INTRODUCTION

Varicella-zoster virus (VZV) infection could lead to meningitis, encephalitis, vasculopathy, stroke, and myelopathy apart from skin lesions. We reported a 14-year-old girl with a combination of possibly interconnected central nervous system (CNS) complications of VZV infection and discussed the clinical features, treatment plan, and follow-up.

It is estimated that the annual incidence of childhood stroke varies from 1.3 to 13 per 100,000 around the globe. Among all the causes, intracranial arteriopathies account for up to 45% of strokes during childhood. They are divided into different subtypes, such as focal cerebral arteriopathy, Moyamoya disease, and diffuse arteriopathy. Localized vessel inflammation due to infectious causes could further lead to secondary thrombus formation and ischemic stroke. The reactivation of the varicella-zoster virus typically results in herpes zoster with specific distribution patterns. However, it could also lead to other complications, including vasculopathy, myelopathy, retinal necrosis, and cerebellitis, while central vascular lesions could present as aneurysms or dissections and lead to ischemic or hemorrhagic stroke.

Here, we describe a 14-year-old girl with facial vesicles, fever, and headache who had meningitis, localized arteriopathy of right-sided cavernous internal carotid artery, and ipsilateral watershed ischemic infarction.

CASE DESCRIPTION

2.1 Initial presentation

A 14-year-old girl presented to the Department of Dermatology with five days of flu-like episodes with recurrent fever and headache and one day of facial pain and blistering papules around the right nostril. She could recall being listless sitting in the classroom at school. She complained about loss of appetite and poor sleep. No additional symptoms were reported. She had an uneventful birth and a normal developmental history and was fully immunized. No past medical history of illness, family history, or drug use was reported. Physical examination showed clustering...
nonerupting vesicular papules involving the right-sided nasal mucosa and skin, the area supplied by the maxillary branch of the trigeminal nerve. No other physical abnormalities were found. Intravenous penciclovir and ceftriaxone were prescribed. Gentamycin and analgesics were applied locally.

The next day, the patient had a more severe headache. Head computed tomography showed no abnormalities other than right-sided maxillary, ethmoidal, and sphenoidal sinusitis (not shown). The patient was transferred to the Department of Neurology for further tests and treatment.

2.2 | Neurological examination and diagnostic testing

Upon presentation in the neurology ward, the patient complained about ongoing right-sided facial pain. Neurological examination revealed nuchal rigidity, bilateral Kernig's sign, and slightly increased tendon reflexes and positive Babinski's sign on the left side. No apparent abnormalities of mental status, cranial nerves, muscle strength, sensations, and coordination were found.

Since meningeal irritation sign and unilateral upper motor neuron sign might suggest meningitis and contralateral corticospinal tract lesions, magnetic resonance imaging (MRI) was performed and demonstrated right-sided maxillary (not shown), ethmoidal, and sphenoidal sinusitis on T2-FLAIR sequence (Figure 1A), right-sided cortical (not shown) and internal watershed infarction on diffusion-weighted imaging (DWI, Figure 1B) and enhancement of tentorium cerebelli and pia mater on T1 contrast sequence (Figure 1C). Regular MR angiography (MRA) performed one week after admission showed some dubiously varying thickness of the right cavernous internal carotid artery (not shown), while high-resolution MRA (HR-MRI) performed two weeks after admission showed heterogeneous signal around the proximal right cavernous internal carotid artery with significant narrowing (arrow) in the coronal view (Figure 2A), and proximal

**FIGURE 1** Magnetic resonance images during the hospital stay and the follow-up after 8 mo. (A) ethmoidal and sphenoidal sinusitis on T2-FLAIR sequence; (B) watershed infarction in the right centrum semiovale on diffusion-weighted imaging; (C) enhancement of tentorium cerebelli and pia mater on T1 contrast sequence upon the initial admission. (D-F) corresponding images to images A-C after 8 mo
narrowing of the arterial lumen (arrow) as well as distal aneurysmal formation (approximate size: 3 mm*4 mm, double arrow) bulging into the cavernous sinus in the sagittal view (Figure 2B) on postcontrast T1 sequence. The arterial narrowing (arrow) and aneurysmal formation (double arrow) were additionally visualized by digital subtraction angiography (DSA, Figure 2C). ECG, echocardiography, and chest X-ray were normal.

Results of laboratory tests including complete blood count, liver function panel, inflammatory markers, immunoglobulins, antistreptolysin-O, thyroid function panel, antinuclear antibodies, antibodies to extractable nuclear antigens, antineutrophil cytoplasmic antibodies, the T-SPOT TB test, and cerebrospinal fluid analysis are listed in Table 1. Specifically, the VZV IgG antibody and DNA in the CSF were not tested due to the unavailability of the tests in our hospital.

2.3 | Therapeutic regimen

Apart from antiviral, antibiotic, and analgesic medications, the patient additionally received 5 mg dexamethasone for three days and 10 mg dexamethasone for another 10 days after positive HR-MRI results were available in the Department of Neurology.

2.4 | Reassessment and discharge

Ten days after treatment, lumbar puncture showed normal count of nucleated cells, slightly increased total protein level, immunoglobulin G, and immunoglobulin A in the CSF (Table 1). By that time, the patient had no more headaches, and her appetite and sleep also improved. Upon discharge, oral methylprednisolone (an initial dose of 40 mg with tapered reduction of 4 mg/wk) and aspirin were prescribed with follow-up in the out-patient clinic.

2.5 | Follow-up

The patient had remained free of symptoms since discharge. Positive neurological findings remained upon follow-up after eight months. MRI demonstrated clear maxillary (not shown), ethmoidal, and sphenoidal sinuses on T2-FLAIR sequence (Figure 1D), resolution of

FIGURE 2 HR-MRI and digital subtraction angiography images during the hospital stay and the follow-up after 8 mo. (A) Luminal narrowing of the proximal right cavernous internal carotid artery (arrow) shown on coronal HR-MRI T1 contrast sequence; (B) luminal narrowing of the proximal segment (arrow) and aneurysmal formation of the distal segment (double arrow) of the right cavernous internal carotid artery on sagittal HR-MRI T1 contrast sequence; (C) luminal narrowing (arrow) and aneurysmal formation (double arrow) shown by digital subtraction angiography. (D-F) corresponding images to images A-C after 8 mo
# TABLE 1  Laboratory testing results

| Laboratory tests (reference range) | Results |
|-----------------------------------|---------|
| **Complete blood count**          |         |
| White blood cell (3.5-9.5*10^9/L) | 11.33*10^9/L, increased |
| Neutrophil (1.8-6.3*10^9/L)       | 7.70*10^9/L, increased |
| Monocyte (0.1-0.6*10^9/L)         | 1.37*10^9/L, increased |
| Red blood cell (3.8-5.1*10^12/L)  | 3.45*10^12/L, reduced |
| Hemoglobin (115-150 g/L)          | 85.0 g/L, reduced |
| Hematocrit (35%-45%)              | 26.6%, reduced |
| Mean corpuscular volume (82-100 fl) | 77.1 fl, reduced |
| Mean corpuscular hemoglobin (27-34 pg) | 24.6 pg, reduced |
| **Liver function panel**          |         |
| Alanine aminotransferase (≤33 U)  | 63 U/L, increased |
| Aspartate aminotransferase (≤32 U) | 33 U/L, increased |
| Direct bilirubin (≤8 μmol/L)      | 12.1 μmol/L, increased |
| γ-glutamyl transpeptidase (6-42 U/L) | 149 U/L, increased |
| Triglyceride (<1.7 mmol/L)        | 2.62 mmol/L, increased |
| **Inflammatory markers**          |         |
| Erythrocyte sedimentation rate (0-20 mm/h) | 65 mm/h, increased |
| C-reaction protein (<1 mg/L)      | 161.3 mg/L, increased |
| Interleukin-6 (<7 pg/mL)          | 108.4 pg/mL, increased |
| Procalcitonin (0.02-0.05 ng/mL)   | 1.84 ng/mL, increased |
| **Others**                        |         |
| Immunoglobulin A (0.58-3.21 g/L)  | 3.26 g/L, increased |
| Immunoglobulin G (7.0-15.6 g/L)   | 15.3 g/L, normal |
| Immunoglobulin M (0.49-2.61 g/L)  | 1.25 g/L, normal |
| Antistreptolysin-O                | Normal |
| Thyroid function panel            | Normal |
| Antinuclear antibodies            | Normal |
| Antibodies to extractable nuclear antigens | Normal |
| Antineutrophil cytoplasmic antibodies | Normal |
| T-SPOT                             | Nonresponsive |
| **Cerebrospinal fluid analysis**  |         |
| Red blood cell (0*10^6/L)         | 22*10^6/L, increased |
| Nucleated cell (0-8*10^6/L)       | 32*10^6/L, increased |
| Total protein (150-450 mg/L)      | 1031 mg/L, increased |
| Albumin (100-300 mg/L)            | 531 mg/L, increased |
| Glucose (3.33-4.44 mmol/L)        | 3.34 mmol/L, normal |
| Immunoglobulin G (≤58.6 mg/L)     | 193 mg/L, increased |
| Immunoglobulin M (≤7.0 mg/L)      | 24.8 mg/L, increased |
| Immunoglobulin A (≤7.0 mg/L)      | 42.1 mg/L, increased |
| Mycobacterium tuberculosis culture | Negative |
| Bacterial culture                 | Negative |
| IgM/G for CMV, HSV-1 and HSV-2    | Normal |

Abbreviations: N/A, not available.
right-sided watershed infarction on diffusion-weighted imaging (Figure 1E), and no enhancement on T1 contrast sequence (Figure 1F). HR-MRI showed normalized arterial lumen (arrow) of the proximal right cavernous internal carotid artery and significantly smaller distal protrusion (double arrow) into the cavernous sinus on postcontrast T1 sequence (Figure 2D,E). Recovery of the proximal (arrow) and distal (double arrow) arterial morphological was also visualized by DSA (Figure 2F). Aspirin was discontinued thereafter.

3 | DISCUSSION

Previous studies have shown that reactivation of varicella-zoster virus not only causes typical herpetic skin lesions, but could also lead to various CNS complications, for example, meningitis, aneurysmal formation, stroke, encephalitis, and myelitis in both immunocompetent and immunocompromised patients.\(^4\) The persistent and aggravating headache of our patient was disproportionate despite her antecedent flu-like episodes. Positive meningeal signs, CSF pleocytosis and widespread enhancement of tentorium and cerebellum on contrast MRI supported a diagnosis of meningitis, in accordance with the reported aseptic meningitis caused by VZV in immunocompetent individuals.\(^7\)\(^-\)\(^9\) The subtle abnormality, that is, slightly asymmetrical tendon reflexes of limbs, and positive Babinski’s sign on the left side were atypical and could be explained by the acute combined right-sided cortical and internal watershed infarction shown on DWI. Previous studies including participants who had an ischemic stroke and a history of VZV infection found that the median interval between VZV infection and stroke was around four months,\(^5\)\(^,\)\(^10\) ranging from the same day to two and a half years. Our patient presented to the clinic with fever and headache of five days and rash of one day, suggesting that her meningitis as a complication of VZV infection might have manifested concurrently if not earlier than the herpetic rash. One study found that the most affected site of cerebral arteriopathy was the M1 segment of the middle cerebral artery,\(^10\) while another study showed involvement of both large and small arteries in half of the participants followed by involvement of pure small-artery and pure large-artery disease.\(^5\) In our case, the segmental luminal narrowing and dilatation of the right cavernous internal carotid artery were in line with some specific morphological pattern of varicella-zoster vasculopathy described in previous publications.\(^4\)\(^,\)\(^11\) Significant narrowing of the arterial lumen, possibly due to inflamed intima, could lead to profound hemodynamic changes that further caused the watershed infarction together with emboli dislocated to distal arterial sites if additional thrombus was formed.\(^6\)\(^,\)\(^12\)

Previous studies showed that individuals exposed to herpes zoster had significantly increased risk of cerebrovascular events, which was most prominent among younger people within the first year after the development of herpes zoster.\(^13\)\(^-\)\(^15\) Another study found that the cumulative recurrence rate of ischemic stroke in children was 6.8% at one month and almost doubled at 1 year. Of all variables including the use of antiplatelet drugs or anticoagulants, definite presence of arteriopathy was found to be the single baseline predictor of stroke recurrence. Specifically, 6.7% of children who developed index stroke due to secondary vasculitis had stroke recurrence within one year. Among all recurrent strokes with a median duration of 2 years, 75% occurred within the first 12 weeks after the index stroke and only 2.5% occurred beyond one year.\(^16\) Our patient has remained symptom-free since the initial discharge. As the follow-up duration is already one and half a year upon the submission of this report, we assume that the risk of stroke recurrence for our patient is minimal.

The pathophysiology underlying our observation has not been fully elucidated. In fact, the unilateral sinusitis involving all major sinuses in our case might be a reflection of inflammatory reaction to the viral reactivation in the trigeminal ganglion.\(^4\) Previous studies have raised the proposal that reactivated VZV could spread transaxonally from the Gasserian ganglion to the nerve fiber terminals in the adventitial layer of the carotid artery. There, fibroblasts infected by VZV could drive neutrophil accumulation and activation with virus migration to media and intima at a later time. These events could cause reduced medial smooth muscle cells, loss of vessel integrity, disrupted internal elastic lamina, and thickened intima composed of myofibroblasts,\(^6\)\(^,\)\(^17\)\(^,\)\(^18\) serving the basis of arteriopathy. A recent study showed that dysregulated expression of programeed death ligand-I and major histocompatibility complex-I might be involved in the failure of viral clearance and prolonged inflammatory response at the site of vasculitis.\(^19\)

One major limitation of our diagnosis is that our viral panel did not include the VZV IgG antibody and we did not have the VZV polymerase chain reaction test to aid the diagnosis of varicella-zoster vasculopathy.\(^4\)\(^,\)\(^6\) Though we performed tests to exclude autoimmune diseases that could contribute to ischemic stroke, another limitation is that we did not perform tests for prothrombotic disorders. Mutations of protein C, antithrombin and prothrombin gene, or increased homocysteine levels resulting from methylene tetrahydrofolate reductase polymorphism could lead to a hypercoagulable state and increased risk of ischemic stroke.\(^2\) However, a full consideration of clinical symptoms, available testing results, response to antiviral agent and steroid, and normalization of arterial morphology after eight months still favors the diagnosis of varicella-zoster vasculopathy concurrent with maxillary herpes zoster in our case.
In this report, we described a 14-year-old girl with typical facial herpetic rash and secondary headache. Neurological examination revealed unilateral upper motor neuron signs that prompted brain and vascular imaging showing watershed infarction, meningitis, and carotid arteriopathy. Despite the significant limitation of a lack of testing for VZV in the CSF, other laboratory and radiological data favor the coexistence of trigeminal herpes zoster, meningitis, cerebral arteriopathy, and watershed infarction most likely due to the reactivation of VZV during a single hospital stay.

CONFLICT OF INTEREST
None of the authors report conflict of interest.

AUTHOR CONTRIBUTIONS
LM: contributed to data collection, data interpretation, figure production, study design, and writing. ZJ: contributed to data collection, data interpretation, and figure production. WM: contributed to data collection. ZM: contributed to data interpretation and study design. All authors: have read and approved this manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
Written informed consent was obtained from a parent of this patient.

CONSENT FOR PUBLICATION
The patient gave permission to be included in the manuscript, and written informed consent for publication of medical information and figures was obtained from a parent of this patient.

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