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## Case Report

# Acute central nervous system vasculitis as a manifestation of neurosarcoidosis: A case report and literature review ☆,☆☆

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## ABSTRACT

Neurosarcoidosis (NS) affects various sites of the central nervous system, including the cranial nerve, meninges, brain parenchyma, hypothalamus, and pituitary gland. NS rarely causes intracerebral vasculitis and subsequent strokes, or cerebral infarction and hemorrhage, which are associated with high mortality. Herein, we report a 71-year-old woman's case of stroke associated with NS, which showed aggressive cerebral vasculitis with brain herniation; it was resolved with corticosteroid therapy after accurate histopathological diagnosis. This case highlights the necessity of expecting NS to sometimes follow an aggressive course, presenting with vasculitis. Most patients with NS satisfactorily respond to corticosteroids, but this is not always the case. In cases of unfamiliar ischemic or hemorrhagic lesions, the possibility of NS must be considered.

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## Introduction

Sarcoidosis is a very rare disease affecting 0.01%–0.02% of the global population, and the infrequent event of sarcoidosis affecting solely the central nervous system (CNS) is defined as an isolated neurosarcoidosis (INS) [1–3]. INS usually

progresses slowly and exhibits a variety of clinical manifestations, making timely, and transparent diagnosis difficult in most cases [2,4,5]. Herein, we describe the case of a 71-year-old woman presenting with atypical INS radiological images and clinical course. The patient's INS involved the entire bilateral cerebral hemisphere with manifestation of aggressive acute cerebral vasculitis. She was successfully treated with corti-

☆ Competing interest: The authors have no competing interest to report.

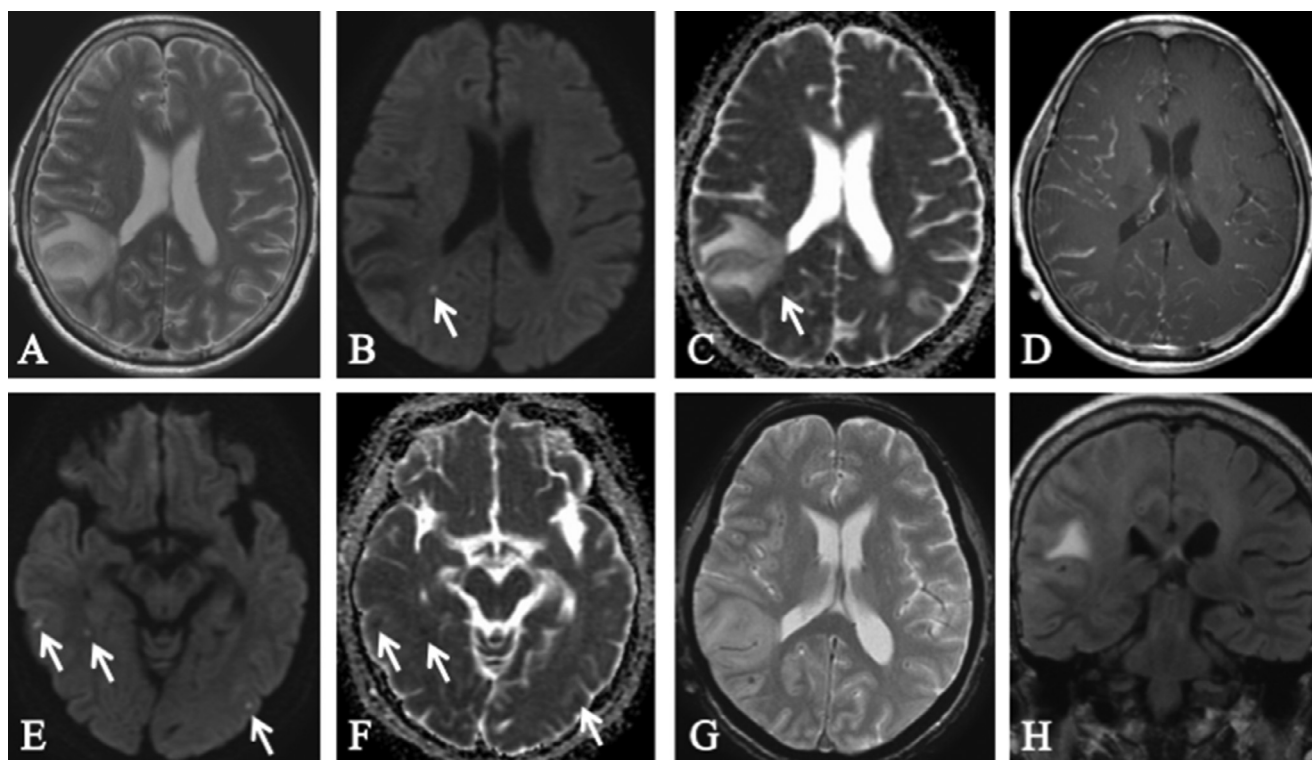
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**Fig. 1** – MRI revealing hyperintensity on T2-weighted images in the right parietal subcortical white matter (A). The lesion showing hypointensity in DWI and increased ADC, reflecting vasogenic edema (B, C). Parenchymal enhancement is not observed, however, leptomeningeal enhancement is noted predominantly in the right convexity (D). DWI images likewise showing multiple hyperintense spots (arrow) in the bilateral cerebral hemisphere with decreased ADC, suggesting acute infarction (E, F). T2 star images showed no hypointense spot, suggesting microhemorrhage (G). Fluid-attenuated inversion-recover (FLAIR) coronal images showing the edematous parietal lesion with no herniation (H).

costeroids after 2 biopsy surgeries. On rare occasions, patients with INS present with cerebrovascular manifestations, such as aggressive vasculitis, that affect the entire brain parenchyma, and such cases have rarely been described in the literature [1,6–11]. Herein, we present such a case report and summarize similar past reports.

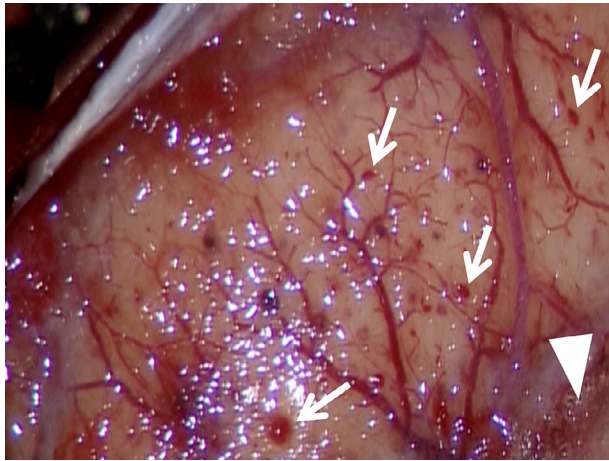
## Case presentation

A 71-year-old woman with a 19-day history of headache, 10-day history of nausea, and left-hand numbness presented at our hospital. Neurological examinations revealed a mildly disturbed consciousness, scoring 14 on the Glasgow Coma Scale (GCS), dysesthesia of all left fingers, and left homonymous hemianopia. Computed tomography (CT) showed a 3-cm lesion in the right parietal lobe. Magnetic resonance imaging (MRI) demonstrated hyperintensity on T2-weighted images in the right parietal subcortical white matter. This area also showed hypointensity on diffusion weighted images (DWI) and increased apparent diffusion coefficient (ADC), implying angioedema. The lesion was not noted in gadolinium enhancement; however, leptomeningeal enhancement revealed a lesion predominantly in the right convexity. DWI images showed multiple spots in the bilateral cerebral hemisphere,

suggesting diffuse acute small infarction across the entire brain parenchyma, but T2 star images showed no hemorrhage. (Fig. 1).

The patient had a medical history of dysthyroidism of Hashimoto's thyroiditis and was receiving thyroid hormone replacement therapy. Therefore, we associated these lesions with her endocrine system or immunity disorder. Endocrinological examinations showed no abnormal scores, except for low levels of free triiodothyronine and elevated levels of thyroid stimulating hormone in accordance with her Hashimoto's thyroiditis. Immunological examinations for antinuclear antibody showed an elevated anti-SS-A antibody score, and she was readily diagnosed with asymptomatic Sjögren's syndrome via lip biopsy. There were no abnormal lesions in her chest, abdomen, or pelvis CT scans, and radiological examination revealed no abnormal lesions apart from the one in her brain. The cerebrospinal fluid analysis showed xanthochromy, pleocytosis (160 leukocytes/mm<sup>3</sup>), elevated protein (371 mg/dL), and elevated levels of IgG index of 1.25.

The CSF culture was negative. Inflammation in blood and neck rigidity was not observed. Therefore, we excluded meningoencephalitis clinically. Based on the patient's clinical manifestations, radiological findings, and serum analysis, we narrowed down the differential diagnosis of the brain lesion to immunity-related vasculitis or neoplasm, such as malignant lymphoma. We conducted a brain biopsy to



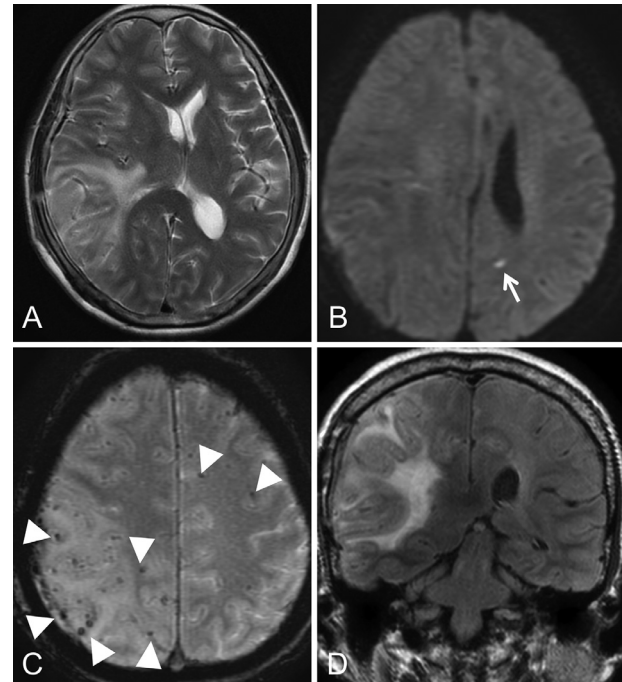
**Fig. 2 – Intraoperative photograph at first biopsy showing multiple small hemorrhages (arrow) around the excised tissue (arrowhead) on the brain surface.**

determine the diagnosis. During the surgery, multiple small hemorrhages were observed on the brain surface of the right parietal lobe (Fig. 2). We obtained an adequate sample from the brain parenchyma. Pathological examination revealed a cluster of inflammatory cells around the blood vessels, where lymphocytes were arranged and filled the vascular endothelium. Based on the pathological findings, malignant lymphoma was suspected. Additional immunohistochemistry examinations of the obtained brain tissue were performed, however, the lymphocytes did not show monoclonality, which would have provided a definitive diagnosis for malignant lymphoma.

One week postbiopsy, the patient's consciousness decreased to GCS 8. MRI revealed exacerbation of the brain lesion in the right parietal lobe. Although we could not decide on a definitive diagnosis, we started administration of betamethasone. Her consciousness level improved immediately up to GCS 13, and we decreased the amount of betamethasone gradually. However, the clinical improvement was transient, and the lesion in the parietal lobe showed enlargement in the imaging studies, indicating impending brain herniation (Fig. 3).

We had 2 possible treatment options at this point: one, chemotherapy based on a nondefinitive diagnosis of malignant lymphoma, or two, a second biopsy to reach an accurate diagnosis. We chose to conduct an immediate second brain biopsy. The pathological examinations revealed aggregating multinucleated giant cells with neutrophils, lymphocytes, eosinophils, plasma cells, and other inflammatory cells around blood vessels; thereafter, the patient was diagnosed with INS (Fig. 4).

Subsequently, we initiated administration of methylprednisolone 1000 mg/day. The patient's consciousness level improved immediately, to GCS 15, and then the dose was gradually decreased to prednisolone 45 mg/day. Her neurological condition continued to improve, and these improvements were reflected in her radiological examinations. She was discharged from our hospital with a modified Rankin Score of 1, while continuing internal use of prednisolone 20 mg/day.

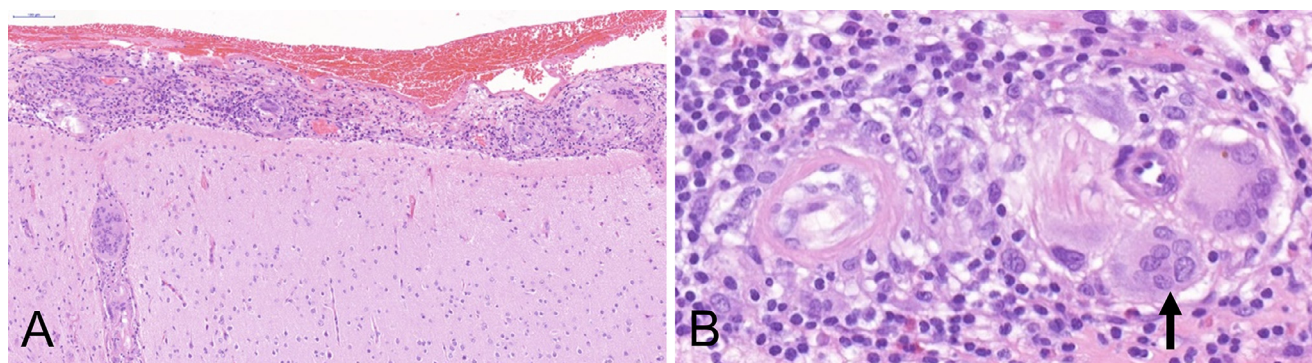


**Fig. 3 – T2 hyperintense lesion in parietal lobe appears enlarged (A). New DWI high intensity spot (arrow) appeared one after another with time (B). New multiple T2 star low intensity spot (arrowhead) appeared with time (C). FLAIR coronal images showing brain herniation due to further edema.**

## Discussion

Neurological symptoms of NS vary widely depending on the site of focal lesion, such as the cranial nerve, dura mater, cerebral cortex, brainstem, and diencephalo-hypophysial area. More than half of the patients with NS primarily show neurological symptoms, making prompt diagnosis difficult. Microvascular changes are identified in the majority of patients with NS according to postmortem studies, however, acute CNS vasculitis as a manifestation of NS usually does not present any clinical symptoms and is not well documented in previous reports. Vincent et al reported a relatively high mortality rate in NS patients with cerebrovascular manifestations (23%) as compared to that in NS without cerebrovascular manifestations (5%) [8]. Although patients with NS rarely present with acute vasculitis, it is crucial for clinicians to be aware of this anomaly when diagnosing patients in their daily medical practice.

The pathogenesis of sarcoidosis remains elusive, although it is believed that type IV allergic reactions occur due to a specific, yet unidentified antigen, and that granulomas are formed in various systemic organs [7]. Although the pathophysiology of cerebrovascular vasculitis in NS also remains unclear, it is thought that cerebrovascular manifestation of NS is multifactorial (increased CNS immunoglobulin G binding, impaired endothelial function, elevated arterial stiffness, elevated level of endothelin-1, etc.) and not caused by vessel



**Fig. 4 – Photomicrograph of the second biopsy specimen. HE stain, original magnification 200 × (A) and 1000 × (B). Aggregating multinucleated giant cells (arrowhead) with neutrophils, lymphocytes, eosinophils, plasma cells, and other inflammatory cells, as it is called noncaseating granuloma and is observed around blood vessels (B).**

wall infiltration alone. Postmortem studies revealed perivascular granulomatous involvement especially along the basal meninges [12,13]. We believe that the main lesion of NS is sometimes in the meninges and extends along the Virchow–Robin spaces. In this case, the right parietal lesion showed increased ADC and leptomeningeal enhancement in the MRI scan and prompt reduction of lesion size after corticosteroid therapy. Therefore, this lesion was assumed to be a secondary edema due to venous return disorder of meningitis resulting from sarcoidosis.

Cerebral MRI imaging presentations of NS show various abnormalities. Pawate et al reported T2 hyperintense white matter lesions (52%) and leptomeningeal enhancement (19%) to be typical images of NS [5]. Vincent et al also reported patients with strokes due to NS via MR imaging, in which T2 hyperintense lesion was the most common (69%), followed by leptomeningeal thickening or enhancement (44%) [8]. Such reports may indicate a correlation between leptomeningeal enhancement and strokes. In this case, MRI scans revealed leptomeningeal enhancement, suggesting meningitis. Therefore, we hypothesize that the cerebrocortical infarcts occurred secondary to involvement of the cortical vessels from surrounding meningeal inflammation. Since vasculitis usually involves small vessels, cerebrovascular angiography would not be useful. Thus, biopsy is crucial for the diagnosis of vasculitis of NS [1,7,8]. In this case, a definitive diagnosis could be obtained at a relatively early stage of the disease, which facilitated the initiation of an adequate adjuvant therapy.

Biopsy of a CNS lesion gave us macroscopic pathological information. Till date, there is just one report on brain surface findings of meningitis due to NS, where yellowish and cloudy discoloration was observed [4]. To the best of our knowledge, our case is the first to report multiple small hemorrhages observed on the brain surface due to NS. Pathological findings revealed not only multinucleated giant cells aggregating with neutrophils but also microscopic infarction and hemorrhage. This patient did not have other systemic lesions and was diagnosed with INS pathologically.

Although there have been no controlled trials of NS treatment, corticosteroids are usually the first-line therapy used.

We need to consider the use of immunosuppressants as a second-line treatment when the effect of steroid treatment is insufficient, or when relapse occurs during steroid reduction. Some reports show that  $\text{TNF}\alpha$  inhibitors are effective when second-line treatment is insufficient [14,15]. Reports regarding the outcome of patients with strokes due to NS who underwent immunosuppressive therapy are particularly scarce. However, some reports demonstrate the efficacy of immunosuppressive therapy over hemorrhagic lesions [16,17]. Multiple reports show that intracranial hemorrhages increase with steroid tapering and discontinuation [17–20]. In this case, microhemorrhages and microinfarct relapsed after corticosteroid reduction, but restarting and continuing corticosteroid treatment was sufficiently effective. No new lesion could be identified in DWI high or T2 star MRI images after corticosteroid therapy. Thus, immunosuppressive therapy may be effective against not only hemorrhagic lesions, but also ischemic ones.

## Conclusion

We demonstrated that it is necessary to keep in mind that NS sometimes shows an aggressive course, presenting with vasculitis. Most patients with NS show satisfactory corticosteroid responsiveness; however, this is not always the case. In cases of unfamiliar ischemic or hemorrhagic lesions, it is essential to consider the possibility of NS.

## Authors' contributions

Conception and design: Maekawa T. Drafting the article: Maekawa T. Patient treatment: Goto Y and Fujii A. Analyzing imaging data: Goto Y and Fujii A. Critically revising the article: Hashimoto. All authors read and approved the final manuscript.

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## Ethics statement

All data identifying the patients were anonymized. This report follows the strict rules of the ethics committee of our institution.

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## Patient consent

This is a report showing that it has been approved by the ethics committee of our institution.

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