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Central nervous system (CNS) Richter's transformation and parvovirus B19 infection

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A 67-year-old man presented to us in January 2010 with progressive fatigue and abdominal discomfort. The referral diagnosis was refractory chronic lymphocytic leukemia (CLL). He was diagnosed with Rai stage I CLL in 2002. In 2004, he was treated with single-agent chlorambucil for 3 months and had a partial response (PR). He received chlorambucil intermittently until 2007. Because of progressive lymphocytosis and abdominal lymphadenopathy, he was treated with single-agent fludarabine (3 cycles), with minimal response, and was observed until July 2009. Four courses of pentostatin, cyclophosphamide, and rituximab were administered until November 2009. The patient experienced clinical improvement but only a PR with bulky abdominal lymphadenopathy, as assessed by computed tomography (CT) scans.

On presentation, his physical examination was normal. His WBC count was 4.5 K/UL, his hemoglobin was 13.1 g/dl, and his platelet count was 197 K/UL. An abdominal CT scan revealed bulky (>5 cm) intra-abdominal lymphadenopathy, with a conglomerate of lymph nodes of up to 9 × 5.3 cm in the peri-pancreatic region. A bone marrow (BM) aspiration biopsy revealed nodular BM infiltration by small lymphocytes and the presence of proliferation centers. Flow cytometry (FC) studies of the BM aspirate were diagnostic of CLL (CD5, CD19, and CD23 – positive monoclonal lambda light chain-expressing B cells). CD38 expression was high (64%), and BM Zap-70 was strongly positive by immunohistochemistry (IHC). A cytogenetic analysis revealed a diploid karyotype and fluorescence in situ hybridization analysis did not detect del13q, del11q, trisomy 12, or del17p. Somatic IgH hypermutation could not be done. The patient was treated with intravenous ofatumumab weekly for 4 weeks (300 mg week 1; 1000 mg weeks 2 to 4),

monthly during months 2–6, and every other month during months 7–24. He was given 10 mg of oral lenalidomide on day 9, which was continued as per research protocol 2009–0283. The lenalidomide dose was reduced to 5 mg every 3 days because of the appearance of blisters on both legs and grade 3 neutropenia and pneumonia, diagnosed within 4 months of the initial therapy. He had stable disease and a PR, with a decrease in the size of abdominal lymph nodes and symptomatic improvement.

In April 2012, the patient experienced acute-onset anemia. His hemoglobin level dropped from 13 mg/dl to 6.5 mg/dl over 2 weeks, with no active bleeding or hemolysis. His WBC was 3.1 K/UL and his platelet count was 222 K/UL. The reticulocyte count was 0. A BM biopsy revealed tri-lineage hypoplasia (10% cellularity) and multifocal small lymphocyte aggregates, consistent with persistent CLL. Of note, the BM revealed severe hypoplasia of erythroid lineage, several giant pro-normoblasts with viral nuclear changes and a ground glass appearance, and enlarged nuclei that positively stained for parvovirus B-19 (IHC antibody Dako) (arrow in Figure 1A, B). He was diagnosed with pure red blood cell aplasia (PRCA) induced by parvovirus B-19 and was treated with one course of 0.5 g/kg intravenous immunoglobulin (IVIG) for 4 days, with a hemoglobin improvement to 13 g/dl that lasted about a month.

In May 2012, he presented again because of fatigue and WBC of 3.4 K/UL, hemoglobin of 10.8 g/dl, platelets of 127 K/UL, RBC count of 3.68 M/UL and a reticulocyte count of 5.7%. He was given 60 mg of prednisone orally, with tapering doses, suspecting auto-immune hemolysis although coombs test was negative. A repeat BM examination revealed tri-lineage hematopoiesis and persistent CLL. A positron emission tomography-CT scan (PET-CT) revealed stable intra-abdominal disease.

The patient presented to the emergency room in June 2012 with worsening symptoms of gait disturbance, tremors, slurred speech, marked fatigue, intermittent confusion, and visual impairment. An examination revealed cerebellar signs, intentional tremor, dysmetria, hearing loss in the right ear, truncal ataxia, and dysarthria. His WBC was 2.2 K/UL, Hb 11.7 g/dl, platelet count 185 K/UL with absolute neutrophil count 0.84K/UL, and RBC count 3.72 M/UL. Other standard biochemical tests were normal, as were vitamin B12 and E levels and a para-neoplastic antibody panel. BM and PET-CT scan findings showed a stable disease, with no evidence of Richter's transformation (RT). Magnetic resonance imaging of the brain and orbits revealed multiple scattered fluid-attenuated inversion recovery hyperintensities in the posterior pons and deep white matter, consistent with chronic microvascular disease, and no leptomeningeal involvement. No evidence of significant carotid stenosis by color doppler sonography or vascular insufficiency by CT angiogram was seen. An ophthalmological examination suggested anisocoria; optic disc pallor (Figure 1C–D) and a bilateral afferent pupillary defect, suggestive of bilateral retrobulbar optic neuropathy. Ocular coherence tomography revealed significant nerve fiber layer loss.

A diagnostic lumbar puncture (LP) revealed clear cerebrospinal fluid (CSF), a WBC of 76/μl, glucose of 80 mg/dl (normal, 40–70 mg/dl), and protein of 60 mg/dl (normal, 15–55 mg/dl). The differential count revealed that 80% of the CSF consisted of small lymphocytes, admixed with numerous large atypical lymphocytes stained with Romanowsky stain (see

arrow in Figure 1E; 60× magnification). Antibody for parvovirus staining for these atypical lymphocytes did not work on cytospin samples of CSF. A FC analysis of CSF cells revealed monoclonal lambda light chain-expressing large lymphocytes that were CD19 and CD20 positive (Figure 1F) and CD5 and CD10 negative, compatible with RT. A small population of CD5-positive T cells was also present. CSF culture, gram, Calcufluor White, fungal, and acid-fast bacillus stains were negative. A polymerase chain reaction analysis of the CSF did not reveal cytomegalovirus, herpes simplex 1 or 2, cryptococcus, Epstein-Barr virus (EBV), Jamestown Canyon virus, human herpesvirus-6, West Nile virus, or varicella virus. However, we did detect parvovirus B19 in both the serum and CSF.

On the basis of this complex clinical presentation, we diagnosed acute-onset basilar meningo-encephalitis and optic neuropathy, secondary to localized CNS-RT to diffuse large B cell lymphoma, with systemic (BM and CSF) parvovirus B-19 infection. The patient was treated with empirical broad-spectrum antimicrobials, antifungals, antivirals, and dexamethasone while serologic and other diagnostic tests were performed. He was then treated with IVIG for the parvovirus infection, along with 50 mg of intrathecal liposomal cytarabine and 10 mg of empirical intrathecal rituximab. He was also treated with high-dose cytarabine (2 g/m² intravenously daily for 5 days) and palliative whole-brain radiotherapy (WBRT) of 24 Gy in 5 fractions. After about 10 days, a repeat LP revealed clearance of atypical lymphocytes, but his cognitive dysfunction and general condition worsened. Because of the palliative nature of the condition and the patient's poor prognosis, he was taken home for supportive care and died within few days. Our patient's clinical presentation was unique and highlighted several important clinical and biological questions. Thus far, no definitive viral etiology for CLL or RT has been identified (1). A few reports have suggested that (EBV)(2), Merkel cell virus (3), and torque teno virus may play a role in CLL (4), but the relevance of parvovirus B19 infection in CLL is unknown.

We detected parvovirus B19 in the CSF of our patient, who also had RT localized to CNS. We hypothesized that either this was mere co-incidental detection with two different pathological processes in the brain or a preexisting parvovirus B19 in the BM and CSF somehow promoted a localized CNS-RT. We do not have any clear evidence that parvovirus promoted the CNS-RT. Very few reports showed an association of parvovirus infection in lymphomas.(5, 6) Parvovirus B19 is known to cause PRCA (7). Neurological involvement by parvovirus infection is uncommon (8), (9). Parvovirus-induced neurological manifestations can involve the CNS or peripheral nervous system. The prognosis for meningeal involvement is poor. Our patient had refractory CLL; he developed parvovirus B19-induced PRCA. Within 3–4 weeks, he presented with pan-cerebellar and basilar meningo-encephalitis and optic neuropathy, with no identifiable etiology. Isolated RT in the nervous system is rare (only 16 cases have been reported) and is associated with a poor prognosis (10), (11). Another complex issue in our case was treatment, as no clear guidelines exist on treating such patients. On the basis of limited evidence and a working diagnosis, we treated our patient with intrathecal liposomal ara-C (12), rituximab (13), high-dose systemic ara-C, WBRT, and IVIG therapy.

A systemic (CSF and BM) parvovirus B19 infection occurring concurrently with isolated CNS RT may lead one to speculate that the parvovirus infection possibly played a role in the

development of CNS-RT. Viral infections induce lymphomatous transformation in immunodeficient and autoimmune conditions by different mechanisms (e.g., direct cytotoxicity, immune stimulation, nuclear transcription factor activation, and endothelial dysfunction). Classic examples of this include Burkitt's lymphoma and EBV infection (14). In one report in acute lymphoblastic leukemia, the DNA methylation pattern of the leukemia cells was associated with a history of parvovirus B19 infection (15). Parvovirus B19 might have precipitated the localized RT in our patient by a similar mechanism because the infection preceded the neurological symptoms.

To our knowledge, this is the first reported case of CNS RT with a coincidental or possible association with parvovirus in CNS. Further research is needed to determine parvovirus B19's role in CLL and RT. Clinicians should be vigilant about the neurological manifestations of parvovirus and localized CNS RT. The development of CNS-specific treatment protocols in CNS RT is also warranted.

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Figure 1.

(A–B) Parvovirus B19 inclusions and giant pro-normoblasts in the BM. (C–D) Bilateral optic disc pallor. (E–F) Lymphomatous cells in CSF and flow cytometry dot plots reveal (CD19+, CD20+ transformed, large lymphomatous cells in the CSF, with small lymphocytes.