

Case report

A case of isolated cortical venous thrombosis presenting radiographically as a subacute multifocal leukoencephalopathy, and review of literature

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SUMMARY

A 55-year-old man presented with brief seizure with associated acute aphasia, right head turn and subsequent generalised convulsion. On imaging, he was found to have patchy juxtacortical and cortical T2 hyperintensity with high radiographic suspicion for subacute multifocal leukoencephalopathy. Serum and cerebrospinal fluid testing were unremarkable. Clinically, the patient recovered completely and had no recurrence of symptoms. On follow-up MRI 1 month later, the T2 hyperintensity had resolved almost entirely while hypointensity on susceptibility-weighted angiography MRI remained, suggesting isolated cortical venous thrombosis.

BACKGROUND

There are no documented cases that describe isolated cortical venous thrombosis (ICVT) presenting radiographically similarly to subacute multifocal leukoencephalopathy. ICVT is a rare condition representing a minuscule fraction of all strokes that typically presents as an occlusion of anastomotic surface vessels. Because of the condition's rarity and its propensity to mimic other conditions, in addition to the non-specific symptoms such as headache or seizure that are typical for first presentation, this can be a very difficult diagnosis to make.

CASE PRESENTATION

We describe a case of a 55-year-old homosexual man on HIV preventative therapy with emtricitabine/tenofovir disoproxil and a history of stable bipolar 1 disorder who presented to the emergency department after an episode of transient, 2–4 min episode of clinical seizure with associated transient aphasia, followed by right head turn and subsequent generalised convulsion. He had been started on Truvada 6 months previous to the presentation for HIV prevention due to anticipation of becoming sexually active with multiple partners.

INVESTIGATIONS

Initial examination demonstrated normal vital signs with non-focal neurological examination. Initial head CT scan was unremarkable, and the head and neck CT angiogram showed no major vascular abnormalities. The subsequent brain MRI with and without contrast showed patchy juxtacortical and cortical T2 hyperintensity with swelling, as well as

associated curvilinear susceptibility within the overlying cortex and minimal superficial enhancement (figure 1A–D). This finding suggested a radiological pattern for a multifocal leukoencephalopathy or encephalitis. Urine toxicology screen, thyroid function panel, liver enzymes, B₁₂ and complete blood count were all unremarkable, excluding other causes for encephalopathy. Lumbar puncture was normal, with a CSF protein count of 36 mg/dL and normal cell counts, decreasing the suspicion for encephalitis. Oligoclonal bands were not present in the cerebrospinal fluid (CSF). Infectious tests from CSF were all unremarkable for JC virus antibody, syphilis, Epstein-Barr virus and varicella zoster. The patient was negative for HIV, but positive for antibody to JC virus in the blood, reflecting past exposure to the virus. Serum was unremarkable with C-reactive protein, erythrocyte sedimentation rate, lactic acid, complement 3c and 4c, and anti-nuclear antibody, all in the normal ranges and slight elevation of c-ANCA titre of 1:40, without clear significance.

DIFFERENTIAL DIAGNOSIS

Findings on MRI suggested progressive multifocal leukoencephalopathy (PML) or encephalitis, with cortical laminar necrosis and iron susceptibility signal considered less likely to support these entities. However, the patient was not immunosuppressed, HIV negative and afebrile, assuaging the concern for the former two options.

TREATMENT

The patient was started on 150 mg oxcarbazepine twice daily for seizure prophylaxis. This treatment has been ongoing. Continued antiepileptic drug therapy will be reevaluated at future visits, and discontinued if there is no new clinical seizure activity or changes on electroencephalogram.

OUTCOME AND FOLLOW-UP

Although CSF results were reassuring, and his clinical seizures completely resolved, there was still a concern for possible PML given the atypical radiological pattern. Thus, subsequent close surveillance was pursued, including close clinical follow-ups and subsequent follow-up serum tests for leukaemia/lymphoma evaluation, anti-dsDNA, anticardiolipin, anti-ribonucleoprotein, anti-Lyme and human T-lymphotropic virus PCR which all



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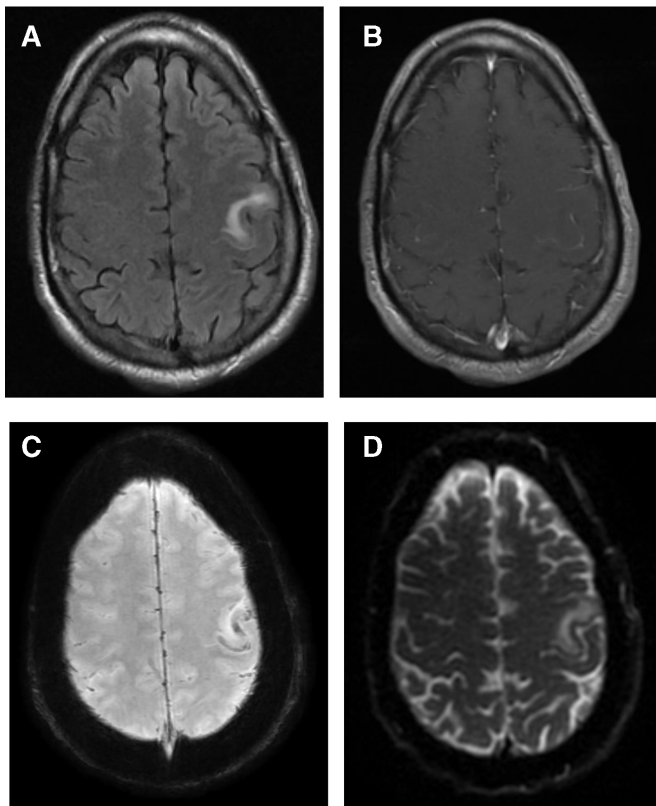


Figure 1 The initial lesion as seen on (A) T2 fluid-attenuated inversion recovery (FLAIR), (B) T1 with contrast, (C) MRI-SWAN and (D) diffusion-weighted imaging (DWI). Patchy juxtacortical and cortical T2 hyperintensity with swelling and curvilinear susceptibility within the overlying cortex with minimal superficial enhancement can be seen. This pattern is common in multifocal leukoencephalopathy or encephalitis. SWAN, susceptibility-weighted angiography.

were unremarkable. His repeat MRI 1 month after his initial presentation showed near complete resolution of the T2 FLAIR hyperintensity in the left frontal cortical-subcortical region, with possible trace residual T2 hyperintensity in the left precentral gyrus (figure 2A and B) which was unusual for possible PML. The hypointensity seen on susceptibility-weighted angiography (SWAN) imaging in the precentral gyrus probably represented

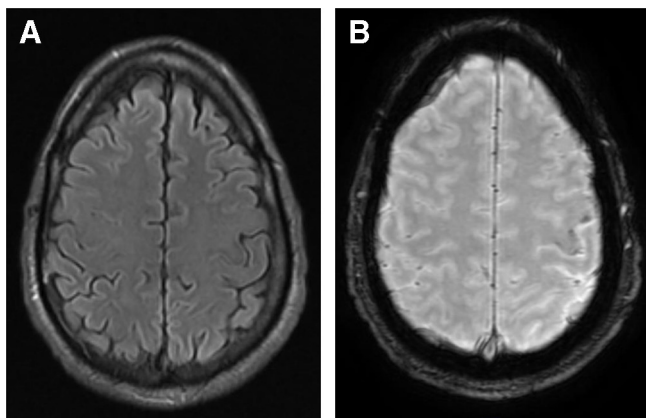


Figure 2 The lesion as seen on follow-up on (A) T2 FLAIR and (B) MRI-SWAN. Near-complete resolution of the previous findings are seen on both images, with some residual hypointensity in the precentral gyrus on MRI-SWAN. SWAN, susceptibility-weighted angiography.

haemosiderin staining, and was also slightly improved. MRI of the cervical spine showed no evidence of demyelinating lesions.

Due to the resolution on imaging and his benign clinical picture, the final diagnosis was ICVT. The patient underwent workup by haematology for occult causes of hypercoagulability. The patient had no family history of clotting disorders and no prior personal history of thromboembolic events. Hypercoagulability workup, including prothrombin gene mutation, factor V Leiden, protein C, protein S and antithrombin III deficiency, was negative. Lupus anticoagulant and anticardiolipin antibody were negative as well. While laboratory tests were benign, the patient admitted to taking over-the-counter testosterone supplementation for a number of months which the thrombosis was attributed to. As there was no worsening of the patient's neurological condition and no clear high risk of reoccurrence in the setting of negative workup, the patient was not started on anticoagulation.

DISCUSSION

ICVT is a rare and poorly understood condition that has only been documented in case reports or case series (116 total patients studied in a comprehensive 2014 review of the literature)¹ and represents less than 0.063% of all cerebral strokes.² It frequently involves anastomotic surface vessels such as the vein of Trolard, the vein of Labbé, the superficial Sylvian vein and the precentral, postcentral and central veins. It has been known to mimic other conditions on MRI, such as subarachnoid haemorrhage, transient ischaemic attack³ or even brain tumour.⁴ ICVT has subtle findings on CT, occasionally presenting with hyperdense vein sign within 7-14 days,⁵ but frequently found to be normal. CT venogram can be useful to visualise a filling defect.⁶ On MRI, a clot will display T1 isointensity and T2 hypointensity, with T1 hyperintensity from a subacute clot and cerebral oedema will typically be present.⁶ Magnetic susceptibility effect can be a valuable tool for diagnosis; a study showed that in ICVT, a venous occlusion could be seen as a homogeneous well-delimited hypointensity which was tubular, serpentine or rounded.⁷ In addition, parenchymal abnormalities were seen close to the occluded vein, including cortical-subcortical hyperintensities.⁷ Both haemorrhagic and edematous parenchymal involvement is frequently seen,¹⁷ and lesion regresses. Clinically, ICVT often presents similarly to dural venous sinus thrombosis, with headache or seizure as the most common symptoms on presentation.¹ However, it should be on the differential diagnosis whenever a patient presents with any acute central nervous system symptomatology, as it is frequently missed or misdiagnosed.⁸ Headache and papilloedema are less common than in dural venous sinus thrombosis, and elevated opening pressure on lumbar puncture is less likely, while haemorrhagic or edematous lesions are more likely.¹ Mortality reportedly range from 2.8% to 6%, but most or all deaths are seen in patients with other intracranial pathology, such as meningitis or encephalitis. In patients presenting with ICVT as a solitary diagnosis, the mortality rate is 0%; with good outcome.¹ While most patients who are diagnosed with ICVT receive anticoagulation and it is considered the standard of care, outcomes may not be different between patients who receive anticoagulation and those who do not.²

In juxtaposition to associated good outcome with ICVT, PML is another rare condition (incidence of 1-4 per 1000 person-years) that is a demyelinating disease of the white matter caused by reactivation of latent JC virus in immunocompromised individuals.⁹ Contrary to ICVT, PML is known to be rapidly progressive, with consistent worsening of symptoms and no remission

on subsequent imaging, and a devastating expected outcome.⁹ In PML, typical lesions consist of T1 hypo/T2 hyperintensity in a multifocal, asymmetric pattern involving subcortical structures. Subcortical U-fibres and peripheral white matter are known to be commonly involved, and the disease is frequently seen in the parieto-occipital region.¹⁰ There is typically little mass effect and no contrast enhancement.¹⁰

In our patient's images, the rounded appearance of the thrombosis mimicked the subcortical U-fibre involvement seen in PML which was further supported by the presence of patchy subcortical T2 hyperintensity. The small amount of swelling and oedema could be typical of either PML or ICVT. The haemosiderin deposition seen as a hypointensity on MRI-SWAN (susceptibility-weighted angiography) is more typical in cases of thrombosis, especially as clot deteriorates or ischaemic cells apoptose, but as the literature shows, it is an occasional finding in PML as well.¹⁰ The presence of low-intensity susceptibility-weighted imaging signal are frequently seen in ICVT,⁷ and while it is a possible finding in PML, the mechanism is unclear and this is not a typical finding.¹¹

Even though the initial read on imaging was highly suspicious for PML especially given the patient's higher risk for HIV infection, overall the aetiologies outside of our final diagnosis of ICVT were thought to be very unlikely, due to the lack of progressive symptoms, the absence of immunosuppression, the grossly normal laboratory tests, the reassuring findings on lumbar puncture and the marked resolution on follow-up MRI. ICVT is known to mimic other neurological conditions radiographically,^{3,4} but to our current knowledge, we believe that this is the first case report demonstrating ICVT mimicking PML. This is an important finding, as the former disease has a good outcome, while the latter is rapidly progressive and fatal.

One other point to highlight is testosterone supplementation as our patient's identified cause of ICVT in the absence of other causes of hypercoagulability. Testosterone products are known as a cause of hypercoagulability,¹² with the US Food and Drug Administration (FDA) and Canada Health both adding warnings for increased risk of venous thromboembolism in 2014,^{13,14} and the FDA also issuing a warning in 2015 for increased risk of heart attack and stroke with testosterone supplementation.¹⁵ In addition, over-the-counter supplements are notoriously under-regulated as to their contents,¹⁶ and the actual dose of testosterone in the supplement as well as the presence of any other ingredients known to incite hypercoagulability is unknown.

Learning points

- ▶ Isolated cortical venous thrombosis (ICVT) is a rare condition that can present in a radiographically diverse manner.
- ▶ ICVT frequently presents idiopathically and resolves spontaneously, with no lasting sequelae.
- ▶ Patients with higher risk of HIV infection presenting with a first onset of seizure and an abnormal subcortical U-fibre involvement leads to the challenging differential diagnosis of progressive multifocal leukoencephalopathy (PML) which can have potential serious implications for morbid outcome. However, ICVT can also mimic PML from neuroradiological perspective, as demonstrated by our case, with a completely different outcome, especially in the absence of non-radiological abnormal findings.
- ▶ MRI with susceptibility-weighted imaging can be a useful diagnostic tool in cases of ICVT as it shows haemosiderin deposition after resolution of the acute clot.

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