

## A Case of Primary Systemic Necrotizing Vasculitis Presenting Primarily with Neurologic Involvement

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### ABSTRACT

**Systemic necrotizing vasculitis (SNV) is a type of vasculitis that presents with necrosis, predominantly involving large, medium-sized and small arteries. Peripheral neuropathy is a major clinical feature of the primary and secondary systemic vasculitides, and is often observed during the early phases of the disease, causing axonal neuropathy. The prevalence of central nervous system (CNS) involvement ranges from 4% to 45%. Encephalopathy, focal neurological deficits, and seizures are the most common manifestations and usually occur late during the course of SNV. In this report, we describe a 61-year-old woman with SNV who had both CNS and peripheral nervous system vasculitic involvement. We also discuss the pathophysiology of nervous system involvement in patients with SNV.**

### INTRODUCTION

Systemic necrotizing vasculitis (SNV) (1) is a type of vasculitis that presents with necrosis, involving predominantly large, medium-sized and small arteries. The most commonly affected sites are the skin, joints, kidneys, gastrointestinal tract, and peripheral and central nervous systems. SNV can manifest as Takayasu's arteritis, polyarteritis nodosa (PNA) or microscopic polyangiitis (MPA), with PNA usually leading to lesions of the nervous system. Peripheral neuropathy is a major clinical feature of primary and secondary systemic vasculitides, and is often observed during the early phases of the disease and frequently causes axonal neuropathy. Peripheral nervous system (PNS) involvement has been reported in 50% to 75% of patients with PNA (2), while central nervous system (CNS) involvement has been reported in 4% to 45% of these patients (3,4). Encephalopathy, focal neurological deficits, and seizures are the most common manifestations of CNS involvement and usually occur late during the course of SNV. In this report, we describe a 61-year-old woman with SNV who had both CNS and PNS vasculitic involvement.

### CLINICAL CASE

A 61-year old woman presented with intermittent headaches and a fever over a span of nine months. Additionally, she complained of weakness and numbness in her limbs for seven months. Initially her headache presented with a fever, but disappeared when her body temperature was within a normal range. Moreover, her headache became aggravated for one week. In October 2011, she was diagnosed with SNV at Peking Union Medical College Hospital and began regular treatment with methylprednisolone and cyclophosphamide. Her pathogenetic condition remained unchanged until November 22, 2011, when her headache relapsed, accompanied with nausea and vomiting. Therefore, she was admitted to the department of neurology in our hospital. Permission to use this material was obtained from the local ethics committee and the informed consent of the patient.

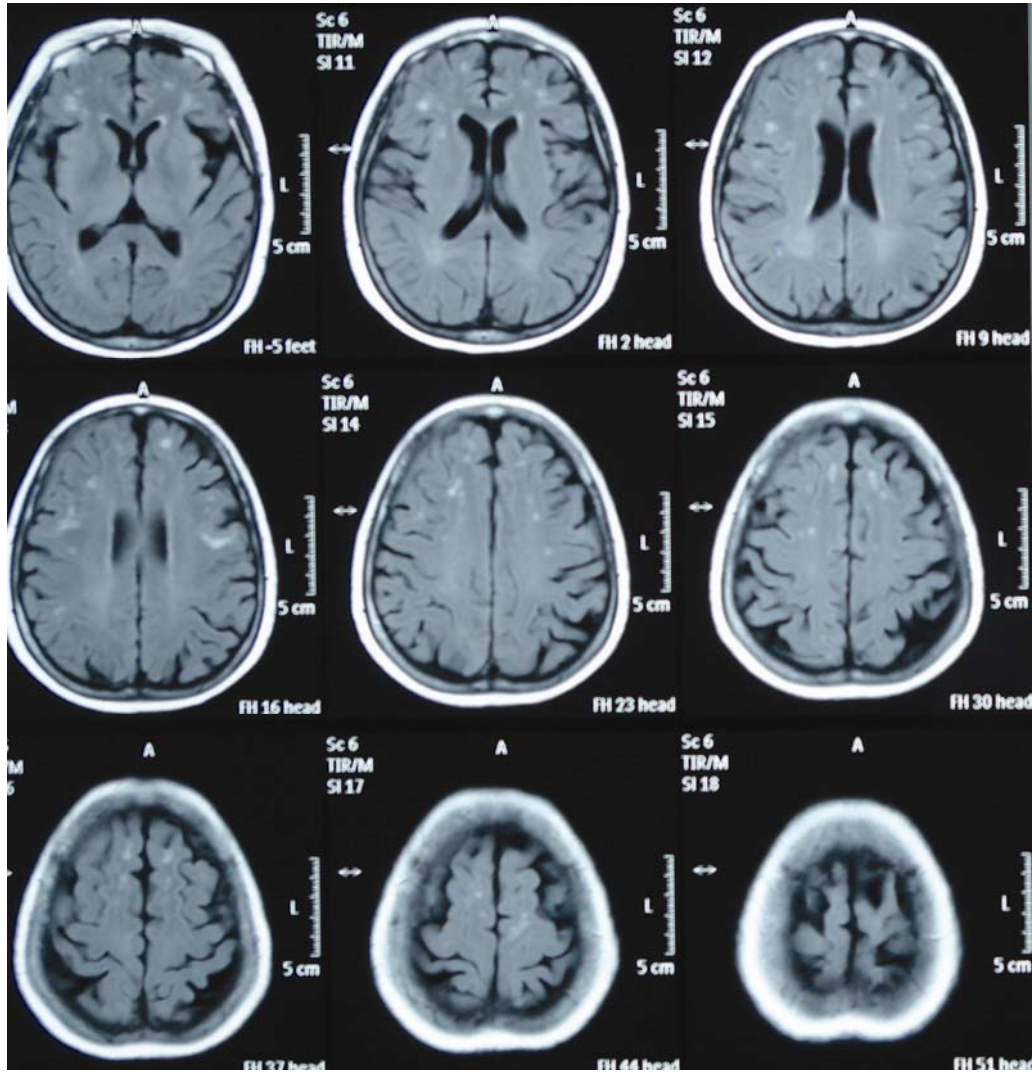
#### Physical examination

On admission, the patient's temperature was 36.7°C, her blood pressure was 150/100 mmHg, and she was slightly anemic. Neurologic examination showed muscle strength of grade 4, with atrophy of her upper limbs and a complete absence of shallow tendon reflexes. Her light-touch sensation was reduced, predominantly in the distal part of all four limbs. She was negative for Babinski's response, neck stiffness and the Kernig sign.

#### Investigation

A brain MRI revealed multiple stippled lesions in the bilateral lobus insularis, lobus frontalis and temporal lobe, with all of these lesions hyper-intense on fluid attenuation IR (FLAIR) (Fig. 1). However, her brain MRA was normal. An electromyogram performed at Peking Union Medical College Hospital showed a neurogenic

pattern in all four limbs, with an abnormal sympathetic skin response (SSR) in her lower limbs. A sural nerve biopsy showed severe neuraxial and active polyneuropathy, with small vessel disease. Lumbar punctures revealed that her intracranial pressure (ICP) was 240 mmH<sub>2</sub>O, her leucocyte count was  $1.5 \times 10^4 / \text{mm}^3$ , her protein concentration was 44.1 mg/dl, and her glucose and chloride concentrations were normal. The IgG index of her cerebrospinal fluid (CSF) was 1.39, and the cytology of her CSF showed 94% lymphocytes and 6% monocytes. She was negative for acid-fast, anti-bacillus, anti-viral antibodies and for a cryptococcus smear. She was serologically negative for HBV, HCV, EBV and HIV.



**Figure 1.** FLAIR sequence of brain MRI in our patient, showing multiple stippled lesions in the bilateral lobus insularis, the lobus frontalis and the temporal lobe.

Hematological analysis showed a white blood cell (WBC) count of  $9.49 \times 10^3 / \mu\text{l}$ , including 88.84% neutrophils, and a hemoglobin concentration of 10.3 g/dl. However, her red blood cell (RBC) and platelet counts were normal. Her erythrocyte sedimentation rate (ESR) was 70 mm/h, her C-reactive protein (CRP) concentration was 10.62 mg/dl, and an antistreptolysin "O" test and RF were normal. She was negative for antinuclear antibodies, antibodies to immunoglobulin and complement components C3 and C4, anticardiolipin antibodies, and ANCA. Her blood clotting analysis was normal, as well as her urinalysis, thyroid, liver and renal functions.

CT examination of her lungs showed bilateral multiple nodules. Color Doppler ultrasound images of her thyroid, lacteal gland, heart, digestive, urinary and gynecological systems, and the veins of her lower limbs were normal.

In October 2011, she was started on corticosteroid therapy at Peking Union Medical College Hospital, consisting of intravenous pulses of 500 mg of methylprednisolone for three days, followed by sequential 2-fold reductions every three days to a dose of 120 mg and 60 mg/day of oral methylprednisolone. She was also given weekly infusions of 600 mg of cyclophosphamide. She was given the same dosage after admission to our hospital.

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Two weeks after the start of treatment, her blood pressure was normalized. Furthermore, clinical examination showed easing of her headache and limb weakness, as well as the disappearance of her nausea and vomiting. Laboratory tests revealed a CRP concentration of 4.55 mg/dL and an ESR of 20 mm/h, both lower than before treatment. Brain MRI and CT examinations, however, yielded the same results as before therapy. Her methylprednisolone dosage was slowly tapered with laboratory monitoring to 12 mg/day, but she continued to receive infusions of cyclophosphamide.

### DISCUSSION

In this report, we described a patient with a headache accompanied by nausea, vomiting and weakness and numbness of her lower limbs due to CNS and PNS damage associated with SNV. Several similar patients have been described (5) with damage caused by PNA. Takayasu's disease and microscopic polyangiitis can also result in neurologic complications (6). The CNS involvement in SNV may result from vasculitis, or may be secondary to immunosuppressive therapy or the side effects of other drugs (7). Additionally, Takayasu's disease and PNA usually cause cerebral infarctions, whereas MPA usually results in intracerebral hemorrhage, subarachnoid hemorrhage or pachymeningitis (8). To our knowledge, only two previous patients have been described with non-hemorrhagic stroke as a complication of MPA (9).

Cerebral lesions may have many causes. For example, a 55-year-old man was described with posterior reversible encephalopathy syndrome (PRES) due to PNA (10). PRES may be due, at least in part, to brainstem vasogenic edema (11), with reversibility rates significantly lower in patients with PRES of the brainstem than in patients with other localizations of PRES lesions (12). Only one patient with PNA has been described with PRES, with the latter associated with type II mixed cryoglobulinemia (13).

Cerebral lesions may also be due to arterial thrombosis or intracerebral haemorrhage (14). For example, our patient had scattered infarctions with no angiographic evidence of vascular malformation. Since early treatment with a combination of steroids and cyclophosphamide might have prevented the exacerbation of her vascular lesions (15), the infarction in our patient might have been secondary to the same necrotizing vasculitis that involved her nerves. Confirmation, however, requires a biopsy of the brain.

Involvement of large intracranial vessels is more likely to result in strokes, subarachnoid or intracerebral hemorrhages, or ischemia. Signs of microvascular disease include encephalopathy and myelopathy (7). Since MPA mainly involves small vessels, including arterioles, capillaries and venules, the mechanism underlying the multiple cerebral infarctions in our patient remains unclear. PNA-associated infarctions are primarily due to vasculitic arterial occlusions (16). However, the association of multiple infarctions and MPA with the susceptibility of small vessels to inflammation may result in dampening of hemodynamics and lead to infarction (9).

Peripheral neuropathy is reported to be a feature in PNA and MPA (15), and is commonly present at the onset of disease (17). The etiology of neuropathy in this setting is ischemic occlusion of the vasa nervosum. Large myelinated sensory and motor fibers are usually affected, as they are more prone to ischemic damage. The insult is axonal rather than demyelinating. Patients often experience pain and may have an acute or subacute presentation (18). Current treatment strategies for vasculitis-associated neuropathy depend largely on extrapolation from trials of treatment for other organ manifestations because few studies have directly addressed the effect of immunosuppression on vasculitic neuropathy (19). Furthermore, there have been few comparisons of the incidence and prevalence of neuropathy with other features of systemic vasculitis or the correlation of responses to treatment of other manifestations with improvements in peripheral neuropathy.

Early treatment with a combination of systemic corticosteroids and cyclophosphamide is usually effective, because it increases the long-term response rate and achieves greater attenuation of the neurologic disability, with no significant increase of adverse effects (20).

SNV should be included in the differential diagnosis of patients presenting with cerebral infarction, peripheral neuropathy, and elevated inflammatory signs. The early recognition of SNV and the prompt institution of immunosuppressive therapy may avoid or limit these complications.

### CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

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