CASE REPORT

Persistent lesion hyperintensity on brain diffusion-weighted MRI is an early sign of intravascular lymphoma

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SUMMARY

A 63-year-old man presented with right-sided hemianopia and unsteady gait. Brain MRI revealed multiple hyperintense infarct-like lesions on diffusion-weighted images (DWI). Hyperintensity persisted in some of these lesions even after 6 weeks, although his symptoms were ameliorated then. The patient developed episodic dizziness and a transient event of apraxia at 18 weeks after the first episode. Brain MRI revealed additional hyperintense lesions on DWI, which persisted even after 7 weeks. Eventually, the patient manifested cauda equina syndrome 39 weeks after the first episode. Brain MRI showed the presence of new lesions in addition to the persistent hyperintense lesions on DWI over 21 weeks in the right frontal lobe. Based on laboratory findings and the pathological assessment of bone marrow and random skin biopsies, the patient was diagnosed with intravascular lymphoma (IVL). Persistent hyperintense lesions on DWI of brain MRI may precede the clinical exacerbation of IVL.

BACKGROUND

Intravascular lymphoma (IVL) is a rare and aggressive subtype of extranodal non-Hodgkin's lymphoma characterised by the preferential growth of lymphoma cells within the lumens of small blood vessels, such as capillaries, venules and arterioles. Most IVLs derive from the B-cell lineage, whereas a small fraction originates from the T-cell or natural killer cell lineage. The antemortem diagnosis of IVL is frequently delayed because of the initial non-specific symptoms and the absence of non-invasive diagnostic markers. The lack of involvement of the bone marrow and lymph nodes in the early stage of the disease also contributes to the difficulty of antemortem diagnosis and autopsy evaluation is frequently required for definitive diagnosis. Furthermore, IVL occasionally progresses rapidly to multiple organ failure that can be fatal, which creates challenges in obtaining tissue samples from patients because of the rapid deterioration of their physical condition. Therefore, early diagnostic strategies need to be established for improved prognosis of IVL. We herein reported a patient with IVL, who developed persistent hyperintense brain lesions on diffusion-weighted images (DWI) of MRI, which preceded the clinical exacerbation by at least several months.

CASE PRESENTATION

A 63-year-old man presented with right-sided hemianopia and unsteady gait. He was diagnosed with polyarthritis since 17 months ago, which was managed with 2.5 mg/day of prednisone. He had a history of coronary stenosis, which was treated with percutaneous transluminal angioplasty, as well as diabetes mellitus and dyslipidaemia. He was afebrile and had neither lymphadenopathy nor skin rash. Neurological examination revealed right-sided hemianopia, mild limb ataxia and wide-based gait. Blood cell count was normal and serum C-reactive protein, lactate dehydrogenase (LDH) and soluble interleukin 2 receptor (sIL-2R) levels were 1.5 mg/dL, 250 U/L and 2430 U/mL (normal range; 124–466 U/mL), respectively. Although cerebrospinal fluid (CSF) analysis revealed mild pleocytosis (5 cells/ μ L) and increased protein content (67 mg/dL), cytological analysis did not detect any malignant cells. Whole-body ¹⁸F-fluorodeoxyglucose-positron emission tomography (¹⁸F-FDG-PET) and contrast-enhanced CT did not reveal any abnormalities. Brain MRI showed multiple hyperintense lesions on DWI in the subcortical white matter of the bilateral parietal lobes and the left occipital lobe, as well as in the corpus callosum (figure 1a, g, m, s). None of these lesions showed enhancement on contrast-enhanced T1-weighted images. While ECG, echocardiography and ultrasound for cervical arteries revealed no abnormal findings, we diagnosed this patient as having embolic stroke of undetermined source because of multiple ischaemic lesions in different arterial territories. The patient was started on oral aspirin and his symptom was getting ameliorated thereafter. However, the hyperintense lesions detected on DWI remained in the right corona radiata and corpus callosum after 6 weeks of treatment, whereas the remaining hyperintense lesions on the initial imaging disappeared and evolved to hyperintense lesions on T2-weighted imaging series (figure 1b, h, n, t and figure 2).

On week 18 after the first episode, the patient started experiencing episodic dizziness. In addition, he had a transient episode of apraxia while taking a shower. Blood tests revealed a serum LDH level of 231 U/L and a sIL-2R level of 2600 U/mL. CSF analysis showed mild pleocytosis (5 cells/ μ L) without malignant cells and an increase in protein content (97 mg/dL). Neither ¹⁸F-FDG-PET nor contrast-enhanced CT indicated any abnormal findings. Brain

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Figure 1 Serial diffusion-weighted images (DWI) of the brain MRI in a symptomatic patient with intravascular lymphoma. Serial DWI of the brain MRI were obtained at the onset of symptoms (a, g, m, s)() and at weeks 6 (b, h, n, t), 18 (c, i, o, u), 25 (d, j, p, v), 39 (e, k, q, w) and 75 (f, l, r, x) after the onset. Lesions in the right corona radiata (g, n, i), corpus callosum (m, n) and periventricular white matter around the posterior angle in the left lateral ventricle (s, t, u, v) showed persistent hyperintensity for 18, 6 and 25 weeks after the onset of symptoms, respectively, and vanished thereafter. A lesion was noted in the left prefrontal cortex (c, d) on week 18 after symptom onset and persisted on week 25. A lesion in the right frontal lobe continued to grow, showing persistent hyperintensity at weeks 25 and 39 (i, j, k). All hyperintense lesions on DWI disappeared following chemotherapy (f, l, r, x).

MRI demonstrated several new hyperintense lesions on DWI in the left precentral gyrus and the right frontal lobe. In addition, a lesion in the right corona radiata detected in the previous study still remained hyperintense, while the other lesions were noted to have vanished on DWI (figure 1c, i, o, u). Apparent diffusion coefficient (ADC) mapping revealed that the new lesions were hypointense, whereas the lesion in the right corona radiata was hyperintense (figure 3). Furthermore, the lesion in the left precentral cortex was also circumscribed by a hyperintense area on ADC mapping (figure 3a, b). Given the persistent inflammatory changes associated with arthritis, we thought the observed changes in intensity of the brain lesions indicated ischaemic changes due to vasculitis; therefore, the dose of oral prednisone was increased to 12.5 mg/day, which led to the disappearance of his symptoms. However, some of the hyperintense lesions were found to persist 7 weeks later on DWI (figure 1d, j, p, v).

On week 39 after the first episode, the patient presented with severe lower back pain originating from the buttocks and posterior thighs, accompanied with urinary retention. He also developed

dyspnoea and weakness of the bilateral lower limbs. Laboratory findings revealed hypoxia, thrombocytopaenia ($5.4 \times 10^4/\mu\text{L}$) and elevated levels of serum LDH (399 U/L) and sIL-2R (8290 U/mL). ^{18}F -FDG-PET showed diffuse increased uptake in the bone marrow, spleen, lungs and kidneys. Spinal cord MRI depicted an intraparenchymal hyperintense lesion from Th12 to the conus medullaris on T2-weighted images. Brain MRI showed persistent hyperintense lesions in the right frontal lobe in addition to several new lesions (figure 1e, k, q, w). While cytological analysis of CSF did not reveal any malignant cells, a random skin biopsy identified CD20-positive cells in the blood vessels of one of the five tissue specimens. Bone marrow biopsy also showed hypercellular tissue with CD20-positive large cells, confirming the diagnosis of intravascular B-cell lymphoma.

OUTCOME AND FOLLOW-UP

The patient underwent four sets of R-CHOP (rituximab, cyclophosphamide, doxorubicin and prednisone) followed by two

Figure 2 Representative images showing serial changes in appearance of lesions on both diffusion-weighted and T2-weighted images. Correspondent images on diffusion-weighted and T2-weighted images at the onset (A and C) and at week 6 (B and D) are presented. Images A and B are the same as figure 1m and 1n, respectively. Two of the three hyperintense lesions observed at the onset (A) vanished in 6 weeks (B) on diffusion-weighted images while they remained on T2-weighted images (C and D, arrow). In contrast, the other lesion in the corpus callosum showed persistent hyperintensity on both diffusion-weighted (A and B, arrowhead) and T2-weighted images (C and D, arrowhead).

sets of R-ICE (rituximab, ifosfamide, carboplatin and etoposide) treatments, which led to the disappearance of the hyperintense lesions on DWI, suggesting that these lesions reflected IVL pathology and not a simple ischaemia (figure 1f, l, r, x).

Figure 3 Correspondent images on diffusion-weighted images and apparent diffusion coefficient mapping. Brain MRI conducted on week 18 after the onset of symptoms demonstrates hyperintense lesions on diffusion-weighted images in the left precentral cortex, right frontal lobe and right corona radiata (a, c). The first two lesions (1, 2) show low intensity, while the lesion in the corona radiata (3) shows relatively high intensity on apparent diffusion coefficient (ADC) mapping (b, d). A hyperintense area on ADC mapping also circumscribed the lesion in the left precentral cortex (a, b). Left panels demonstrate magnified images of the lesions in the white squares.

DISCUSSION

Although the radiological findings of IVL are considered to be non-specific, brain MRI commonly shows five abnormal patterns: (1) infarct-like lesions, (2) non-specific white matter lesions, (3) meningeal enhancement, (4) mass-like lesions and (5) hyperintense lesions in the pons on T2-weighted images.¹ Accordingly, multiple hyperintense lesions observed on DW-MRI in the present case can be defined as infarct-like lesions. However, persistence for at least 6–7 weeks discriminates these hyperintense lesions from those formed as a result of thrombus formation during ischaemia, as the latter usually disappear within 2 weeks in most cases of cerebral infarction.² The persistence of hyperintensity on DWI in IVL lesions may therefore reflect not only ischaemia but also other pathological changes, including vasculitis and/or infiltration of tumour cells in small blood vessels.³ Various ADC patterns and reversibility associated with treatment with either corticosteroids or chemotherapy lend further support for this hypothesis.

Similar findings of persistent hyperintense lesions on DWI were previously reported in two patients with IVL. Oomura *et al* reported that an enlarging mass-like IVL lesion in the right basal ganglia showed restricted diffusion over 2 weeks.⁴ Sato *et al* also reported the growth of infarct-like lesions, which were hyperintense on DWI, over the course of 21 days in a patient with intravascular large B-cell lymphoma.⁵ These findings also suggest the high cellularity of the IVL lesion as a cause of restricted diffusion. Therefore, persistent lesion hyperintensity on DWI might be more valuable than lesion enlargement for the diagnosis of IVL, even in patients presenting with infarct-like lesions.

It should be noted that the persistent lesion hyperintensity on DWI was observed prior to other laboratory and radiological findings except for the elevated sIL-2R level in the present case. Increased serum sIL-2R levels, which are usually observed in patients with malignant lymphoma, are not necessarily sufficient for the definitive diagnosis of IVL as sIL-2R levels can be elevated in patients with other malignant tumours or certain inflammatory diseases.⁶ Compared with pathologically diagnosed IVL cases, the initial sIL-2R level in the present case was rather low and non-specific.⁷ Therefore, as illustrated in the present case, persistent lesion hyperintensity in the brain on DWI may be one of the earliest signs of IVL. In combination with other diagnostic indicators, such as the elevation of LDH, β 2-microglobulin and sIL-2R, the presence of persistently hyperintense brain lesion on DWI may facilitate earlier diagnosis of IVL and may improve prognosis.

The major limitation of the present study is the report of a single IVL case. Additionally, oral prednisone administered for

Learning points

- ▶ Diagnosis of intravascular lymphoma (IVL) is frequently delayed because of the initial non-specific symptoms and the absence of non-invasive diagnostic markers.
- ▶ Persistent hyperintense lesions on diffusion-weighted images (DWIs) of brain MRI may precede the clinical exacerbation of IVL.
- ▶ Subacute, progressive neurological deficits and persistent DWI hyperintense lesions on brain MRI should raise a high level of suspicion of IVL, and lower the threshold to biopsy an abnormal lesion or to perform a random skin biopsy to establish the diagnosis.
- ▶ Repeated brain MRI studies including DWI should be considered in patients with possible IVL.

arthritis might influence the radiological findings in our case. Future studies are needed to confirm the same phenomena in the absence of corticosteroid treatment and clarify the following questions for the successful implementation of DWI of brain MRI as a diagnostic tool in IVL: (1) the minimum time window to confirm the persistence of hyperintense lesions for IVL diagnosis, (2) the temporal correlation of persistent hyperintense lesions with other disease markers such as LDH and sIL-2R as well as certain invasive diagnostic procedures and (3) the impact of the timing of detection of these persistent hyperintense lesions on the prognosis of IVL. The potential significance of our observations should also be confirmed by examination of IVL patients without specific neurological symptoms by brain DW-MRI, since hyperintense lesions on DWI were previously reported to occur in these patients.⁸

In conclusion, repeated brain MRI study including DWI should be considered in patients with IVL for early diagnosis.

Contributors TK took care of the patient in this case as primary physician and wrote this article as a corresponding author. HY is a senior resident of the Department of Neurology, who discovered the novel findings on diffusion-weighted images in this case as well as his own unreported case of intravascular lymphoma in our department and made a lot of suggestions for this article. FN worked on the chemotherapy for this patient as a haematologist. TS is the director of the Department of Neurology and supervised this case.

Competing interests None declared.

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