Angiocentric lymph proliferative disorder (lymphomatoid granulomatosis) in a person with newly-diagnosed HIV infection: a case report

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Abstract

Background: Angiocentric lymph proliferative disorder (ALPD) is a granulomatous lymphoproliferative condition associated with various primary and secondary immunodeficiency states. ALPD is so rare that its prevalence has not been established. Typically affecting middle-aged adults, this condition is often found in the context of Epstein Bar Virus infection and consists of angiocentric and angioinvasive pulmonary infiltrates. Herein, we present a biopsy-proven case of a patient manifesting with a viral meningoencephalomyelitis-like picture with brain, spinal cord, renal and splenic lesions. The diagnosis was confirmed to be ALPD in the context of newly diagnosed HIV infection.

Case presentation: A 35 year-old homosexual man presented with a 5-week history of headaches followed by a 3-week history of horizontal diplopia, limb weakness and right 6th cranial nerve palsy. Lumbar puncture revealed a lymphocytic pleocytosis, high protein and low glucose. Magnetic Resonance Imaging showed scattered lesions throughout the brain and spinal cord and Computed Tomography of the abdomen and pelvis revealed hypodensities involving the kidneys and spleen. HIV testing was positive, with a viral load of 11,096 copies/mL and CD4 count of 324 cells/µL. Serum Epstein Bar virus PCR was positive with 12,434 copies/ml. Right frontal brain biopsy revealed gray matter containing angiogentric cerebritis with organizing infarction but Epstein Bar Virus-in situ preparations were negative and no viral inclusions were identified. A diagnosis of ALPD (also known as lymphomatoid granulomatosis) was made. The patient was initiated on antiretroviral therapy and treated with intravenous rituximab every 3 weeks for 4 cycles and made progressive improvements. By the time of discharge his strength had improved and he was ambulating again although with a walker. Within 2 months, his HIV viral load was suppressed. Magnetic Resonance Imaging of the brain 6 months later revealed interval improvement. At his most recent follow-up, 34 months later, his neurological symptoms had almost completely resolved.

Conclusion: Albeit rare, ALPD should be considered in the differential diagnosis of central nervous system lesions in persons with HIV once common etiologies have been eliminated. Furthermore, ALPD involving the central nervous system may occur in the absence of documented EBV infection in the central nervous system.

Keywords: Angiocentric lymph proliferative disorder, Lymphomatoid granulomatosis, HIV
Background

Angiocentric lymph proliferative disorder (ALPD), formerly known as lymphomatoid granulomatosis, is a member of a group of angiocentric and angiodestructive lesions [1]. Lesions are typically composed of EBV positive B-cells intertwined with reactive T-cells [1–3]. The lungs are the most common sites of involvement, followed by the brain [3–5]. Prognosis is generally very poor, especially for persons with central nervous system involvement, and carries a high mortality rate [3, 4, 6]. Although the majority of cases have been reported in immunocompetent individuals, rare cases have been described in individuals with HIV infection [1–16]. Herein, we present the case of 35-year old man with ALPD as the initial presentation of HIV infection.

Case presentation

A 35 year-old man was transferred from a peripheral hospital to the Montreal Neurological Hospital (MNH) in March 2015 for the diagnostic work-up of a viral encephalitis. Past medical history was significant for cocaine abuse and high-risk sexual behavior with male partners. Human immunodeficiency virus (HIV) testing two years earlier was negative. The patient had initially presented to a community hospital with a 5-week history of headaches and 3-week history of horizontal diplopia. Upon this first presentation, a non-contrast cerebral CT scan was unremarkable and he was treated as having migraines. While at home, he developed right upper extremity weakness, bilateral lower extremity weakness in addition to fecal and urinary incontinence. The patient also endorsed a 20-pound weight loss over 5 weeks. Prior to transfer to the MNH, he underwent lumbar puncture (LP) and his cerebrospinal fluid (CSF) had demonstrated a lymphocytic pleocytosis at 280 cells (0–10 cells), increased protein at 1.55 g/L (1.55 g/L) and low glucose of 1.7 mmol/L (2.5 mmol/L). CSF EIA was negative. JC virus PCR was ordered but returned negative with a plasma viral load (VL) of 11,096 copies/mL, Histoplasma capsulatum serum antigen enzyme immunoassay (EIA) was negative, Lyme disease EIA was negative. JC virus PCR was ordered but due to insufficient quantity of CSF, this test was not performed. Toxoplasmosis immunoglobulin (Ig) G was indeterminate at 2.7 IU/mL and IgM was negative. Serum syphilis EIA was negative. HIV testing then returned positive with a plasma viral load (VL) of 11,096 copies/mL and CD4 count of 324 cells/μL (27%), at which point he was treated with emtricitabine 200 mg, tenofovir 300 mg, darunavir 800 mg and ritonavir 100 mg p.o. daily.

Over the course of the first two weeks, the patient displayed signs of improvement with return of DTR and improvements in strength although he was still incontinent of stool. Furthermore, a trial of spontaneous voiding failed and he required reinserterion of the Foley catheter.

During the third week of his admission, the patient underwent brain biopsy of the right frontal lobe. The pathology revealed prominent angiocentric inflammatory patterns, composed of lymphocytes, plasma cells and occasional epithelioid histiocytes. Many of the cortical
vessels showed an obliterative endothelialitis. The cortical inflammation overlaid and was adjacent to areas of sub-acute organizing infarction. Immunohistochemistry for CD45, CD3 and CD20 confirmed that the majority of the cells were CD3+ and only rare B cells were seen. Most of the lymphocytes were T cells and this finding was suggestive of a reactive process. Immunohistochemistry was performed in both blocks of tissue due to the patchy nature of the pathology. Glial fibrillary acidic protein (GFAP) was lost in areas of infarction. There was concomitant loss of neurofilament, indicating true infarction (as opposed to demyelination). The perivascular lymphoplasmacytic inflammatory infiltrates were composed of primarily CD3 positive T cells with fewer CD20 positive B cells. CD68 showed diffuse microglial activation throughout the cortex and was expressed in the lipid laden macrophages in the regions of infarction. The Ki67 expression was surprisingly low, staining only
occasional cells in a perivascular distribution. Stains for both Polyoma virus and toxoplasmosis were negative. There were no viral inclusions and EBV-in situ preparations were also negative. These findings were consistent with grade 1 angiocentric lymph proliferative disorder with a positive EBV PCR in serum (Fig. 3). As the pathology exam yielded the diagnosis, PCR for *Toxoplasmosis gondii* or JC virus DNA were not performed on the brain biopsy. A CT scan was performed following his brain biopsy to ensure no evidence of post-surgical complication. Here it was noted that several of the lesions seen on MRI had partial calcification.

The patient was treated with rituximab 10 mg/kg over 3 weeks for a total of 4 treatments, along with adjunctive steroids. Due to drug interactions, darunavir and ritonavir were replaced by raltegravir 400 mg twice daily. The patient received his first treatment in mid-April 2015 and was discharged 2 weeks later. At the time of discharge, he had a normal mental status. Cranial nerve exam continued to show a right 6th cranial nerve palsy. He also had widespread weakness with upper motor neuron signs, worse in the lower extremities but which had significantly improved. He was also able to ambulate with a walker. Viral load on discharge was 2339 copies/mL and CD4 was 683 cells/μL (CD4 (27%). Fungal cultures of CSF and brain tissue were negative at four weeks and as were Mycobacterial cultures at 12 weeks.

The patient was followed as an outpatient and made progressive improvements. MRI of the head performed in September 2015 showed interval improvement since March 2015 with disappearance of some lesions and reduction of the size of other lesions. No new lesions were identified. At 34 months, his neurological exam and ability to ambulate was normal. However, due to ongoing fatigue he remained off work. His most recent CD4 count in January 2018 was 643 cells/μL (39%) and his HIV viral load has remained undetectable since May 2015.

**Discussion and conclusions**

The first sentinel study on ALPD, or lymphomatoid granulomatosis, was published in the early 1970s by Dr. Averill Liebow and described a series of 40 cases of ALPD [5, 17]. At that time, it was known that ALPD was a unique condition which shared many features with Wegener’s granulomatosis and lymphoma [5]. Involving predominantly extra-nodal sites, ALPD is considered to be a lymphoproliferative disorder [18]. Individuals most often affected are those with underlying immunodeficiencies, either hereditary or acquired [18]. Evolution in the techniques used in the field of pathology occurred over the decades. In the mid 1990s, immunohistochemical staining of paraffin-embedded formalized-fixed tissue enabled confirmation of the presence of clonal B cells and reactive T lymphocytes in a majority of the cases previously described [5]. Today, ALPD is considered a large B-cell lymphoma but distinct from Diffuse Large B-cell Lymphoma (DLBL) [4, 8, 19].

In 2010, Katzenstein et al. reviewed the cases of ALPD over 4 decades, and examined the 8 largest reported case series ranging in size from 11 to 152 cases [5]. Less than 20 case have been HIV-associated [1–16]. The lungs are the sites most often involved and contain bilateral infiltrates or nodules. Pulmonary nodules may display central necrosis and cavitation [5]. The central nervous system, notably the brain, is the second most commonly involved site although both central and peripheral nervous system involvement may occur. Other commonly involved sites include kidneys, liver and skin. Lymph nodes and spleen are rarely involved [4, 5, 8, 19]. The most common clinical symptoms, experienced by more than half of patients, are cough and fever (> 50%). Rash
or nodular skin lesions (40%), malaise and weight loss (35%), neurological symptoms (30%), dyspnea (30%) and chest pain (15%) are also prevalent features [4, 5, 8, 19].

Various radiological features of ALPD may be found. With lung involvement, radiological findings may include pulmonary nodules, cavities, cysts and small pleural effusions [10, 20]. Mediastinal adenopathy is a common finding in over half of patients. However, there are no radiological features of ALPD which are pathognomonic of the condition [10, 20]. With brain involvement, cerebral lesions on CT may consist of multiple, diffusely enhancing lesions in the supratentorial parenchyma [6, 14] which may require intravenous contrast to be visualized [6]. In patients with advanced HIV/Acquired Immune Deficiency Syndrome, Toxoplasmosis and primary CNS lymphoma are the most common causes of ring-enhancing lesions [6]. Moreover, these diseases frequently involve the basal ganglia [6]. Lesions are usually unifocal, situated in the periventricular, temporal, tempoparietal and posterior fossa [6, 21]. These may appear as solid tumor masses or leptomeningeal and parenchymal infiltrates with edema and mass effect [6, 22].

Tissue is required to make a diagnosis of ALPD. Classical histological findings include infiltrates with significant necrosis, usually with a few atypical large B cells in a pleomorphic background of lymphocytes, plasma cells and histiocytes. The infiltrate is characterized pathologically by the accumulation of varying numbers of T cells with variable numbers of atypical clonal EBV-positive B cells which are angiocentric and angioinvasive in a polymorphous inflammatory background [19, 23]. Usually, the large atypical B cells represent a neoplastic component and show evidence of EBV infection [19, 24]. The condition is sub-classified using a grading system based on the number of EBV-positive large B-cell malignant cells. As established by the World Health Organization (WHO) in 2008, three grades of ALPD exist: Grade 1: Large transformed cells are rare (EBV < 5/HPF); Grade 2: Occasional large cells with small clusters (EBV 5–20/HPF); Grade 3: Large aggregates of Reed Sternberg (RS)-like cells (EBV positive cells > 50 HPF). Grading is important to distinguish grade 3 (DLBCL) from grades 1–2 [19], which differ in prognosis. Lower-grade ALPD occasionally undergoes spontaneous remission and is best managed with strategies designed to enhance the host’s underlying immune system. In contrast, high-grade ALPD is best managed by combination chemo-immunotherapy but has inferior outcomes [23].

Our patient had newly diagnosed HIV infection and had undergone negative HIV testing 2 years prior to his presentation. Due to the rare nature of ALPD and limited number of cases in HIV-infected persons, it is unclear whether symptoms in HIV-infected individuals differ from those without HIV. Similarly, due to the overall small number of cases involving HIV-infected persons, it is unknown whether the incidence or clinical presentation of ALPD has changed since the widespread use of HIV antiretroviral therapy in the mid-1990s [3]. The fact that our patient’s CD4 count was 324 cells/μL suggests that he was not severely immunosuppressed. There is one case report which describes ALPD in the context of HIV immune reconstitution inflammatory syndrome (IRIS), which refers to the paradoxical deterioration in the context of improving CD4 count following antiretroviral treatment initiation [3]. In our patient, HIV CSF viral load was not performed since the association between HIV CSF level and cognitive disturbances are not clearly defined [25].

Interestingly, our patient had a high serum EBV viral load but his brain pathology did not display EBV inclusion. This finding may have occurred since the quantity of EBV in the brain was below the level of detection. EBV RNA detected by in situ hybridization is also helpful in establishing the diagnosis. However, sampling error accounts for some of the EBV-negative cases, especially when small biopsies are taken and where patchy EBV positivity could be missed. Furthermore, it is controversial if truly EBV-negative cases of ALPD exist [23]. Like EBV, it has been suggested that HIV itself may cause cellular transformation [2, 6, 10]. Our patient also had a history of cocaine use, similar to the patient reported by Wyen et al. [3]. Whether these patients’ cocaine use contributed to their development of ALPD is unknown.

Brain biopsy may be a necessary tool in the diagnosis of difficult-to-diagnose clinical syndromes. As discussed by Gilkes et al., brain biopsies are especially important for disorders requiring disease-specific therapy which may be toxic, in cases of rapid neurological deterioration and for prion disease diagnosis [26]. Brain biopsies are also especially helpful in cases of CNS lesions in immunosuppressed populations, dementias without a diagnosis, angiogram-negative cerebral vasculitis in addition to cryptogenic neurological diseases [26]. However, there are no clear guidelines to facilitate the selection of the patient, time or location for performing a brain biopsy [26]. The optimal treatment strategy for ALPD is unknown, although steroids, cyclophosphamide, interferon alpha-2b and monoclonal antibodies have all been used [5, 10]. The role rituximab played towards the clinical improvement observed in our patient is unclear, since he began to exhibit some neurological improvement even before rituximab was started. It is also possible that our patient’s HIV antiretroviral therapy, which was commenced prior to rituximab, contributed to his recovery. The natural course of ALPD is variable and
spontaneous remissions have been reported [3, 4]. However, generally the prognosis is very poor, with mortality rates ranging between 38 and 71% [5]. Therefore, albeit rare, ALPD should be considered in the differential diagnosis of CNS lesions in HIV-infected patients and even in the absence of detectable EBV infection.

Abbreviations
ALPD: Angiocentric Lymph proliferative disorder; CNS: Central nervous system; CSF: Cerebral spinal fluid; CT: Computed tomography; DLBL: Diffuse Large B-cell Lymphoma; DTR: Deep tendon reflexes; EBV: Epstein Barr virus; EIA: Enzyme immunoassay; HIV: Human immunodeficiency virus; HPF: High power field; IRIS: Immune reconstitution inflammatory syndrome; iv: intravenous; LP: Lumbar puncture; MNH: Montreal Neurological Hospital; MRI: Magnetic resonance imaging; PCR: Polymerase chain reaction; RNA: Ribonucleic acid; RS: Reed Sternberg; WHO: World Health Organization

Funding
No funding was received for the preparation of this manuscript.

Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study. If a reader would like additional information about the pathology slides or investigations, he or she should contact the corresponding author. In addition, the treatment of pathology slides is currently within the patient's medical files in the Pathology Department of the Montreal Neurological Hospital and can be obtained by contacting the corresponding author. Any identifying information will be removed prior to sharing of images.

Authors' contributions
CTC drafted the manuscript. JK performed the histological examination and provided the histology slides and interpretations. AB provided the radiological images and descriptions. JPR, JS and CF were involved in the clinical work-up and management of the patient. All authors read, edited and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
The patient provided informed written consent for the preparation of this case report and publication of data, including clinical data, imaging and pathological images, in an open access journal. The patient understood that the details/images would be freely available on the internet and may be seen by the general public.

Competing interests
None of the authors have any competing interests.

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Received: 13 February 2018 Accepted: 2 May 2018
Published online: 08 May 2018

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