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Intravascular large B-cell lymphoma masquerading as stroke successfully treated with R-Hyper-CVAD

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A B S T R A C T

Intravascular large B cell lymphoma (IVLBCL) is exceedingly rare and difficult to diagnose. We describe a case of IVLBCL in a 56-year-old male which was identified after recurrent strokes. Right partial nephrectomy was then performed which demonstrated renal oncocytoma and IVLBCL. Chemotherapy was initiated with standard R-Hyper-CVAD which included intrathecal methotrexate and cytarabine. R-CHOP is largely considered the treatment of choice in IVLBCL, however low doses of chemotherapy in this regimen do not cross the blood brain barrier like in R-Hyper-CVAD. The patient achieved complete remission after completion of treatment and has remained in remission for 5 years after diagnosis.

1. Introduction

Diagnosing intravascular large B cell lymphoma (IVLBCL) is a difficult task with an incidence less than 1 in 1000,000 [1]. Symptoms are non-specific and can include fever, sensory and motor deficits, vertigo, vision loss, poorly circumscribed violaceous plaques, or other organ-specific symptoms [2,3]. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) is the therapy of choice. In cases with brain or CSF infiltration by lymphoma cells, methotrexate may be added to cross the blood brain barrier (BBB) [4]. Intrathecal therapy particularly in cases with CNS involvement is poorly understood, however high dose methotrexate with intrathecal chemotherapy appears to be effective in patients without this factor [5,6].

We describe a case of IVLBCL presenting with recurrent stroke symptoms that were of unclear etiology. The patient underwent a partial nephrectomy performed for a right renal mass ultimately diagnosed as concurrent oncocytoma and IVLBCL. This was treated with standard R-Hyper-CVAD that included intrathecal methotrexate and cytarabine (Appendix for treatment protocols) [7]. Complete remission was achieved and has been maintained for 5 years following diagnosis.

2. Case presentation

A 56-year-old male with a new diagnosis of IVLBCL was referred to our clinic for management. His past medical history included well-controlled diabetes and hyperlipidemia. He initially presented to the hospital for stroke symptoms, including vertigo, hearing loss and tinnitus in the right ear, emesis, diaphoresis, and right facial paresthesia. An MRI showed bilateral restricted diffusion in the frontal lobe. A transesophageal echocardiogram and a carotid Doppler were both negative. Aspirin was started at this time.

Following this episode, he continued to present with symptoms of TIA and stroke. A repeat MRI without contrast was performed a month later and subacute ischemic injury in the right inferior frontal lobe, right parietal lobe, and left frontal lobe were noted (Fig. 1a). Hypercoagulability workup was negative at this time. Due to recurrent strokes, apixaban was started but was switched to enoxaparin after new subacute changes in the right frontal lobe, occipital lobes, right pons, and left parietal lobe were observed on new MRI (Fig. 1b). Cardiology workup for thromboembolism including echocardiogram and Holter monitor was negative. Shortly after this, blurry vision and impaired depth perception prompted a repeat angiogram suggestive of vasculitis. Prednisone was started, though workup for vasculitis was later negative. A lumbar puncture revealed negative cytology, low WBC count of 2 WBC/cmm (1 % neutrophils, 84 % lymphocytes, 15 % monocytes), and elevated proteins of 108 mg/dL with a normal multiple sclerosis profile. Flow cytometry was negative along with CSF culture.

Near the same time, a CT chest/abdomen/pelvis revealed splenomegaly and a right kidney mass concerning for renal cell carcinoma. After stabilization, he underwent a right partial nephrectomy for the mass measuring 1.9 × 1.8 × 1.7 cm. On pathology, there were focal areas with intravascular clusters of large, transformed lymphocytes with

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small nucleoli consistent with centroblasts (Fig. 2a). Immunohistochemistry revealed that the cells were CD20+, PAX5+, CD10 trace+, BCL-6+, BCL-2+, MUM-1+ and negative for BCL-1 and CD34 (Fig. 2a/b). Both the morphology and immunophenotype were diagnostic for diffuse large B-cell lymphoma, best classified as IVLBCL. Ki-67 staining was 100 %. Concurrent oncocytoma was also noted.

Bone marrow biopsy, lumbar puncture, and flow cytometry were performed and found to be negative for lymphoma involvement prior to chemotherapy initiation. There was a normal cytogenetic result with a 46, XY chromosome complement. CBC noted the following: hemoglobin of 13.8 g/dL, WBC count of 7.8 thou/cmm (46 % neutrophils, 19 % lymphocytes, 24 % monocytes, 0 % eosinophils, 2 % basophils, 5 % band, 4 % myelocytes), and platelets of 187,000. Peripheral smear revealed slight anisocytosis, spherocytes, and stomatocytes. LDH was 603 U/L. CT showed adrenal lesions along with a right anterior renal mass measuring 2.4 × 1.7 cm. The treatment regimen included 8 cycles of R-Hyper-CVAD given over 8 months [8]. Odd cycles included high doses of cyclophosphamide, vincristine, doxorubicin, and dexamethasone. Even cycles had high doses of methotrexate and cytarabine. Rituximab and two doses of intrathecal chemotherapy, one dose each of methotrexate and cytarabine, were utilized in both odd and even cycles (Appendix). PET scan revealed size reduction to 1.4 × 1.3 cm in the right renal lesion after 2 cycles of chemotherapy. Following completion of all 8 cycles, no evidence of hypermetabolic malignancy remained on skull base to mid-thigh PET scan. Prednisone and enoxaparin were discontinued at this time. An MRI of the brain one year later demonstrated only chronic stable infarcts. Further imaging over the next 4 years after finishing chemotherapy has been negative for recurrence, and the patient has experienced no further cerebrovascular accidents or symptoms related to IVLBCL.

3. Discussion

IVLBCL is a rare type of extranodal diffuse large B-cell lymphoma characterized by the proliferation of large lymphoma cells within the lumina of small blood vessels. IVLBCL is a Stage IV systemically disseminated disease with an International Prognostic Index score of high-intermediate to high in most cases [9]. In the United States, the incidence is reported as less than 1 case per every 1000,000 people [1]. Biopsy is the gold standard for diagnosis. Bone marrow, brain, lung, or skin lesions are the most prototypical biopsy sites to confirm the diagnosis, but incidental biopsies from unaffected organs have also been reported [10]. IVLBCL is extremely difficult to diagnose due to heterogeneity of clinical symptoms and a lack of focal disease [10]. This varied presentation is because of the indiscriminate occlusion of small vessels in different tissues and a global dysregulation of cytokines [10]. Elevated levels of serum lactate dehydrogenase (LDH) and soluble interleukin 2 receptor can be suggestive of disease [10]. Due to delays in diagnosis, prognosis is poor in most cases with a median survival time of 340 days in 182 cases studied between 2008 and 2018 [4,10]. Consequently, over half of patients are diagnosed postmortem [10]. CNS involvement is a particularly poor prognostic factor (HR = 2.2, 95 % CI 1.1–4.7, $P = 0.04$) [4]. High KI-67 proliferative index, as with our patient, is also a poor prognostic factor associated with shorter survival [4]. Renal involvement is rarely described in IVLBCL [11]. Of 28 cases reported in the literature, 50 % of patients were alive 6 months after kidney biopsy proven IVLBCL. 32 % had died, while the remainder had follow-up that was too short [11].

CHOP is acknowledged as the primary combination of choice for IVLBCL [4]. Rituximab has recently been added to this regimen (R-CHOP), and it has led to significantly higher rates of complete response, two-year progression free survival, and two-year overall survival [12]. R-CHOP, however, does not cross the BBB [4]. R-Hyper--CVAD, on the other hand, does contain CNS-penetrating agents [8]. This regimen has been primarily utilized in various aggressive non-Hodgkin's lymphomas and acute lymphoblastic leukemia which is known for its high rate of CNS involvement [13–16]. CNS penetration and bioavailability is achieved with high dose methotrexate and cytarabine, along with the same agents also administered intrathecally [13]. The extensive CNS involvement seen with our patient thus provoked the use of R-Hyper-CVAD [4].

Analysis of regimens utilizing BBB penetrating drugs on IVLBCL with CNS involvement have not yielded significant conclusions thus far [4]. Liu et al. explored the use of BBB-penetrating agents in IVLBCL but were only able to compare 11 patients with this method versus 77 patients without. There was no significant difference in complete response ($p =$

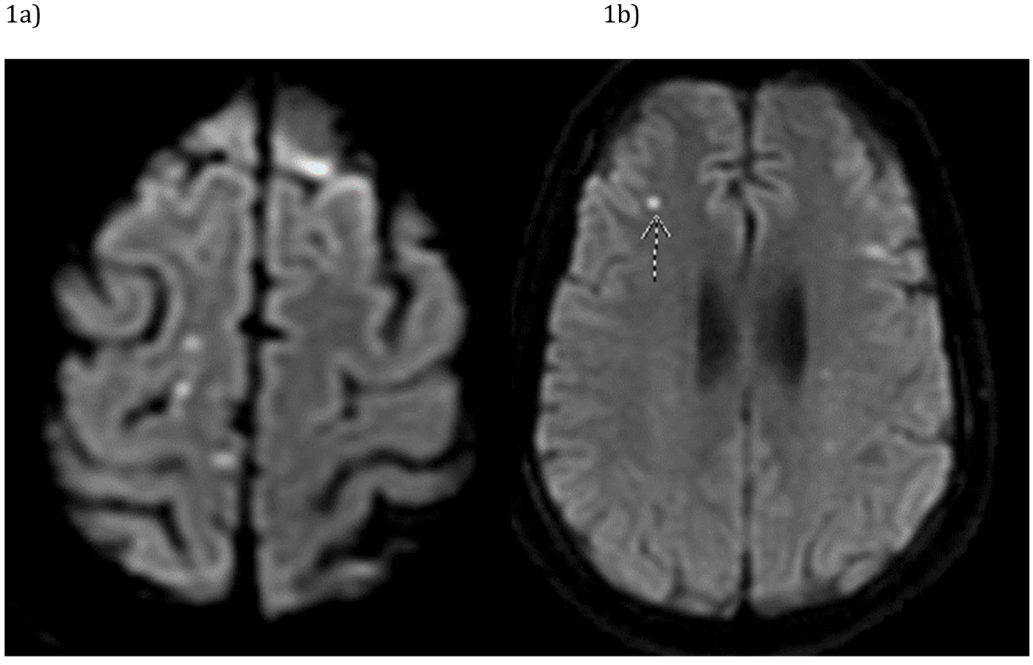

Fig. 1. (a) MRI without contrast that noted subacute ischemic injury in the right inferior frontal lobe, right parietal lobe, and left frontal lobe (b) MRI demonstrating subacute changes in right frontal lobe, occipital lobes, right pons, and left parietal lobe.

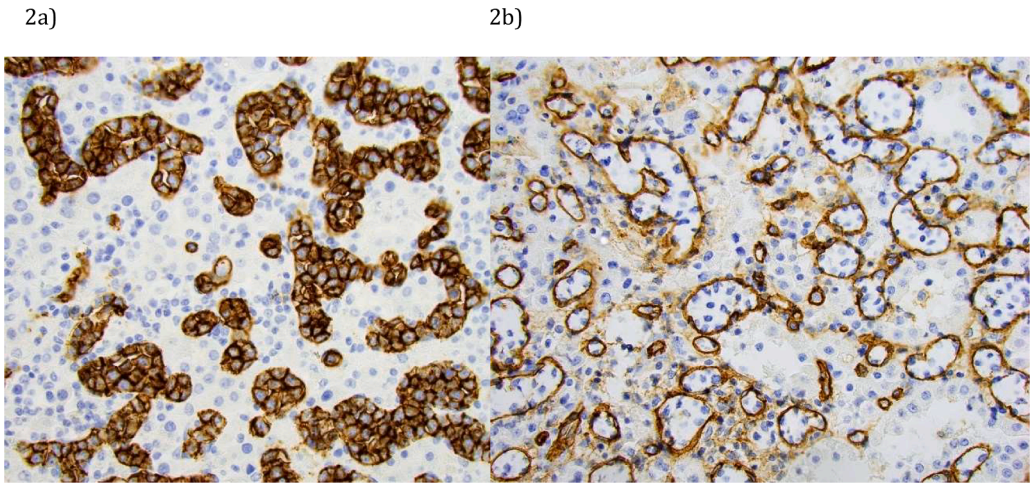

Fig. 2. (a) CD20 highlighting large intravascular B-lymphocytes, 40x magnification (b) CD31 highlighting vascular endothelium, 40x magnification.

0.163) or longer overall survival ($p = 0.144$), although the patients with the use of BBB-penetrating agents performed better in each category. R-Hyper-CVAD has been previously utilized in the case of a 47-year-old woman with a pontine lesion without neurological symptoms and a normal CSF analysis. In this case, R-Hyper-CVAD/R-MTX-Ara-C with intrathecal methotrexate was utilized for 5 cycles of chemotherapy and achieved complete remission for 2 years [17]. The utilization of intrathecal chemotherapy in patients without CNS involvement has been described as a safe and active treatment when combined with R-CHOP, rituximab, and high dose methotrexate [5]. No clinical trials for IVLBCL with CNS involvement utilizing intrathecal chemotherapy have been initiated, although case reports have reported successful use [17,18]. The differential use of therapy in IVLBCL is likely due to the primary mechanism by which IVLBCL causes stroke symptoms not being completely understood [4]. Shimada et al. also noted a need for further analysis on patients with IVLBCL who have CNS involvement at diagnosis [19].

Concerns have been shared regarding the Hyper-CVAD regimen in the IVLBCL population due to the toxicity of the escalated regimen [19]. The patient in our case tolerated R-Hyper-CVAD well without any adverse effects, citing only mild constipation and vomiting.

Immunohistochemical analysis among patients with IVLBCL is largely homogenous. CD10 positivity like in our case has been seen in 12 % of patients, although the significance of this is currently uncertain [20,21].

4. Conclusion

A case of IVLBCL in a 56-year-old male discovered by right partial nephrectomy after recurrent strokes was treated successfully with R-Hyper-CVAD and intrathecal methotrexate and cytarabine with possible cure 5 years after diagnosis. This represents the first published utilization of this combination to our knowledge in a patient with symptomatic CNS involvement, and it provides further experience with the treatment of IVLBCL in this subset of patients. IVLBCL, though rare, must be considered in cases of recurrent stroke without clear etiology. Additional research is necessary to fully understand the optimal treatment regimen in such a rare pathology especially considering the nebulous nature of how IVLBCL causes stroke symptoms.

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Informed consent

Informed consent was obtained.

Declaration of Competing Interest

None.

Appendix: R-Hyper-CVAD regimen

R-Hyper-CVAD - Cycles 1, 3, 5, 7:

Day 0: METHOTREXATE 12 mg INTRATHECAL.

Day 1: Pre-medicate with chlorphenamine 10 mg IV, paracetamol 1 g 30 min before rituximab. Give day 1 dexamethasone at least 30 min prior to rituximab. RITUXIMAB 375 mg/m^2 IV infusion daily in 500 mL sodium chloride 0.9 %.

Days 1–3: MESNA 600 mg/m^2 per day IV continuous infusion in 1000 mL sodium chloride 0.9 % over 24 h (to begin 1 h before cyclophosphamide and stopping 12 h after final dose).

Days 1–3: CYCLOPHOSPHAMIDE 300 mg/m^2 twice a day IV infusion in 250 mL sodium chloride 0.9 % over 2 h for 6 doses.

Days 1–4: DEXAMETHASONE 40 mg PO/IV daily (2 mg tablets).

Day 4: DOXORUBICIN 50 mg/m^2 IV infusion daily in 100 mL sodium chloride 0.9 % over 2 h.

Day 4: VINCRISTINE 1.4 mg/m^2 (maximum 2 mg) IV infusion in 50 mL sodium chloride 0.9 % over 10 min. Consider capping at 1 mg in the over 70-year-old age group. Day 5 G-CSF as per local policy. Continue until neutrophils $>1.0 \times 10^9$/L for 3 consecutive days.

Day 7: CYTARABINE 100 mg INTRATHECAL.

Days 8–11: DEXAMETHASONE 40 mg PO/IV daily (2 mg tablets).

Day 11: VINCRISTINE 1.4 mg/m^2 (maximum 2 mg) IV infusion in 50 mL sodium chloride 0.9 % over 10 min. Consider capping at 1 mg in the over 70-year-old age group.

R-MA - Cycles 2, 4, 6, 8:

Day 0: Hydration/Alkalinization – Pre-methotrexate. Refer to supportive treatment section below.

Day 1: RITUXIMAB 375 mg/m^2 IV infusion daily in 500 mL sodium chloride 0.9 %.

Day 1: METHOTREXATE 1 g/m^2 IV in exactly 500 mL sodium chloride 0.9 % over 24 hrs.

Calcium folinate (Folinic acid) post methotrexate (starting 36 h from the start of methotrexate). Refer to supportive treatment section below.

Day 2 METHOTREXATE 12 mg INTRATHECAL (following completion of IV methotrexate).

Days 3 & 4 CYTARABINE* 3 g/m^2 IV infusion (at 24, 36, 48 and 60 h after completion of IV methotrexate) in 500 mL sodium chloride 0.9 %

over 2 h. *In patients aged 60 years or more, reduce cytarabine to 1 g/m^2

Day 5 G-CSF as per local policy. Continue until neutrophils >1.0 × 10^9/L for 3 consecutive days.

Day 7 CYTARABINE 100 mg INTRATHECAL.

Supportive Treatment for R-MA:

Intravenous Hydration

Start: 12 h before methotrexate. Fluid: 1000 mL glucose 2.5 %, sodium chloride 0.45 % with potassium chloride 20 mmol and sodium bicarbonate 100 mmol added. Following completion of methotrexate infusion, decrease amount of sodium bicarbonate in fluids to 50 mmol/L.

Flow rate: 200 mL/hour (or 150 mL/hour if BSA less than 1.6 m^2).

Duration: Continue fluids during methotrexate infusion (run concurrently with methotrexate, through one arm of Y extension). Administer fluids until methotrexate level < 0.1 micromol/L

Methotrexate Levels

Check 48 h after the start of the methotrexate infusion, and every 24 h thereafter until methotrexate level less than 0.1 micromol/L

Urine Output

Check: Every 4 h. Aim: 400 mL/m^2/4 h (approx. 700 mL over 4 h). Furosemide: Administer 20–40 mg to maintain urine output.

Folinic Acid Rescue

Start: 36 h from the start of methotrexate infusion. Dose: 30 mg every 3 h for 5 doses, then every 6 h until methotrexate level is less than 0.1 micromol/L. Administration: Give intravenous boluses for at least the first 4 doses then change to oral if the patient is compliant and not vomiting.

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