J Neuropathol Exp Neurol
Vol. 80, No. 1, January 2021, pp. 89–92
doi: 10.1093/jnen/nlaa106

OXFORD

LETTER TO THE EDITOR

Reversible Small Vessel Vasculitis and Encephalitis in HIV Antiretroviral Resistance

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To the Editor:

A radiographic pattern of radial perivascular enhancement on MRI, coupled with a cortico-steroid responsive encephalitis has been described as a hallmark feature of autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy (1, 2). However, this radiographic pattern can also be seen in the context of human immunodeficiency virus (HIV) infection. GFAP astrocytopathy has previously been described in the context of HIV infection (2). Radiographically, patients with the phenomenon of HIV cerebrospinal fluid (CSF) escape—where there is discrepantly greater CNS HIV viral replication compared to systemic—can also develop an identical pattern of radial perivascular enhancement (3). It is thought that HIV CSF escape may be a harbinger of combination antiretroviral therapy (cART) resistance. In this report, we evaluated a patient with well-controlled HIV who presented with cognitive dysfunction, ataxia, and radial perivascular enhancement on MRI. The patient provided his informed and written consent for his case to be published. We present the patient's pathology and discuss a novel phenomenon of encephalitis and vasculitis arising in the context of arising cART resistance and increasing HIV viral loads, all of which were responsive to cART modification.

A 58-year-old man with controlled HIV infection for 19 years presented with 3 months of progressive cognitive and gait decline. He was adherent to cART, and his serum CD4 count was 560 cells/μL and viral load was undetectable previously.

Neurologic examination revealed gait ataxia and his Montreal Cognitive Assessment (MoCA) score was 20/30. Brain MRI revealed a leukoencephalopathy with confluent white matter hyperintensities involving the subcortical and periventricular white matter as well asradial perivascular enhancement (particularly evident within the posterior peritrigonal and splenial regions along the expected course of the deep medullary veins) (Fig. 1A–C).

The radial perivascular gadolinium enhancement noted was suspicious for GFAP astrocytopathy (1, 2), but given concomitant HIV infection other considerations including lymphoma, vasculitis, sarcoidosis, and opportunistic infection had to be excluded. A lumbar puncture revealed a lymphocytic pleocytosis (18 WBC/mL; 92% lymphocytes). Autoimmune and paraneoplastic panels (including CSF assayed on rodent brain slices for GFAP-IgG at Mayo Clinic; CSF and serum N-Methyl-d-aspartate receptor IgG, and serum aquaporin-4 IgG) as well as CSF analyses for infection and malignancy were all negative. Corticosteroids were initiated for presumed encephalitis and/or vasculitis, with marked clinical improvement. A repeated MRI 2 months later revealed resolution of perivascular enhancement (Fig. 1D) and his MoCA improved (25/30); however, his HIV viral load had increased to 879 copies/mL. Therefore, HIV resistance assays were ordered. His corticosteroids were subsequently tapered over a month, but he deteriorated and a repeated MRI demonstrated reemergent perivascular enhancement (Fig. 1E). Another lumbar puncture revealed worsened lymphocytic pleocytosis (76 WBC/mL; 92% lymphocytes). Cytology/cytometry revealed no malignancy; B cells—3%; T cells—69% (CD4: CD8 ratio 0.2:1); and Natural Killer cells—16%. A bone marrow biopsy was unremarkable. HIV viral load increased to 980 copies/mL with new elvitegravir resistance. His cART was subsequently changed to bictegravir and darunavir.

A brain biopsy revealed a small vessel vasculitis with a predominant T-cell transmural inflammatory infiltrate and encephalitis (Fig. 2). Masson trichome stain demonstrated direct infiltration and collagen disruption within vessel walls, thereby demonstrating that the inflammatory process is consistent with vasculitis and not just perivenous lymphocytic cuffing. Immunohistochemistry demonstrated mostly CD3+ T lymphocytes and many CD163+ macrophages/microglia in the vascular and parenchymal infiltrates, with a few CD20+ B lymphocytes in the parenchymal infiltrates. Acid-fast bacilli, varicella-zoster virus (VZV), herpes simplex viruses

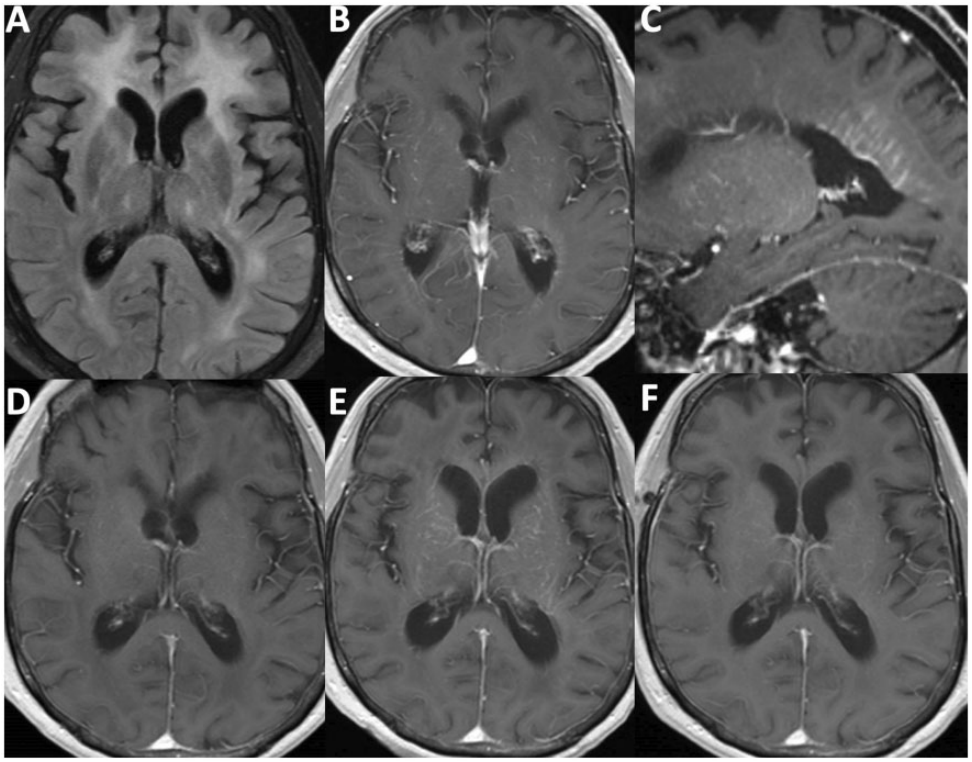

FIGURE 1. MRI brain with gadolinium at various time points. **(A–C)** At initial presentation. **(A)** Axial T2-FLAIR highlighting confluent white matter hyperintensities involving the subcortical and periventricular white matter. **(B)** Axial post-gadolinium T1-weighted images demonstrating prominent perivascular enhancement involving the subcortical deep and periventricular white matter of both cerebral hemispheres. **(C)** Sagittal postgadolinium T1-weighted images highlight prominent perivascular enhancement within the posterior peritrigonal and splenial regions along with the expected course of the deep medullary veins. This is particularly notable within the splenium of the corpus callosum and parieto-occipital white matter regions. **(D)** Axial postgadolinium T1-weighted MRI, acquired 2 months after initial presentation while on prednisone, demonstrated resolution of prominent perivascular enhancement. **(E)** Axial postgadolinium T1-weighted MRI, acquired 3 months after initial presentation, after completion of prednisone taper and in the context of neurologic decline, demonstrates reemergence of perivascular enhancement**. (F)** Axial postgadolinium T1-weighted MRI, acquired 5 months after initial presentation, and 8 weeks after the initiation of a new cART regimen, demonstrates improvement of previously demonstrated perivascular enhancement.

(HSV); Epstein Barr virus, cytomegalovirus (CMV), Human polyomavirus 2 (JC virus), cryptococcus, toxoplasmosis, spirochetes, and fungi were not detected. No granulomatous or malignant causes were identified.

Eight weeks after the initiation of the modified cART regimen, the perivascular pattern of enhancement had improved (Fig. 1F) and, at 4 months, his viral load was undetectable again. His MoCA (27/30) and ataxia improved along with demonstrated radiographic stability on repeated neuroimaging. To this day, he remains stable without recurrence, with the only modification being a new cART regimen.

We describe a rare and reversible pattern of small vessel vasculitis and encephalitis in HIV, driven primarily by T lymphocytes. The preponderance of CSF CD8+ lymphocytes suggests CD8+ encephalitis (CD8+E), which arose in the context of cART resistance and a rising serum HIV viral load. HIV-associated CD8+E is rarely reported in patients on cART (4). Minor infection, CNS immune reconstitution inflammatory syndrome (IRIS), cART interruption, and CNS virologic escape are proposed triggers (4). However, recent reports suggest that cART resistance can also precipitate CD8+E (5, 6). HIV CD8+E can also manifest with radial perivascular enhancement similar to our case, but pathologic reports have only demonstrated perivascular cuffs of lymphocytes (5–7). Pathologic demonstration of vasculitis with transmural T-cell infiltrates in the context of cART resistance has not been previously described.

Our patient's pattern of perivascular enhancement on MRI, which was steroid responsive, did evoke other important differential diagnoses. Lymphoma can have a similar perivascular pattern of enhancement on MRI with pathology demonstrating angiocentric lymphocytic infiltrates affecting deep penetrating medullary veins (8). Furthermore, we also considered GFAP astrocytopathy. GFAP was first described in 2016 as a novel cortico-steroid responsive meningoencephalitis with radial perivascular enhancement on MRI. Pathologic studies of GFAP astrocytopathy, however, reveal important differences from the pathology of our case. In GFAP astrocytopathy, the inflammatory process is characterized by predominantly parenchymal T lymphocytes and perivascular B lymphocytes with many CD138+ plasma cells in Virchow-Robin spaces (9). This inflammatory pro-

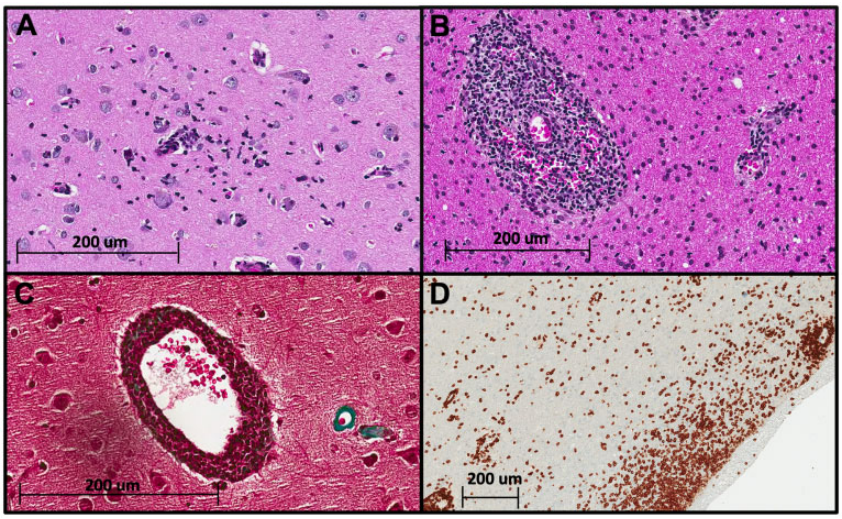

FIGURE 2. (A, B) Hematoxylin and eosin stain, **(C)** Masson Trichome stain, and **(D)** CD3+ Immunohistochemistry of right temporal lobe biopsy. Hematoxylin and eosin stain of right temporal lobe biopsy demonstrates an encephalitis and small-vessel vasculitis. Inflammatory infiltrate involving the brain parenchyma **(A)** and parenchymal small vessel walls (transmural infiltrate) and perivascular spaces **(B)**. The infiltrate consists of lymphocytes, histiocytes, and plasma cells. While **(A)** highlights microglia within the brain parenchyma, **(B)** highlights mostly lymphocytes within and around vessel walls. There is no evidence of infarction. Fibrinous necrosis of vessel walls is not demonstrated. No atypical cells, including lymphoma cells, are identified. Vascular amyloid and IGG4 immunohistochemistry are negative. There is no evidence of intracellular or extracellular bacteria. **(C)** In the Masson trichome stained section collagen is stained green. As depicted, there is an intact adjacent blood vessel contrasting an affected blood vessel where collagen strands are among the inflammatory cells, demonstrating that the inflammatory infiltrate occurs within, not around, the vessel wall. **(D)** Demonstrates CD3+ T-lymphocytes within blood vessels and brain parenchyma.

cess, along with microglial activation, in GFAP astrocytopathy has been observed to surround, but not infiltrate blood vessel walls. This is in contrast to our case where a mostly T-lymphocyte predominant encephalitis and vasculitis with T-cell infiltrates of vessel walls occurred with very few B cells and plasma cells. While there has been one reported case of HIV-associated GFAP astrocytopathy (2), our patient's CSF GFAP-IgG antibody studies were negative. A recent report does suggest that meningoencephalomyelitis with radial perivascular gadolinium enhancement on MRI brain may not always be associated with a positive GFAP-IgG antibody (1).

There are many proposed mechanisms of HIV-associated vasculitis. Often it manifests as a result of either opportunistic infections of blood vessels such as VZV, HSV, CMV, tuberculosis, cryptococcus, syphilis, or malignancy such as lymphoma. Nonetheless, even the absence of opportunistic infection or malignancy, primary CNS vasculitis has also been reported in HIV. Other reports support a mechanism that may depend on CD4 count. In one study, all patients with HIV-associated vasculitis had CD4 counts <200 and many had recently initiated cART, suggesting that their vasculitis may be a consequence of IRIS, in the absence of opportunistic infection (10). IRIS has also been reported as a mechanism of HIV-associated CNS vasculitis in response to an underlying opportunistic infection such as tuberculosis, CMV, or VZV. Our patient's mechanism, however, was unlikely due to IRIS as he had a CD4 count of 560 cells/μL and had been adherent to cART for many years.

Our patient's sustained clinical and radiographic responses to a modified cART regimen, in the absence of infectious, autoimmune, or neoplastic etiologies, supports an HIV-driven mechanism that ensued from emerging antiretroviral resistance. HIV-antigens may mediate a vessel directed immune response. The phenomenon of HIV CSF escape occurs when HIV viral RNA levels persist in the CSF despite adequate serum control (3). HIV CSF escape could drive an aberrant CD8+ response (3, 6). Radiographically, patients with HIV CSF escape do develop leukoencephalopathy and perivascular enhancement—strikingly similar to our case (3). As we did not obtain a CSF HIV viral load, we cannot definitively conclude that viral escape was the cause, but the fact that this (i) emerged in the context of HIV resistance (ii) rising serum HIV viral loads and (iii) there was a sustained response to a modified cART regimen are suggestive.

In conclusion, we describe a vasculitis and encephalitis in the setting of HIV cART resistance, manifesting with leukoencephalopathy and perivascular enhancement on MRI and an associated CD8+ T-cell lymphocytic pleocytosis in CSF. We hypothesize that cART resistance with rising HIV viral loads may have precipitated an HIV antigen and/or CD8+ T-cell mediated mechanism of vasculitis and encephalitis that was both clinically and radiographically responsive to corticosteroids and cART optimization.

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