, 2025, showed improvement: opening pressure 160 mmH_2O, white blood cell count 4 × 10^6/L, glucose 3.04 mmol/L (decreased; simultaneous blood glucose 6.60 mmol/L), chloride 128.3 mmol/L (simultaneous blood chloride 104.1 mmol/L), and protein 892 mg/L (elevated).

The patient's hospital course was complicated by gastrointestinal bleeding, pulmonary infection, and respiratory failure, requiring intensive care unit admission. Due to financial constraints, the family requested transfer to a local hospital for continued care.

Discussion

CM complicated by cerebral infarction is a severe complication in immunocompromised patients[3]. In this case, the patient initially presented without the classic acute symptoms of CM, subsequently manifesting with progressive stroke as the predominant clinical feature. This atypical presentation posed a diagnostic challenge and delayed the initiation of appropriate antifungal therapy.

The pathogenesis of cerebral infarction in CM involves multiple interconnected mechanisms. First, the patient's underlying immune compromise represents the critical foundation upon which disseminated infection developed. Two interconnected factors contributed to this susceptibility: the autoimmune disease itself (the patient has a history of RA) and, more significantly, suspected long-term use of corticosteroid-containing health supplements. Corticosteroid use has been reported in 17.5% – 28% of HIV-negative patients with CM and represents a significant risk factor by impairing cell-mediated

immunity[4, 5]. Glucocorticoids suppress T lymphocyte proliferation, reduce pro-inflammatory cytokine production, and impair macrophage phagocytic activity, thereby creating favorable conditions for fungal dissemination to the central nervous system. Importantly, the patient's underlying RA may independently contribute to susceptibility. Williamson et al. note associations between cryptococcosis and various autoimmune diseases including systemic lupus erythematosus, dermatomyositis, and ankylosing spondylitis [1, 6]. The markedly elevated rheumatoid factor (672.8 IU/mL) and anti-CCP antibodies (> 500 U/mL) confirm active autoimmune disease. The Th17/IL-17 axis is vital for immunity to fungi. Accumulating evidence suggests that patients with RA exhibit functional defects in Th17-mediated immunity, characterized by an impaired antigen-specific response to fungi. Thus, the inherent Th17 functional deficits in RA, combined with the immunosuppressive effects of therapeutic agents such as corticosteroids, may collectively create a permissive immunological environment that facilitates the proliferation of Cryptococcus neoformans[7].

Once this permissive immunological environment is established, Cryptococcus neoformans is able to disseminates from the basal cisterns through Virchow-Robin spaces to the basal ganglia, internal capsule, and brainstem, where perivascular accumulation causes inflammatory infiltration, endothelial injury, and small vessel occlusion[3, 8]. Concurrently, direct fungal invasion of arterial walls and strangulation of vessels by basal exudates may induce vasculitis, vasospasm, and thrombosis, culminating in cerebral infarction[9]. Notably, non-HIV patients with CM have a higher risk of cerebral infarction compared to HIV-infected individuals[3, 10]. This paradox may reflect an exaggerated host inflammatory response in immunocompetent patients, leading to more severe vasculitis and thrombosis. In our patient, markedly elevated D-dimer levels (2790 ng/mL) suggested a hypercoagulable state contributing to thrombus formation, consistent with the vascular inflammatory mechanism described by Mishra et al.[3]. The absence of traditional vascular risk factors and normal MRA further supported an infectious rather than atherosclerotic etiology.

Tuberculous meningitis (TBM) also frequently occurs in immunocompromised patients. Its clinical manifestations and routine CSF profiles are similar to those of CM, and it is also commonly complicated by cerebral infarction[11]. Infarction in TBM results from basal exudates causing strangulation of perforating arteries, predominantly affecting the thalamus, anterior limb of internal capsule, and cerebral lobes[10, 12]. CM-associated infarcts show a predilection for deep nuclear structures and posterior circulation territories. In a comparative study by Kumar et al.[10], 54.5% of CM patients developed cerebral infarctions, with caudate head (41.7% vs. 9.4%, p = 0.01) and cerebellar (33.3% vs. 9.4%, p = 0.05) involvement significantly more common in CM than in TBM. Basal ganglia (41.7%) and corona radiata (66.7%) were also frequently involved. Lan et al. [9]reported infarctions in 32% of CM patients, predominantly in the basal ganglia and internal capsule. Our patient's neuroimaging findings align with these patterns, showing acute infarctions in the bilateral basal ganglia, corona radiata, and pons—the latter representing posterior circulation involvement characteristic of CM. The initial symptom of vertigo may have reflected brainstem/cerebellar ischemia, though early imaging did not capture these lesions.

In this patient, the clinical presentation of weight loss with recurrent afternoon fevers, along with a positive T-SPOT.TB result, initially raised suspicion for TBM co-infection. However, TBM was ultimately ruled out by two key findings: an infarction pattern involving the pons and basal ganglia without thalamic involvement, and negative CSF results for M. tuberculosis by PCR, culture, and next-generation sequencing. It is particularly noteworthy that T-SPOT.TB, an interferon-gamma(IFN-γ) release assay (IGRA), is an important tool for detecting tuberculosis infection[13]; however, false-positive results may occur in the setting of cryptococcal infection. The underlying mechanism may involve the activation of T lymphocytes by Cryptococcus neoformans, leading to increased IFN-γ release[14, 15]. This finding suggests that positive T-SPOT.TB results in the context of cryptococcal infection should be interpreted with caution and must be evaluated in conjunction with direct pathogen evidence.

Current ECMM/ISHAM global guidelines for the management of cryptococcosis outline a standard three-phase regimen. Induction therapy consists of at least 2 weeks of high-dose amphotericin B (0.7–1.0 mg/kg/day) combined with flucytosine (100 mg/kg/day) for rapid CSF sterilization. This is followed by an 8-week consolidation phase with high-dose fluconazole (400–800 mg/day) monotherapy, and subsequently, low-dose fluconazole (200 mg/day) maintenance therapy to prevent relapse until immune reconstitution is achieved with ART[16]. In a cohort study from China, the triple regimen of amphotericin B + flucytosine + fluconazole resulted in a superior 2-week CSF sterilization rate relative to amphotericin B + flucytosine alone (75.9% vs. 69.2%). Notably, within the amphotericin B + flucytosine ± fluconazole regimen, a lower amphotericin B dose (0.4–0.5 mg/kg/day) not only reduced the frequency of adverse effects but also yielded clinical efficacy comparable to that of the conventional 0.6–0.7 mg/kg/day dose [17]. Accordingly, our patient received induction therapy with amphotericin B (0.5 mg/kg/day), flucytosine (100 mg/kg/day), and fluconazole (400 mg/day). When renal dysfunction was identified on monitoring, a timely switch to high-dose fluconazole (600 mg/day) was implemented, achieving a balance between treatment efficacy and safety.

Clinical Implications

This case offers several important lessons for clinicians:

1. In immunocompromised patients presenting with cryptogenic multiple deep cerebral infarctions, particularly involving the basal ganglia and posterior circulation with concomitant meningeal enhancement, CM should be included in the differential diagnosis.
2. The absence of traditional vascular risk factors and normal MRA does not exclude stroke—infectious vasculopathies should be considered.
3. Positive T-SPOT.TB in suspected CM patients may represent false-positive results from fungal-induced IFN-γ release and requires confirmation with CSF direct pathogen detection.
4. Early CSF examination including cryptococcal antigen, culture, and next-generation sequencing is essential for timely diagnosis and treatment initiation.
5. Close monitoring for amphotericin B-associated nephrotoxicity is mandatory, with prompt regimen adjustment when indicated.

Conclusion

CM with cerebral infarction is a severe complication in immunocompromised patients that can mimic atherosclerotic stroke. The characteristic infarction pattern involves the basal ganglia, corona radiata, and posterior circulation territories. Clinicians should maintain a high index of suspicion for opportunistic fungal infections in patients with cryptogenic cerebral infarctions, particularly those with risk factors for immunosuppression. Early diagnosis through CSF analysis and prompt initiation of antifungal therapy are essential for improving outcomes in this devastating condition.

Declarations

Ethics approval and consent to participate

Not applicable.

Clinical trial number

Not applicable.

Consent for publication

Written informed consent was obtained from the legal guardians for the anonymized information to be published in this article.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there is no conflict of interest.

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Author contributions

Yi-Hui Qiu: Clinical data acquisition, analysis, and interpretation; manuscript drafting and revision.

Teng-Yun Ma: Clinical data acquisition; patient follow-up and outcome assessment; literature review.

Li-Juan Wang: Critical manuscript revision; study coordination; funding acquisition.
Jie-Hao Zhao: Conceptualization, study design, data acquisition, analysis, and interpretation; manuscript

drafting and revision; study supervision; final approval.

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Figures

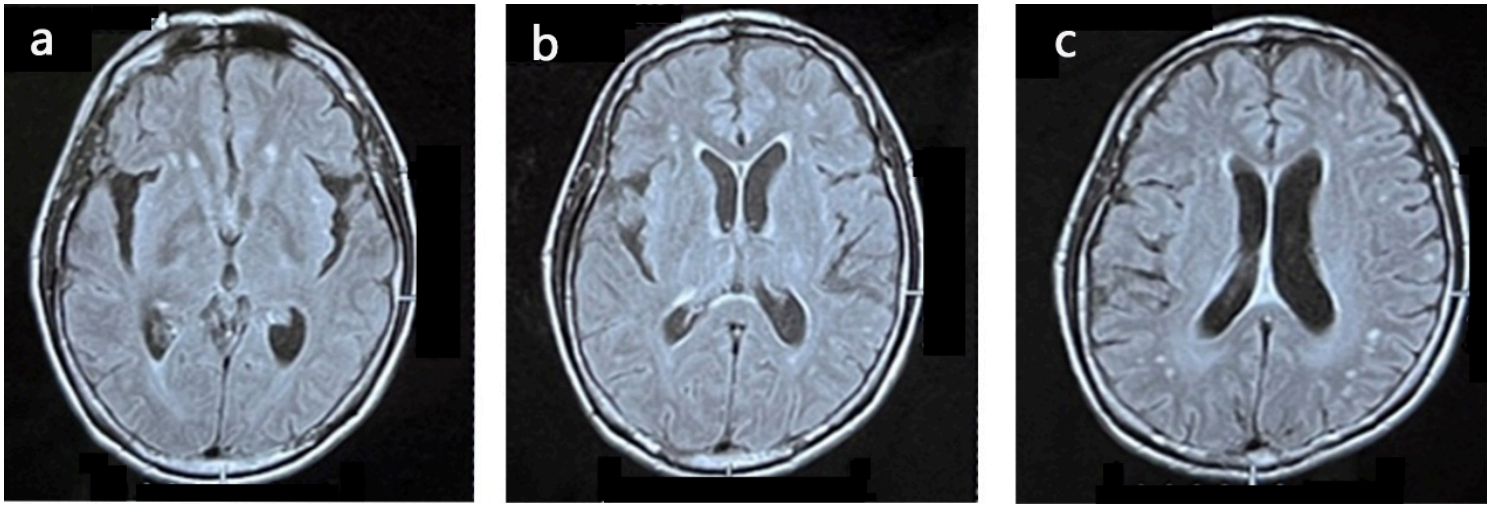


Figure 1

Cranial MRI scanning of the patient. (a-c) High t2-FLAIr signal in the bilateral basal ganglia, temporal, and parietal lobes by transection plane scan. Abbreviations: *MRI,* magnetic resonance imaging; *FLAIR,* fluid-attenuated inversion-recovery sequence.

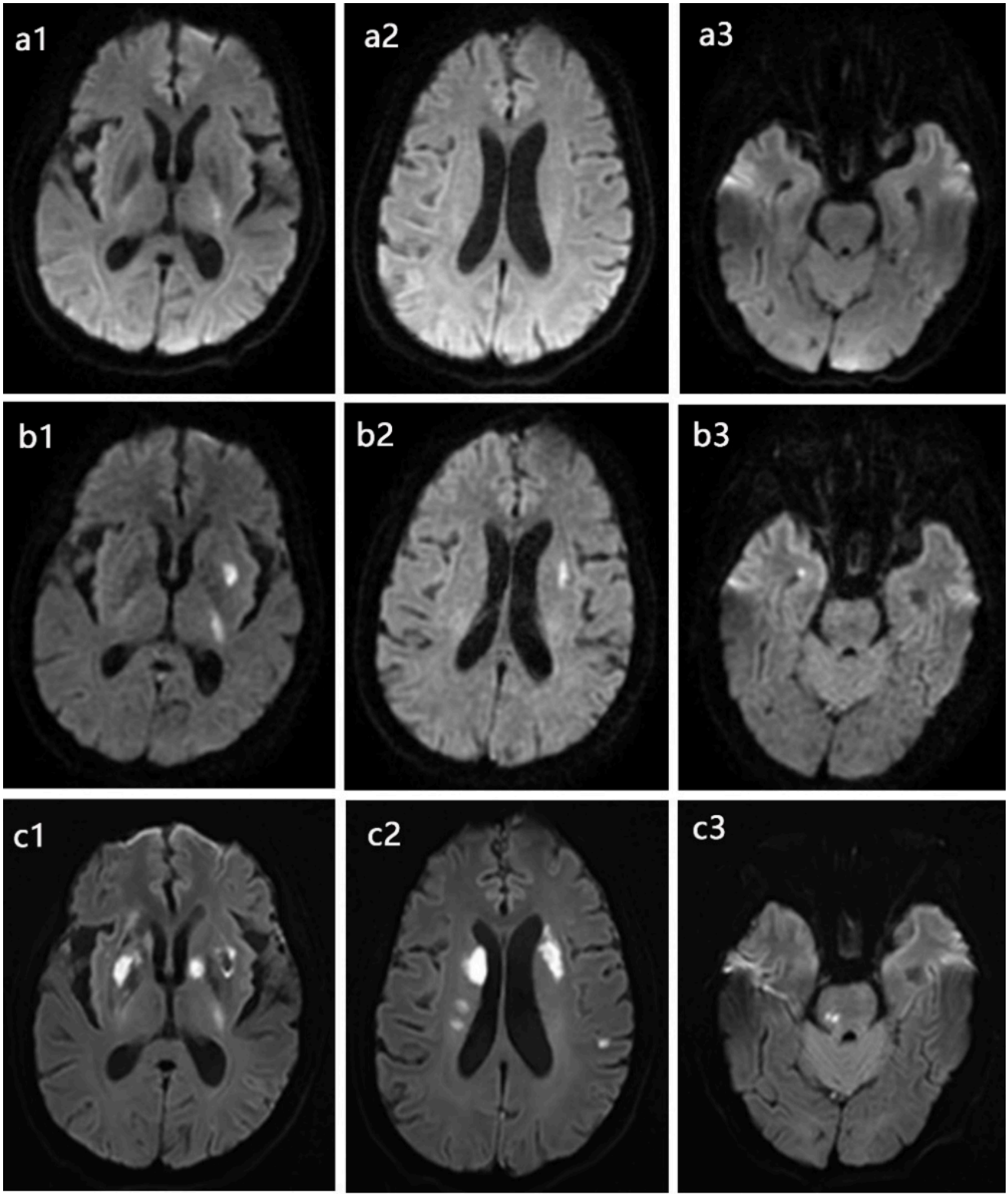


Figure 2

Serial DWI findings. (a1-a3) Initial DWI shows restricted diffusion in the left posterior limb of the internal capsule, indicating acute infarction. (b1-b3) Follow-up DWI demonstrates enlargement of the left basal ganglia infarct with extension into the putamen and corona radiata, along with a new infarct in the insular lobe. (c1-c3) Subsequent DWI reveals additional areas of restricted diffusion in the right putamen, right

corona radiata, right pons, and left temporal lobe; the prior left basal ganglia infarct has further enlarged, now involving the genu of the internal capsule.

Abbreviations: *DWI,* diffusion-weighted imaging.

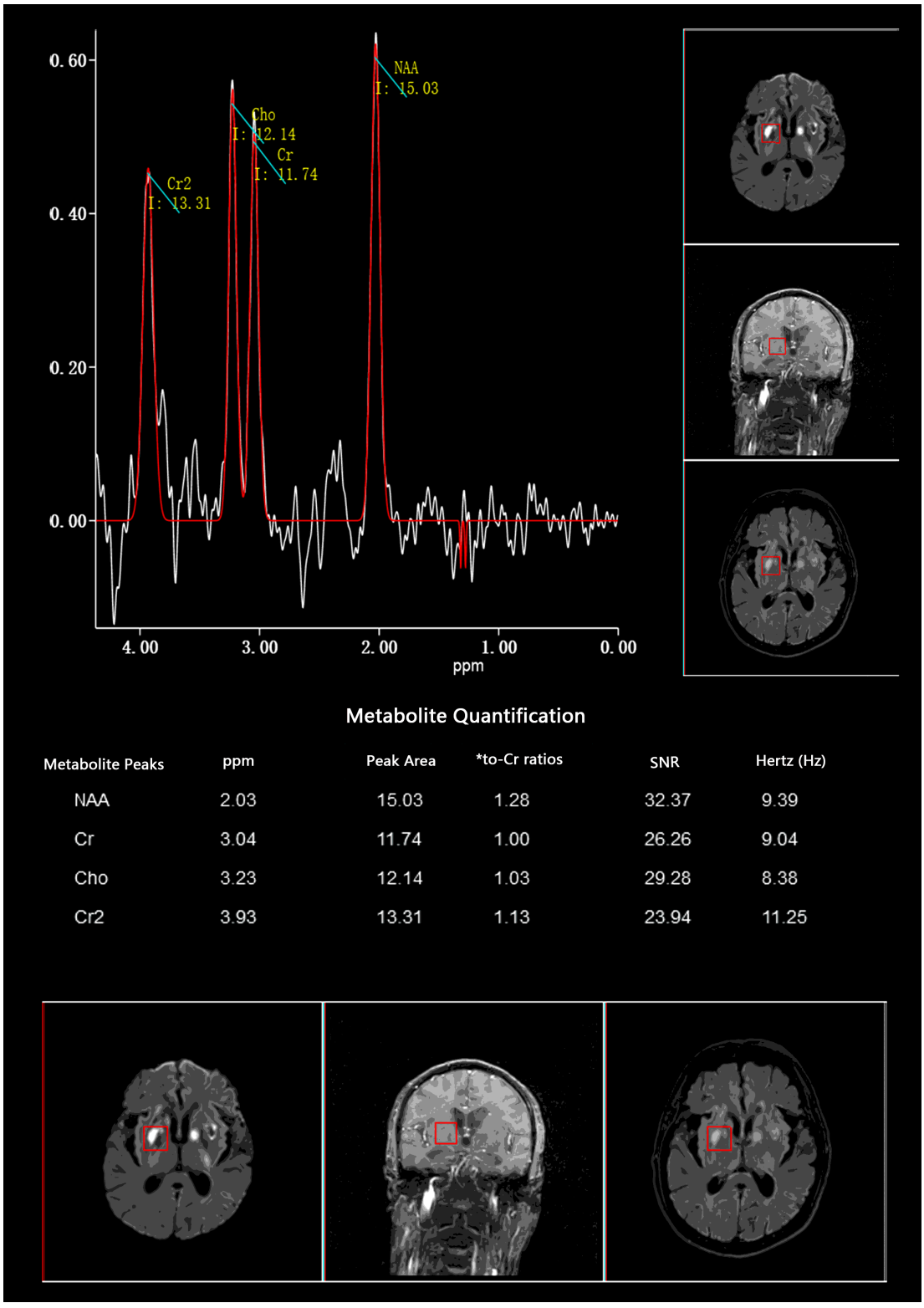


Figure 3

MRS scanning of the patient. MRS with the right putamen as the region of interest demonstrates a decreased NAA peak, an elevated Lac doublet, with NAA/Cr = 1.28 and Cho/Cr = 1.03, confirming acute infarction.

Abbreviations: *MRS,* Magnetic resonance spectroscopy; *NAA,* N-acetylaspartate; *Lac,* lactate; *Cho,*choline; *Cr,* creatine.

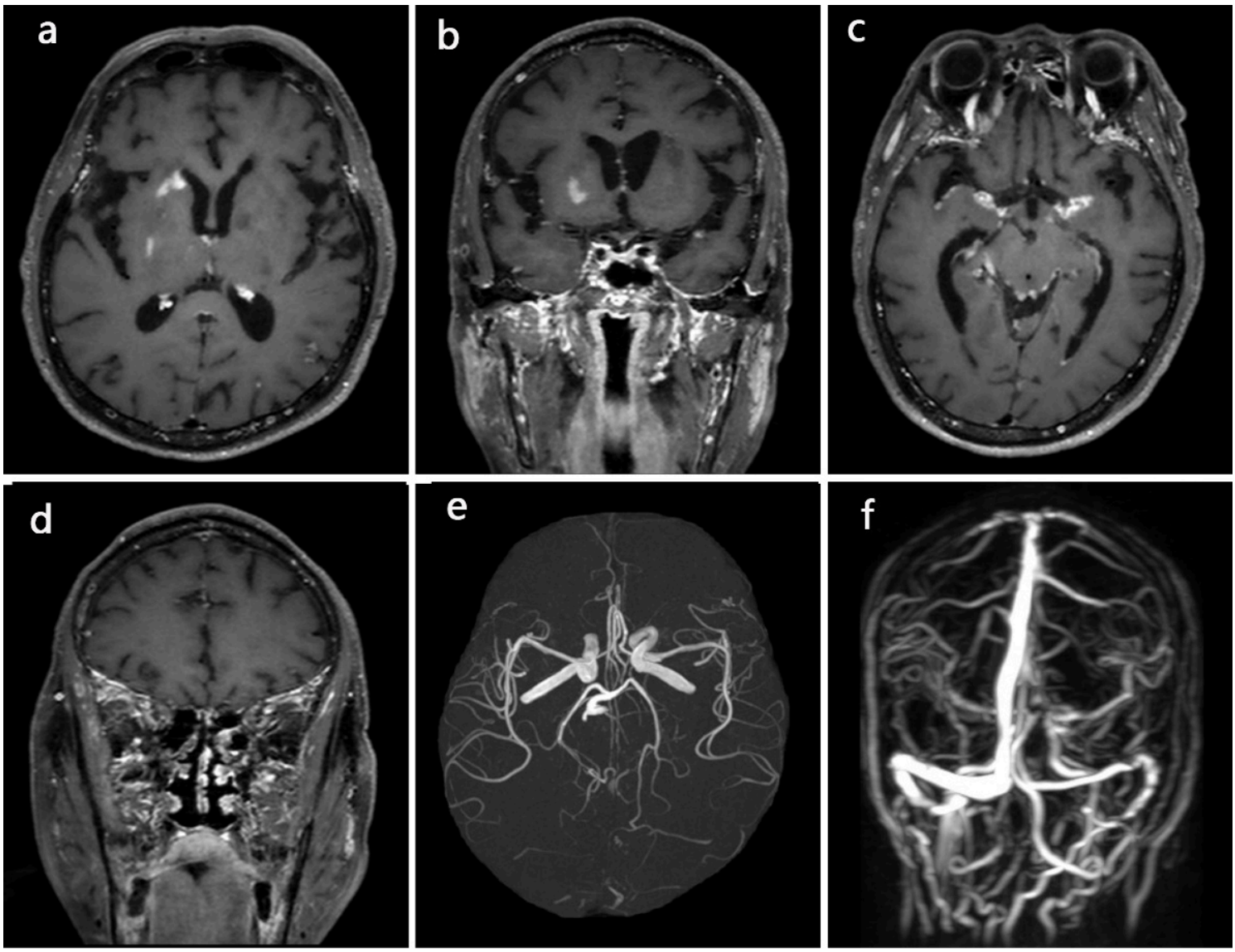


Figure 4

Contrast-enhanced imaging and MRA/MRV. Contrast-enhanced T1-weighted imaging(a-d) demonstrates meningeal enhancement. MRA(e) and MRV(f) were unremarkable.

Abbreviations: *MRA,* magnetic resonance angiography; *MRV,* magnetic resonance venography.