

# Varicella vasculopathy presenting with thunderclap headache

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## Lesson

Our report serves to highlight Varicella vasculopathy as a rarity not to be overlooked in the differential diagnosis of subarachnoid haemorrhage.

## Keywords

clinical, emergency medicine, infectious diseases, neuroimaging, neurology

## Case history

A 62-year-old lady presented to the Emergency Department with a severe sudden onset thunderclap headache originating over the occiput radiating into the neck with associated vomiting and photophobia but without loss of consciousness. She had a medical history of well-controlled hypertension and plaque psoriasis but had recently been systemically well. General and neurological examinations, including fundoscopy, were normal. Routine bedside observations of temperature and haemodynamic status were unremarkable. An urgent plain computerised tomography brain scan revealed acute subarachnoid blood located over the right superior frontal convexity but subsequent computerised tomography angiography, computerised tomography venography, and magnetic resonance brain imaging were all otherwise normal (Figure 1). Routine blood analyses of the full blood count, renal profile, liver function, thyroid function, C-reactive protein, erythrocyte sedimentation rate, anti-neutrophil cytoplasmic antibody and antinuclear antibody were normal. Serological screens for human immunodeficiency virus-1 and -2, and syphilis, were negative. Cerebrospinal fluid obtained on first pass demonstrated clear and colourless fluid with a normal opening pressure of 18 cm of cerebrospinal fluid, red cell count 481 per mm<sup>3</sup>, white cell count 2 per mm<sup>3</sup>, protein level 403 mg/dL and glucose 3.1 mmol/L, giving a normal ratio with a paired serum glucose of 5.4 mmol/L.

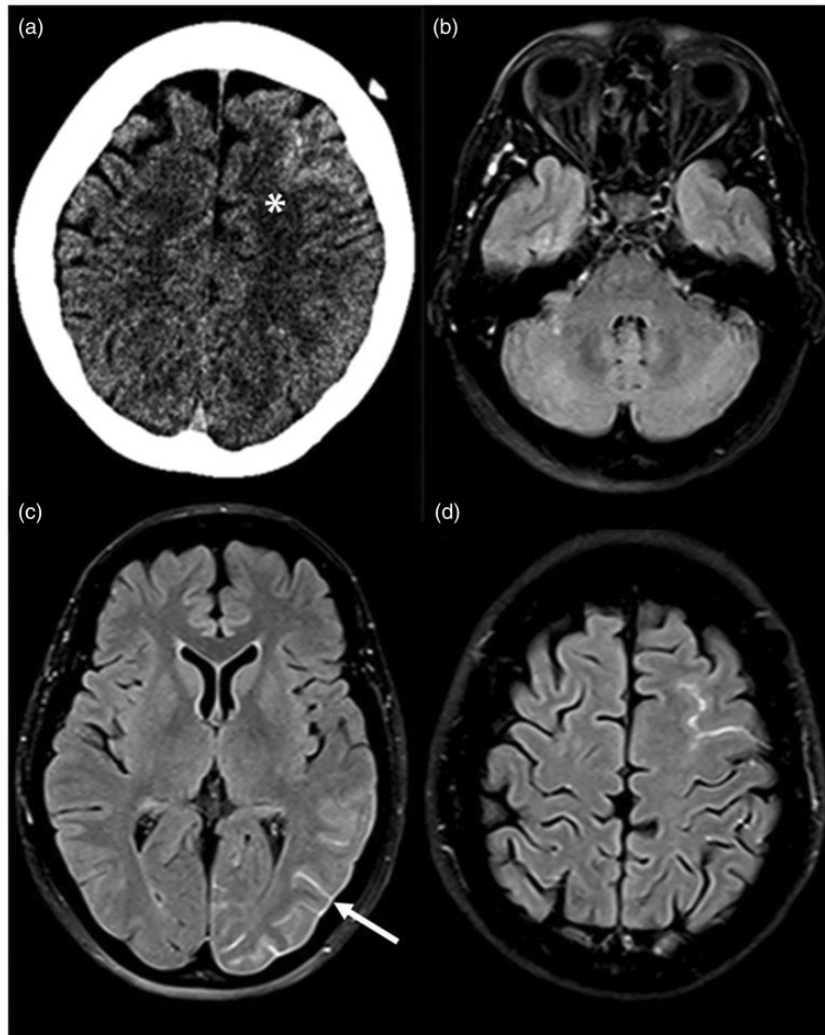
The patient's headache remained persistent but fluctuated in intensity over several days. A formal

digital subtraction catheter angiogram demonstrated multifocal irregularities of the intracranial small- and medium-sized vessels. Bilateral branches of the anterior and posterior circulations were involved, as too were the external carotid arteries with mild focal irregularity of the superficial temporal arteries (Figure 2). There was no evidence of aneurysm or arteriovenous malformation to account for the subarachnoid haemorrhage. Biopsy of the right superficial temporal artery was performed which revealed only non-specific findings of intimal thickening with occasional foci of fibroblastic activity and, in a few places, disruption of the internal elastic lamina. No evidence of vasculitis was seen.

The following day there ensued a marked clinical deterioration with mixed dysphasia, left-sided hemiparesis, bilateral limb ataxia and right-sided visual and somatosensory neglect in the context of a further acute exacerbation of headache. Computerised tomography brain imaging revealed a fresh haemorrhage in the right cerebellar hemisphere and a subacute infarct in the left. Magnetic resonance brain imaging had now become floridly abnormal with multiple additional cortical and subcortical areas of acute infarction involving both parietal and occipital lobes, and the left frontoparietal junction (Figure 3). Magnetic resonance angiography demonstrated middle-sized vessel irregularity and attenuation (Figure 3). Real time polymerase chain reaction results on the cerebrospinal fluid were reported as 'strongly positive' for Varicella zoster deoxyribonucleic acid prompting immediate commencement of both intravenous aciclovir and methylprednisolone for presumed Varicella-associated vasculopathy. Cerebrospinal fluid oligoclonal bands were negative and blood serology detected Varicella IgG antibody but not immunoglobulin M, consistent with past infection.

Following treatment, no further lesions developed and the patient's condition slowly improved. A repeat cerebrospinal fluid analysis after three weeks' treatment demonstrated normal constituents and negative viral polymerase chain reaction. The patient was

**Figure 1.** Subarachnoid blood demonstrated on imaging following thunderclap headache. Plain computed tomography shows subarachnoid haemorrhage within the left superior frontal sulci (a). Magnetic resonance FLAIR sequences (panels b-d) confirm subarachnoid blood within the left superior frontal sulci (d) but also within the left parieto-occipital sulci (c, arrow). Parenchymal appearances are normal.



discharged home with only persistent visuoperceptual difficulties remaining. Follow-up magnetic resonance brain imaging one year later remained stable and the magnetic resonance angiogram had returned to normal.

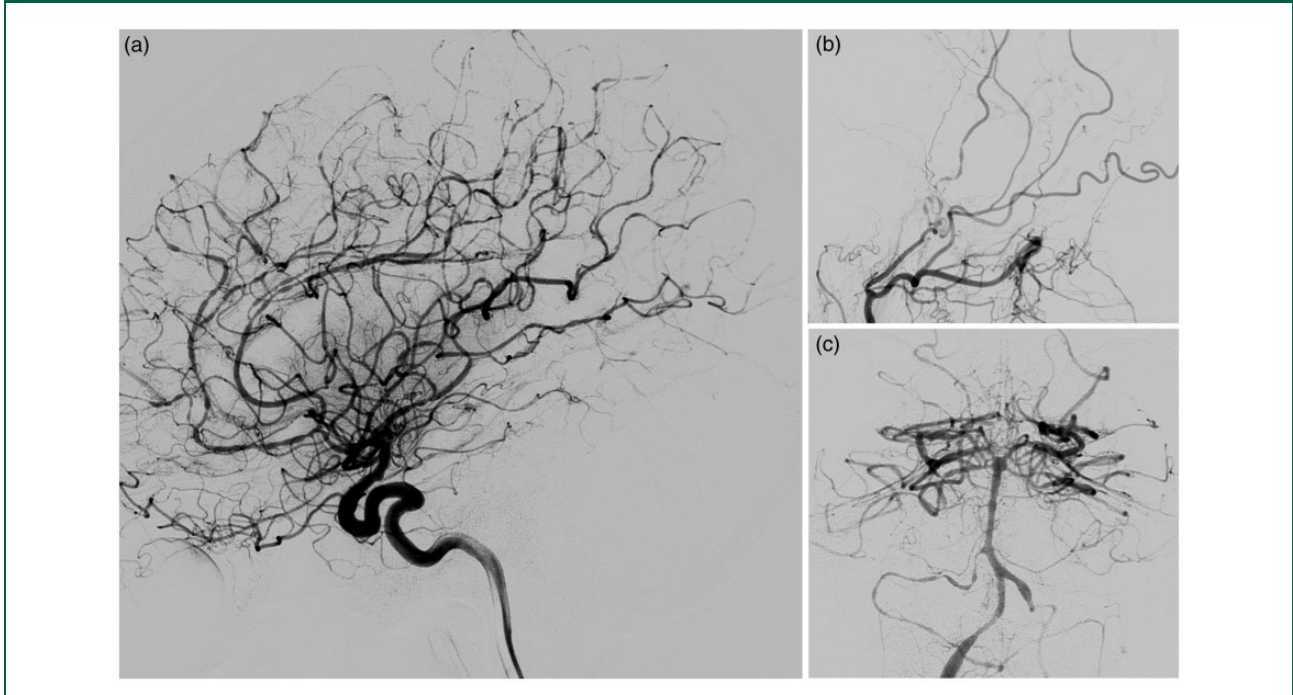
## Discussion

This case illustrates the rapidly evolving picture of intracranial Varicella zoster virus vasculopathy in an immunocompetent patient presenting initially with acute thunderclap headache in the absence of a cutaneous zoster rash. Isolated subarachnoid haemorrhage was soon followed by the development of multiple intraparenchymal haemorrhages and infarcts

in all three cerebral artery territories in the context of a marked clinical deterioration. In such circumstances, differential diagnoses would include systemic and primary cerebral vasculitides, reversible vasoconstriction syndrome and infective vasculopathies. However, a high index of suspicion for Varicella zoster virus vasculopathy should be maintained as routine cerebrospinal fluid analyses may provide false reassurance and management varies significantly from its potential mimics.

Varicella zoster is a human deoxyribonucleic acid virus which can mediate neurological manifestations during primary infection, usually in childhood, or following reactivation from its dormancy phase within the ganglia of the nervous system, perhaps

**Figure 2.** Cerebral catheter angiography showing multifocal irregularity of the intracranial and extracranial small, medium and large sized vessels. Contrast via the left internal carotid artery (a) demonstrates multifocal irregularity of the middle and anterior cerebral artery branches extending into the periphery of the arterial tree. Similar changes are seen in the right external carotid and middle meningeal arteries (b). Contrast injected through the right vertebral artery (c) also confirms involvement of the posterior circulation with the vertebral, basilar, anterior inferior cerebellar and posterior inferior cerebellar arteries all abnormal.

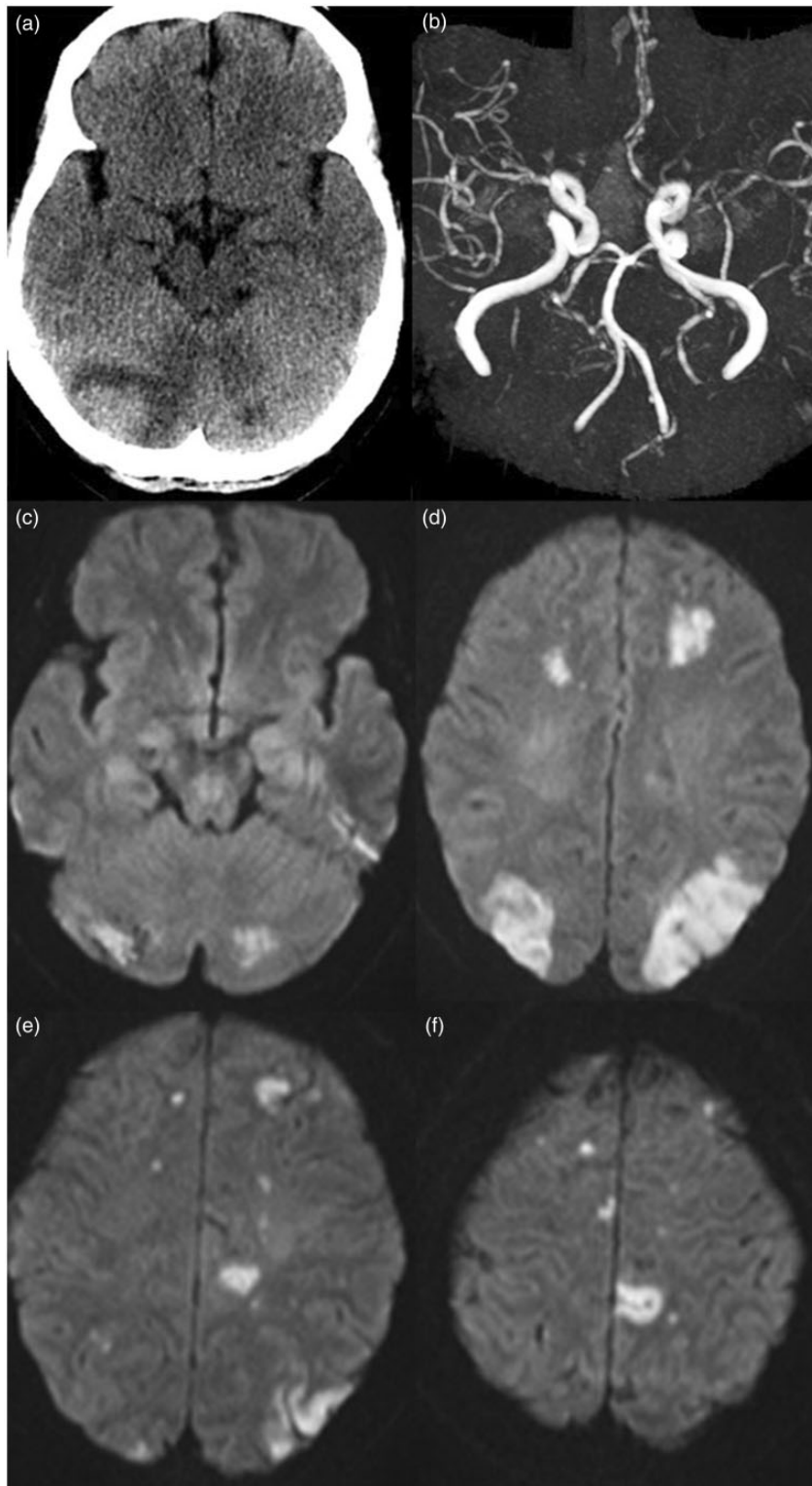


precipitated by a decline in cell-mediated immunity with age or a state of frank immune paresis.<sup>1</sup> Most widely recognised in this regard is the painful cutaneous zoster rash, or shingles, whereby newly synthesised virions are transported along the axon to keratinocytes of the corresponding dermatome to cause a localised, infectious, vesicular skin eruption. Reactivated Varicella infection can also give rise to conditions such as brachioplexitis, meningoradiculitis and acute inflammatory polyneuropathy in the peripheral nervous system, possibly as a result of anterograde spread from ganglia, as well as central nervous system manifestations including cerebellitis, myelopathy and encephalitis. Direct invasion of cerebral blood vessels results in vasculopathy;<sup>2,3</sup> indeed, Varicella zoster is the only virus so far known to replicate within the walls of blood vessels.<sup>1,3</sup>

An association between recent primary chickenpox infection or shingles and subsequent stroke has been long-recognised through anecdotal reports and larger study groups in both children<sup>4</sup> and adults.<sup>5</sup> In a retrospective analysis by Kang et al. of an adult patient cohort who had experienced an attack of shingles, their risk of stroke over the ensuing 12 months was significantly increased compared to the control group. Even adjusting for known cardiovascular risk factors,

the hazard ratio was 1.31 for those patients with somatic zoster rash and 4.28 after herpes zoster ophthalmicus, with the latter furthermore associated with subsequent contralateral neurological deficits.<sup>5</sup> Apart from haematogenous spread, this has led to the suspicion that the virus is delivered to the cerebral blood vessels transaxonally via ipsilateral trigemino-vascular afferents in parallel with a herpes zoster ophthalmicus breakout.<sup>6</sup> Supportive pathological case studies in a small number of patients with Varicella zoster virus vasculopathy have implied that vessel wall structure changes sequentially with respect to the length of time neurological symptoms have been experienced by means of a transmural viral migration.<sup>7,8</sup> Invasion is believed to begin in the outer adventitial layer with an accompanying leukocyte infiltration and then spread inwards towards the intima. En route, the smooth muscle and internal elastic lamina layers become disrupted and the intima thickened, thereby leading to luminal narrowing and vessel weakening. Histology may reveal multinucleated giant cells, nuclear Cowdry A inclusion bodies and even viral particles themselves in affected cells.<sup>2,3,9</sup> Cerebral artery susceptibility to this 'outside-in' invasion may be facilitated by the lack of an external elastic lamina,<sup>7</sup> although extracranial and

**Figure 3.** Intracranial haemorrhage and multiple infarcts following marked clinical deterioration. An area of high density within the right cerebellar hemisphere and a further small low density area in the left cerebellar hemisphere seen on plain computed tomography represent new intraparenchymal haemorrhage and infarct, respectively (a). Magnetic resonance imaging (c-f) confirms the cerebellar findings along with multiple cortical and subcortical areas of acute infarction involving both parieto-occipital lobes (d), the left medial parietal lobe (e) and frontoparietal junction (f). Intracranial time-of-flight MR angiography sequences showed irregularity of the anterior cerebral arteries and loss of flow void in the middle cerebral artery (b).



systemic arteries can also be affected by Varicella zoster virus vasculopathy. The distribution of affected cerebral vasculature can be unifocal or multifocal and 40%–50% of Varicella zoster virus vasculopathy affects both large vessels and small vessels simultaneously, with predominance of only small penetrating vessels supplying deep structures seen in approximately one-third of cases.<sup>10,11</sup> The pathological wall remodelling renders the affected vessels prone to occlusion, distorted morphology (including aneurysms) and rupture. Clinical features may range from territorial infarcts, intracerebral haemorrhage and arterial dissection to non-specific headache, fever, changes in mental state and ischaemic optic neuropathy which are thought to arise secondary to involvement of the much smaller microvasculature and blur together with effects from direct parenchymal infection.<sup>12</sup> The relative contribution from neuronal, glial and small vessel endothelial cell viral invasion in presentations such as Varicella-associated myelopathy and encephalitis is not fully characterised but is likely to lie on a continuum, with evidence pointing to elements of all three.<sup>2,9,13</sup> Vessel irregularity can often be illustrated best by formal catheter angiography but this does not visualise the distal-most branches of the arterial tree. High-resolution magnetic resonance imaging with contrast has recently been shown to depict vessel wall thickening, luminal narrowing and enhancement in Varicella zoster virus vasculopathy patients, although primarily in the proximal branches of the internal carotid.<sup>14</sup> Neither imaging modality is specific for Varicella zoster virus vasculopathy with respect to other causes of vasculopathy and involvement restricted to the smaller arteries may evade detection.

Therefore, onset of neurological symptoms and signs in the context of recent or concurrent Varicella infection, including zoster, should prompt active exclusion of underlying cerebral Varicella zoster virus vasculopathy.<sup>6</sup> Around 30%–40% of Varicella zoster virus vasculopathy occurs in immunocompromised individuals<sup>10,15</sup> in whom there may be haematological dysfunction, retroviral infection or pharmacological suppression, along with an impression that the small vessel form predominates in this patient group.<sup>10</sup> However, the visible clue of a zoster rash does not automatically become manifest at any stage and can be absent in up to a third of patients with Varicella zoster virus vasculopathy.<sup>10</sup> Moreover, ancillary investigations may provide non-specific information or even be normal,<sup>2</sup> and so a high index of suspicion is crucial for a prompt diagnosis. Brain magnetic resonance scans are abnormal in the vast majority of cases,<sup>10,15</sup> often showing ischaemic grey and white matter changes sited both cortically

and in deep cerebral structures, as well as haemorrhage less frequently.<sup>10</sup> Nagel et al. suggest that lesions at the grey–white matter junction are a red flag for Varicella zoster virus vasculopathy, although not specific for it. Subarachnoid haemorrhage is unusual<sup>2</sup> and far less likely to be the presenting feature. Indeed, to the authors' knowledge, there are only two prior case reports in which Varicella zoster virus vasculopathy first became manifest with subarachnoid bleeding: one had a zoster rash recently beforehand<sup>16</sup> and the other concurrently.<sup>17</sup> The first of these patients died following massive haemorrhage from a fusiform basilar artery aneurysm in the context of what was considered to be pathologically confirmed 'granulomatous angiitis' (now known as primary angiitis of the central nervous system) but with Varicella antigen virus particles visualised within the infiltrating histiocytes.<sup>16</sup> The second patient described with subarachnoid haemorrhage experienced thunderclap headache with imaging revealing frontal convexity blood, similar to our case but without further progression.<sup>17</sup> Non-traumatic subarachnoid haemorrhage located within the cerebral convexities is highly atypical for acute presentation of aneurysmal rupture. This radiological finding should prompt an onward search for alternative conditions including amyloid angiopathy, reversible vasoconstriction syndrome, venous thrombosis, vasculitis, Varicella zoster virus vasculopathy and septic emboli from subacute infective endocarditis (reviewed in Marder et al.<sup>18</sup>).

Our diagnosis was aided by identifying Varicella deoxyribonucleic acid in the cerebrospinal fluid but a negative result does not exclude Varicella zoster virus vasculopathy as it can be absent in 30%–40% of cases.<sup>10,15</sup> Deoxyribonucleic acid detectable by polymerase chain reaction may disappear with time<sup>2</sup> and so cerebrospinal fluid Varicella-specific IgG antibodies should be requested which are believed to be positive in over 95% of the cases.<sup>15</sup> These antibodies may develop after several weeks of Varicella zoster virus vasculopathy and be responsible for a positive intrathecal oligoclonal band result.<sup>2</sup> Given that the case described here presented so acutely and is assumed to have a recent onset vasculopathy, this may explain why the Varicella deoxyribonucleic acid was positive and oligoclonal bands negative. The cerebrospinal fluid was otherwise unremarkable, except for a mildly elevated red cell count; specifically, the white cell count was normal as were the other basic parameters. Gilden et al.<sup>2</sup> have reported that a mononuclear pleocytosis, usually amounting to fewer than 100 cells per mm<sup>3</sup>, is absent in a third of cases and the protein level may be elevated or normal.

Treatment with intravenous aciclovir 10–15 mg/kg for at least two weeks along with a five-day course of

oral steroids to reduce arterial wall inflammation is currently recommended as treatment,<sup>2,10</sup> based upon pooled observational outcomes as there are no randomised controlled data. Prolonged immunosuppression is not deemed necessary, or indeed helpful, due to the risk of delayed Varicella reactivation. Our patient received aciclovir for three weeks and sustained no further neurological deficits. Repeat lumbar puncture analysis demonstrated a return to normal cerebrospinal fluid parameters and follow-up brain magnetic resonance imaging, with time-of-flight magnetic resonance angiography, at one year revealed no additional asymptomatic lesions with a return to normal appearances of the visualised arterial tree.

## Conclusion

Varicella zoster virus vasculopathy is one manifestation of reactivated Varicella infection and may present to general practitioners, emergency departments and adult neurology services with an array of clinical syndromes. Our report serves to highlight that Varicella vasculopathy is a rarity not to be overlooked in the differential diagnosis of subarachnoid haemorrhage or (rapidly) evolving cerebral vascular syndromes because intravenous aciclovir is a highly effective treatment which can halt progression. Helpful diagnostic clues such as a zoster rash are often absent and cerebrospinal fluid analysis may not detect Varicella deoxyribonucleic acid following a routine polymerase chain reaction request. Cerebrospinal fluid Varicella IgG antibodies need to be specifically requested and, for this reason, it is vital that Varicella zoster virus vasculopathy should be considered within the differential diagnosis.

## Declarations

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**Ethical approval:** Written informed consent for publication was obtained from the patient.

**Contributorship:** AWB performed the literature search and review of the literature and drafted the article. SV provided expert review of radiology and provided critical appraisal of the article for submission. PJH directed management of the clinical case and provided critical appraisal of the article for submission.

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