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ORIGINAL ARTICLE

Rapidly progressive dementia due to intravascular lymphoma: A prion disease reference center experience

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Abstract

Background: Intravascular large B-cell lymphoma (IVLBCL) is a rare extranodal lymphoma that is characterized by the selective growth of neoplastic cells in blood vessels, representing a potentially treatable cause of rapidly progressive dementia (RPD). Given its diverse clinical and instrumental presentation, it is often misdiagnosed with more common RPD causes, for example, Creutzfeldt-Jakob disease (CJD) or vascular dementia.

Methods: This study presents the clinical and histopathological characteristics of four IVLBCL cases that we diagnosed post-mortem over 20 years among over 600 brain samples received as suspected CJD cases at our prion disease reference center.

Results: Our patients exhibited various presenting symptoms, including behavioral disturbances, disorientation, and alertness fluctuations. The diagnostic tests performed at the time, including blood work, cerebrospinal fluid (CSF) analyses, electroencephalography, and neuroimaging, yielded nonspecific and occasionally misleading results. Consequently, the patients were repeatedly diagnosed as variably having CJD, epilepsy, vascular dementia, and encephalitis. The stored CSF samples of two patients tested negative at prion real-time quaking-induced conversion (RT-QuIC), which we performed afterwards for research purposes. Neuropathological analysis revealed a differential involvement of various brain areas, with frontotemporal neocortices being the most affected.

Conclusions: Our results confirm the significant clinical and instrumental heterogeneity of IVLBCL. Neuropathological evidence of the preferential involvement of frontotemporal neocortices, potentially conditioning the clinical phenotype, could be relevant to reach an early diagnosis. Finally, given the therapeutic implications of its misdiagnosis with CJD, we emphasize the utility of prion RT-QuIC as a test for ruling out CJD in these patients.

KEYWORDS
Creutzfeldt-Jakob disease, intravascular lymphoma, prion, rapidly progressive dementia, RT-QuIC

INTRODUCTION

Intravascular large B-cell lymphoma (IVLBCL) is a rare extranodal lymphoma characterized by the selective growth of neoplastic cells within the lumen of small and medium-sized blood vessels [1–3]. Three main clinical variants have been described: a classical variant showing multi-organ involvement, a cutaneous variant with skin lesions and negative systemic staging, and a hemophagocytic

syndrome-associated variant characterized by bone marrow involvement, fever, hepatosplenomegaly, and thrombocytopenia. As IVLBCL prognosis has significantly improved with the introduction of rituximab, it is important to achieve a clinical diagnosis as quickly as possible [4, 5]. However, this is frequently hampered by the nonspecific symptoms of IVLBCL in the absence of a tumor mass.

Although the clinical manifestations of the IVLBCL classical variant are highly heterogeneous depending on which organ is mainly involved, neurological signs, isolated or within a systemic syndrome, manifest in up to 35% of patients [4]. IVLBCL is a rare cause of rapidly progressive dementia (RPD) [6], and brain biopsies to identify neoplastic cells are fully integrated into RPD diagnostic algorithms [7, 8]. Nevertheless, the diagnosis is often missed or delayed, especially when the clinical presentation, laboratory, neurophysiology, and imaging findings meet the diagnostic criteria for more common causes of RPD, such as sporadic Creutzfeldt-Jakob disease (sCJD) or vascular dementia [7–9].

This article stems from our 20 years of experience in RPD as a reference center for prion diseases in Italy, during which we diagnosed four IVLBCL cases. Here, we describe their clinical and histopathological characteristics and discuss the clinical hints that could be useful in elucidating the syndrome's etiology.

METHODS

We identified four cases with a post-mortem diagnosis of IVLBCL from over 600 brains received at the Neuropathology Laboratory of the *Istituto delle Scienze Neurologiche di Bologna* from January 2001 to April 2022 as suspected CJD cases. In all of them, the diagnosis of prion disease was excluded by prion protein immunostaining and Western blotting. We reviewed the medical records and retrieved the clinical, blood, and cerebrospinal fluid (CSF) testing data (including protein 14–3-3 Western blot [WB] assay results and total tau [t-tau] levels), electroencephalographic recordings (EEG), computed tomography (CT), and magnetic resonance imaging (MRI) findings. In addition, when CSF was available for analysis, second-generation CSF prion real-time quaking-induced conversion (RT-QuIC) assays were performed as previously reported [10]. Eventually, neuropathological and immunohistochemical examinations were performed (see Supplementary material for further details).

Ethical standards

The study was conducted according to the revised Declaration of Helsinki and Good Clinical Practice guidelines and approved by the local ethics committee (approval number AVEC:18025, 113/2018/OSS/AUSLBO). Written informed consent was given by study participants or the next of kin.

RESULTS

Clinical data and instrumental findings are shown in Table 1.

Case #1

A 71-year-old retired teacher with a medical history of hypertension and chronic obstructive pulmonary disease was admitted after a 1-month history of apathy, depression, episodes of spatial disorientation, inability to find words, and impaired computational skills. The neurological examination was unremarkable, and a head CT showed no central nervous system injury signs. Two weeks after her release, she was found in bed in an acute confusional state, unable to recognize and interact with her relatives. Upon readmission, her mental state improved, and the neurological examination, besides slight dysarthria, was normal. A head CT showed a mild left frontotemporal hypodensity. An MRI performed a week later revealed, in T2-weighted sequences, multiple bilateral hyperintense lesions in the cortex and the white matter of centra semiovale and corona radiata. The patient was diagnosed with ischemic stroke in the context of severe chronic vascular encephalopathy. During the next 2 months, her health condition deteriorated. She started experiencing complex visual and auditory hallucinations, sudden mood swings, and further cognitive decline. Another head CT showed no change compared to the previous one. Two months after the disease onset, she was admitted to the Internal Medicine Department, feverish and incapable of speaking and walking. Neurological examination showed an acute confusional state, left sensory-motor hemisyndrome, and bilateral Babinski sign. Routine blood work and CSF testing showed no significant abnormalities. The EEG showed signs of widespread cerebral dysfunction. A chest X-ray reported pulmonary infiltrates. She developed respiratory failure and electrolyte imbalance in a few days, slipped into a coma, and died.

Case #2

A 74-year-old man, with a medical history of coronary artery disease, hypertension, and dyslipidemia, presented with a 1-month history of progressive cognitive decline, behavioral disturbances, emotional lability, and vision loss. He had experienced an episode diagnosed as a transient ischemic attack 3 weeks before. The neurological examination was unremarkable. Blood testing showed mild anemia, erythrocytopenia, elevated lactate dehydrogenase (LDH), and C-reactive protein (CRP). A head CT disclosed bilateral multiple hypodense areas in the cortex and the white matter of centra semiovale and corona radiata, mainly in the bilateral frontal and left parieto-occipital areas. He received a diagnosis of chronic vascular encephalopathy and was sent home. During the following months, he rapidly lost his functional autonomy. Three months later, he was admitted to the

TABLE 1 Clinical characteristics, laboratory, and imaging findings in the four patients.

Case	#1	#2	#3	#4
Age at onset, years	71	74	73	81
Ethnicity	White	White	White	White
Sex	Female	Male	Male	Female
Presenting clinical features	Apathy, depression, episodes of spatial disorientation, inability to find words, and impaired computational skills	Behavioral disturbances, emotional lability	Spatial–temporal disorientation, fluctuating cognition	Transitory loss of consciousness and acute confusional state
Blood testing results[a]	None	Anemia, high LDH, and CRP	Anemia, thrombocytopenia, high LDH, ACE, and CRP	Anemia, thrombocytopenia, hyperleukocytosis with normal differential leukocyte count, high CRP, and positive anti-Ro60 antibodies
CSF testing results[a]	None	-	Hyperproteinorrachia, altered Link index, positive oligoclonal bands, high t-tau levels, and negative 14–3-3 WB assay	Hyperproteinorrachia, high t-tau levels, and positive 14–3-3 WB assay
CSF prion RT-QuIC	-	-	Negative	Negative
EEG[a]	Diffuse slowing of background activity	Diffuse slowing of background activity and generalized PSWC	Diffuse slowing of background activity with delta waves in the anterior regions and generalized PSWC	Diffuse slowing of background activity, prevalent in the right hemisphere
Imaging findings[a]	MRI: multiple bilateral hyperintense lesions in the cortex and the white matter of centra semiovale and corona radiata on T2-weighted imaging	CT: bilateral multiple hypodense areas in the cortex and the white matter of semioval centra and corona radiata, mainly in the bilateral frontal and left parieto-occipital areas	MRI: multiple cerebral hyperintense white matter lesions in both hemispheres on FLAIR sequences; no contrast enhancement on T1-enhanced images	MRI: multiple bilateral hyperintense lesions in the white matter of corona radiata in both the cerebral hemispheres on long TR sequences
Clinical diagnosis	Vascular dementia, suspected sCJD	Vascular dementia, possible sCJD	Epilepsy, vascular dementia, encephalitis, suspected sCJD	Epilepsy, vascular dementia, encephalitis, suspected sCJD
Disease duration (weeks)[b]	10	16	8	4

Abbreviations: ACE, angiotensin-converting enzyme; CRP, C-reactive protein; CT, computerized tomography; FLAIR, fluid-attenuated inversion recovery; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PSWC, periodic sharp wave complexes; sCJD, sporadic Creutzfeldt-Jakob disease; t-tau, total tau.

[a]Only abnormal findings are reported.

[b]Disease duration is defined as the timespan between the symptoms' onset and death.

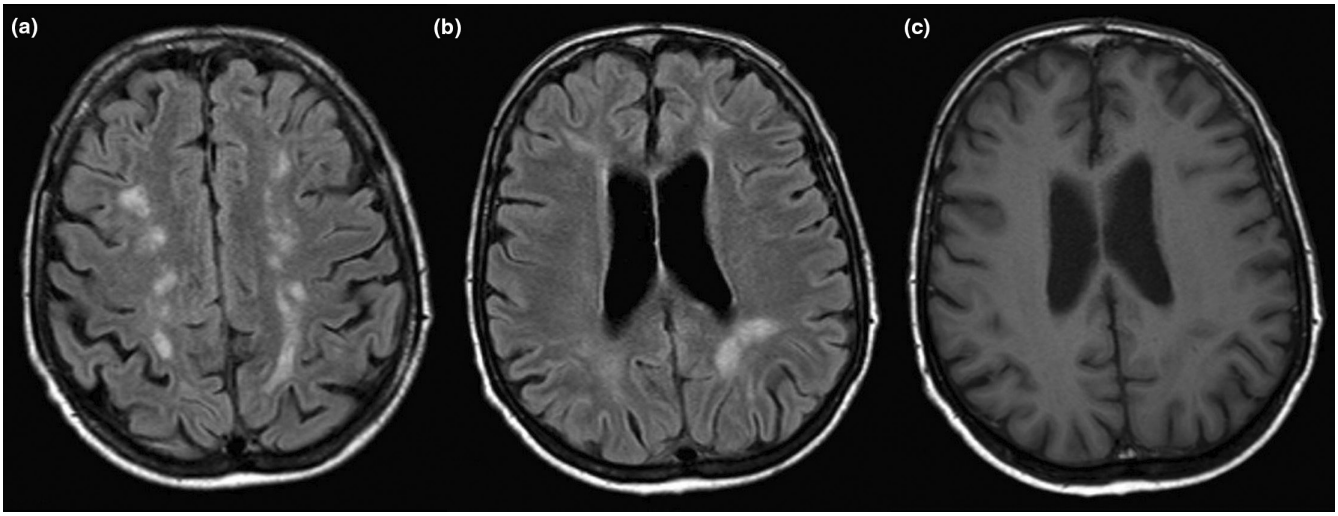

FIGURE 1 Case #3 brain magnetic resonance imaging. (a, b) Axial T2-fluid attenuated inversion recovery images of the brain showing bilateral multiple subcortical hyperintense white matter lesions sparing the "U" fibers, prevalent on the left hemisphere, interpreted as signs of demyelinating/inflammatory disease. (c) Axial T1 contrast-based imaging showing no contrast enhancement of lesions.

Internal Medicine Department for acute bronchopneumonia. On examination, he was in a confusional state and presented spastic hypertonia of limbs, bilateral Babinski sign, and cerebellar signs. The EEG showed diffuse slowing of background activity and generalized periodic sharp wave complexes (PSWC) of approximately 1–1.5 Hz. In a few days, he developed akinetic mutism and died a week after his admission.

Case #3

A 73-year-old man with no relevant medical history presented with a 1-month history of spatial–temporal disorientation, confusion, growing difficulties in daily activities, and new-onset episodes of complex partial seizures. Two weeks before, he had been diagnosed with a transient ischemic attack after an episode of acute dysarthria. Moreover, because of recently detected splenomegaly and multiple lymphadenopathies, he had undergone whole-body fluorodeoxyglucose(FDG)-positron emission tomography (PET), showing intense hyperfixation of both the adrenal glands. On examination, he showed consciousness fluctuations and no focal signs. Blood and urine testing showed mild anemia, erythrocytopenia, thrombocytopenia, elevated CRP, and bacteriuria. Head CT was unremarkable. In suspecting a urinary tract infection, ceftriaxone was started. During the following days, the patient's clinical condition rapidly deteriorated. Further testing revealed elevated LDH and angiotensin-converting enzyme levels. CSF analysis showed elevated proteins, albumin, and IgG levels, altered Link index, positive oligoclonal bands, negative 14–3-3 WB assay, and high t-tau concentrations. Results of the search for onconeural antibodies and viral or bacterial markers for suspected encephalitis were negative. EEG showed diffuse slowing of background activity with delta waves in the anterior regions and widespread PSWC. MRI showed multiple cerebral hyperintense white matter lesions in both hemispheres on T2 fluid-attenuated inversion recovery sequences, exhibiting no contrast enhancement on T1-enhanced images (Figure 1). High-dose steroid therapy was tried unsuccessfully in suspicion of encephalitis. He died just 1 week after admission.

Case #4

An 81-year-old housewife with no remarkable medical history was admitted after her family had found her lying unresponsive on the floor. On examination, she was confused and disoriented in time and space and had no signs of focal deficits. Routine blood work showed no abnormalities. Head CT and brain MRI showed no pathological findings. At the EEG, she presented bilateral slow-wave abnormalities. Her neurological status spontaneously improved in a few days, and she was sent home with a suspected diagnosis of new-onset seizures of unknown origin. After just 2 weeks, she was found unconscious in the bathroom. Neurological examination and head CT were unremarkable. Her mental status improved, and she was sent home to await admission to a level 3 center. Two weeks later, she was found in bed, feverish and unresponsive. Upon readmission, she presented diffuse spastic hypertonia and akinetic mutism. Routine blood and urine testing showed moderate anemia, erythrocytopenia, hyperleukocytosis with normal differential leukocyte count, and elevated CRP. Screening tests for autoimmune diseases revealed positivity for anti-Ro60 antibodies. EEG showed diffuse slowing of background activity, more evident in the right hemisphere. Head CT showed bilateral paramedian frontal white matter and basal ganglia lesions. CSF revealed significantly increased protein levels, positive 14–3-3 WB assay, high t-tau concentrations, and negative bacterial or viral infection markers. MRI revealed, on long TR sequences, multiple bilateral hyperintense lesions in the

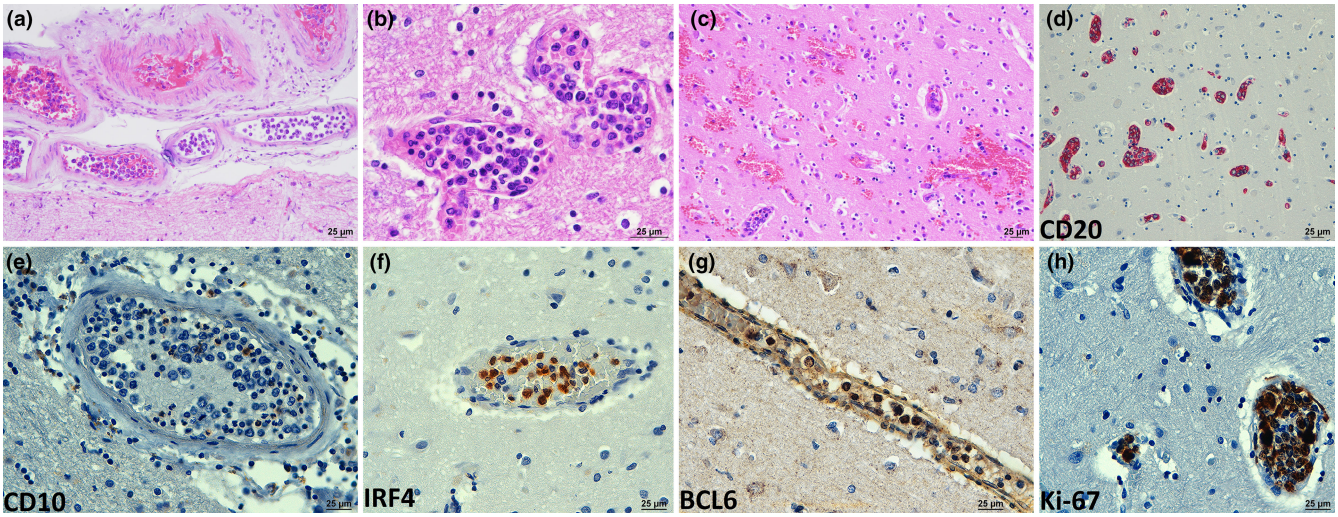

FIGURE 2 Neuropathological and immunohistochemical findings. (a) Intravascular mononuclear cells occluding medium-caliber meningeal blood vessels (temporal cortex-case #3). (b) Intravascular medium-size cells exhibiting vesicular and pleomorphic nuclei, scant cytoplasm, and prominent nucleoli (frontal cortex-case #1). (c) Small and numerous hemorrhagic petechiae and occluded small-size blood vessels (temporal cortex-case #1). (d) Immunohistochemistry for CD20 (clone L26). (e) Immunohistochemistry for CD10 (clone SP67). (f) Immunohistochemistry for IRF4 (clone EP190). (g) Immunohistochemistry for BCL6 (clone GI191E/A8). (h) Immunohistochemistry for Ki67 (clone 30–9). Hematoxylin and eosin staining (a–c).

TABLE 2 Neuropathological findings.

	Lymphomatous involvement of vessels				Neuronal loss/Gliosis				Petechiae			
Case number	**#1**	**#2**	**#3**	**#4**	**#1**	**#2**	**#3**	**#4**	**#1**	**#2**	**#3**	**#4**
Frontal cortex	+++	++	+++	+++	+++	++	+++	+++	+++	+	–	+++
Temporal cortex	+++	+++	++	+++	+++	++	++	+++	+++	–	–	–
Occipital cortex	+++	+++	++	++	++	+++	++	++	+++	–	–	–
Hippocampus	+	+	++	++	+	+	+	+	–	–	+	++
Amygdala	+++	++	+++	+++	++	++	++	++	++	–	–	+++
Striatum	++	+	+	++	++	+	+	++	–	–	–	–
Thalamus	++	+	+	+	+	+	+	+	+	–	–	++
Pons	++	++	++	++	+	+	+	+	+	–	+	+++
Cerebellum	++	+	+	++	+	–	+	–	++	–	–	++

white matter of corona radiata in both cerebral hemispheres. Her neurological status deteriorated during the hospitalization, and she died 3 weeks after her admission.

Neuropathological findings

Gross examination of the brain showed no abnormalities apart from mild cortical atrophy (cases #3 and #4). In case #1, serial coronal slices of the formalin-fixed cerebral hemispheres revealed numerous brownish hemorrhagic areas, mostly punctiform (average diameter 1–2 mm), focally reaching larger sizes (max. 7 mm). Frontal, temporal, and occipital poles showed more and larger hemorrhagic lacunae, significantly involving both gray and subcortical white matter. Punctiform hemorrhagic areas were also evident in the coronal sections of the cerebellum.

Microscopic examination showed diffuse occlusion and distension of small- and medium-caliber intracerebral and meningeal blood vessels (arterioles, capillaries, and venules; Figure 2a) by mononuclear cells of the white series with neoplastic features associated with a modest perivascular and interstitial infiltrate. The intravascular component consisted of medium-sized lymphocyte-derived cells exhibiting vesicular and pleomorphic nuclei, frequent mitotic figures, scant cytoplasm, and, sometimes, prominent nucleoli (Figure 2b). In contrast, the perivascular/interstitial infiltrate consisted of small lymphocytes with normal morphology and was particularly abundant in case #3. The neoplastic cells revealed heterogeneous growth patterns, not cohesive (forming pseudo-aggregates into the

vessels' lumen), cohesive (completely filling the lumen), and marginating (sparing the central portion of the lumen). Vascular involvement by neoplastic cells was present in all sections. The most heavily affected regions were the neocortical areas (with a greater extent in the subcortical white matter in cases #2, #3, and #4), mainly in the frontotemporal lobes and the amygdala. The hippocampus, pons (primarily the tegmentum in cases #2 and #3), and cerebellum (mainly the white matter) showed medium-grade involvement. Diencephalic areas appeared relatively spared.

Vascular occlusion was associated with small infarcts, sometimes hemorrhagic, in heterogeneous developmental stages, with associated perivascular lesions (neuronal loss, demyelination, vacuolization, reactive gliosis, and hemorrhagic petechiae) of variable degrees (Figure 2c). Despite some variability among cases, neuronal loss and gliosis predominantly affected the neocortices and the amygdala, with other areas relatively spared. Case #1 showed many hemorrhagic lesions, mainly in the neocortical lobes, where they were numerous and confluent, and, to a lesser extent, in the amygdala and the cerebellum. Case #4 showed severe hemorrhagic involvement of the frontal cortex and subcortical white matter with relative sparing of the other lobes, amygdala, pons, and, to a lesser extent, hippocampus, cerebellum, and thalamus. The other two cases showed no significant hemorrhagic lesions, except for rare and isolated petechiae in the hippocampus and pons (case #3) and frontal lobe (case #4). The results of the semi-quantitative assessment of lymphomatous involvement of vessels, neuronal loss/gliosis, and hemorrhagic lesions are reported in Table 2 (see Table S1 for the assessment criteria).

Immunohistochemistry

In all four brains, neoplastic cells were positive for a pan B-cell marker (CD20), were negative for a T-cell marker (CD3), had a non-germinal center B-cell immunophenotype [11], expressed MUM1/IRF4 and had a high Ki-67 index (range 60%–100%). All cases were positive for Bcl2, while only three (#1, #3, and #4) out of four cases tested positive for Bcl6. Assessing the c-MYC protein at immunohistochemistry provided suboptimal weak stains, likely due to post-mortem antigen degradation. Fluorescence in situ hybridization analyses only succeeded in case #4, which showed few evaluable lymphoma cells with c-MYC gene copy-number gain. The immunohistochemical results are summarized in Table S2 and shown in Figure 2d–h.

DISCUSSION

The term RPD is commonly used to indicate a heterogeneous set of diseases leading to a dementia syndrome (multi-domain cognitive decline with functional impairment) within a variable timeframe, generally considered less than 1 or 2 years [7]. Despite being a rare condition (3%–4% of dementia cases in clinical practice), early etiological diagnosis is critical due to the high frequency of, at least partially, treatable causes [9, 12]. The IVLBCL classical variant is increasingly recognized as a rare and potentially treatable cause of RPD [6, 8] whose diagnosis is often missed or delayed, especially if the clinical and instrumental findings meet the diagnostic criteria for more common causes of RPD, such as sCJD, encephalitis or vascular dementia [7–9]. Over the past few years, its early identification has become even more relevant given the recent improvement in prognosis achieved with rituximab-containing chemotherapy regimens [4, 5]. In this study, we reported four cases of IVLBCL identified during our 20-year experience at a referral center for prion disease in Italy, intending to raise awareness of this disease as a possible cause of RPD and contribute to characterizing its clinical presentation and neuropathological features.

As happens in up to 20% of IVLBCL cases [4], all our patients were only diagnosed post-mortem. During the disease course, patients were repeatedly misdiagnosed as variably having epilepsy, vascular dementia, stroke, encephalitis, or CJD. The median age of IVLBCL patients is 70 (34–90) years, without sex prevalence, while the mean age of individuals considering all causes of RPD spans from 48 to 63 years in tertiary centers [4, 8]. IVLBCL may occur in patients with a medical history of various types of lymphoma (small lymphocytic lymphoma, follicular lymphoma, gastric mucosa-associated lymphoid tissue lymphoma, and diffuse large cell lymphoma not otherwise specified) or Waldenström macroglobulinemia [4, 13]. Disease onset with cognitive impairment or dementia, often fluctuating, is reported in more than 60% of patients with neurological manifestations [6]. Most cases undergo a global cognitive deterioration variably associated with speech disorders, temporospatial disorientation, or behavioral disturbances [14]. Other relatively common presentations include encephalopathy, stroke-like symptoms, and seizures [6, 15]. In our case series, cases #1, #2, and #3 had a chronic onset, the first two with neuropsychiatric symptoms (apathy, depression, emotional lability, and behavioral disturbances), and the third with disorientation and alertness fluctuations. Case #4 had an acute onset with transient loss of consciousness followed by a delirium-like state. Patients usually show a rapidly progressive course, sometimes, as in our cases, characterized by ictal episodes with altered alertness and/or focal neurological signs, variably diagnosed as new-onset epilepsy, transient ischemic attack, or stroke [4, 15]. Systemic symptoms (most commonly fever of unknown origin) are present in more than 50% of IVLBCL patients. Cutaneous involvement, variably manifesting as painful indurated erythematous eruption, “peau d'orange”, cellulitis, tumors, ulcerated nodules, small red palpable spots, and erythematous and desquamated plaques, may be present at diagnosis in 40% of patients [4]. Despite the frequent association with skin manifestations, IVLBCL can be limited to the central nervous system (CNS) [4]. When this happens, the lack of extra-neurological manifestations, especially without systemic symptoms, can significantly hamper reaching a correct diagnosis, as in cases #1, #2, and #4. Only in case #3, splenomegaly,

lymphadenopathies, and bilateral adrenal glands hypercaptation on whole-body FDG-PET prompted the suspicion of a systemic inflammatory/neoplastic disease. Disease duration in IVLBCL patients with neurological involvement is highly heterogeneous [6]. CNS involvement and LDH levels predict poor prognosis, while data on age at onset as a prognostic factor are conflicting. Skin lesions are associated with longer median survival, probably due to early-stage biopsy and diagnosis [5, 16].

There are no specific laboratory tests for IVLBCL diagnosis. Anemia, thrombocytopenia, leukopenia, elevated inflammation markers (erythrocyte sedimentation rate [ESR] and PCR) levels, abnormal LDH, β2-microglobulin, and interleukin-2 receptor concentrations have been reported to be helpful for the diagnosis. A monoclonal serum component is present in only 14% of cases [4, 13, 17]. In our patients, as recommended by the guidelines for RPD diagnosis [7, 8, 12], routine blood tests, including blood cell count, electrolytes, kidney and liver function markers, thyroid hormones, and B vitamins, were repeatedly performed to exclude metabolic causes of RPD. Specific tests for syphilis, borreliosis, HIV, viral encephalitis, and autoimmune encephalitis were variably used to exclude inflammatory causes of RPD. Rheumatological screening (including at least ESR, PCR, and antinuclear antibodies) was performed to detect systemic inflammatory and/or autoimmune processes. Notably, only cases #3 and #4 had increased levels of inflammation markers. Cytolysis markers were assayed only in cases #2 and #3, which showed high LDH levels. Nevertheless, these results did not prompt further investigations.

Cerebrospinal fluid analysis often shows increased CSF protein concentrations. Most patients have pleocytosis, while atypical cells and oligoclonal bands have rarely been reported [13, 15]. In our patients, CSF testing showed elevated proteins, altered Link index, and positive oligoclonal bands in case #3, while case #4 presented only hyperproteinorrachia. Specific CSF tests to rule out inflammatory or infectious encephalitis were performed in cases #3 and #4 with negative results. CSF flow cytometry was never ordered since the diagnosis of lymphoma was not suspected. Consistent with previous reports [18], two of our patients presented significantly high t-tau levels, and one had a positive 14–3-3 WB assay result that supported the diagnosis of probable sCJD. CSF prion RT-QuIC was not available then and was performed only afterwards for this study and provided negative results.

Changes observed on EEG in IVLBCL are not specific [14]. In cases #2 and #3, the presence of generalized PSWC further corroborated the suspicion of sCJD.

Brain MRI can show variable patterns of CNS involvement, including multiple infarct-like lesions, nonspecific white matter lesions, meningeal enhancement, or abnormal signals in the central pons. Contrast-based imaging can display different types of parenchymal and meningeal enhancement dynamically evolving with the resolution of some enhancing lesions and the new appearance of others'. Markedly T2 hyperintense lesions on long TR images and lack of enhancement on T1 images are common. Brain CT reveals changes suggestive of ischemic lesions in most cases [14, 19, 20]. In cases #1, #3, and #4, brain MRI showed multiple cerebral hyperintense white matter lesions in both hemispheres on T2-weighted sequences.

In contrast, case #2 presented bilateral multiple hypodense areas in the cortex and the white matter on head CT scan. Contrast-based imaging showed no lesion enhancement when performed (only in case #3). The imaging results of our case series were interpreted as severe white matter disease signs or inflammatory lesions and supported a diagnosis of vascular dementia or encephalitis.

Regarding the misdiagnosis with sCJD that brought the patients to our attention, these cases highlight the importance of not over-relying on markers of limited specificity (40%–92% for CSF 14–3-3 WB assay, and 91% for EEG [21]), and support the potential usefulness of MRI and CSF RT-QuIC (specificity 74%–98% and 99%–100%, respectively [21]) as confirmatory tests for the CJD diagnosis [22], especially in the presence of atypical clinical-instrumental findings.

From a neuropathological point of view, our results reflect the typical IVLBCL histological presentation: neoplastic cells mostly exhibiting a high nuclear/cytoplasmic ratio and scant cytoplasm selectively growing within the lumen of almost all-sized blood vessels with heterogeneous growth patterns. Despite a certain degree of variability among cases, we found that frontotemporal neocortical cortices were the most affected by lymphoma, neuronal loss, and gliosis. To our knowledge, no systematic study has ever assessed the differential involvement of various brain areas in CNS IVLBCL, and the preference for frontal areas has only been hypothesized by Fonkem et al. [6]. Such evidence may explain why IVLBCL often presents with neuropsychiatric symptoms, behavioral changes, executive dysfunction, speech disorders and spatiotemporal disorientation [14]. Future studies with larger case series should confirm these findings and investigate possible causes for the preferential involvement of these regions.

With regard to immunohistochemistry, CD20 is positive in most cases; when negative, another pan B-cell marker is required for the diagnosis. Most cases of IVLBCL have a non-germinal center B-cell immunophenotype [23, 24], according to the Hans algorithm [11], with a more frequent expression of MUM1 and Bcl2, variable Bcl6, and high proliferation index [23, 24]. Our results were consistent with this immunophenotype.

In conclusion, this study adds four new IVLBCL cases clinically manifesting as RPD to those already described in the literature. From the perspective of a prion disease referral center, we emphasize the importance of ruling out all potentially treatable causes when facing a rapidly progressive neurological syndrome, even if the laboratory and instrumental data support the diagnosis of more common diseases. Moreover, albeit in a small number of patients, our results support prion RT-QuIC as a confirmatory test for the in vivo diagnosis of sCJD. Finally, although this finding needs to be replicated in larger case series, we report for the first time the possibility that IVLBCL differentially affects various

brain areas, preferentially involving the frontotemporal cortices. This could significantly influence the clinical phenotype, especially at disease onset. Future studies should investigate IVLBCL pathological and immunophenotypic features in large cohorts to understand its pathogenesis, facilitate its ante-mortem recognition, and offer new therapeutic perspectives.

AUTHOR CONTRIBUTIONS

Conceptualization and design of the study: Giuseppe Mario Bentivenga, and Piero Parchi. Drafting/revision of the manuscript for content, including medical writing for content: Giuseppe Mario Bentivenga, Simone Baiardi, and Piero Parchi. Neuropathological analyses: Giuseppe Mario Bentivenga, Simone Baiardi, and Piero Parchi. Immunohistochemical analyses: Lorenzo Righini and Elena Sabattini. Major role in the acquisition of data: Anna Ladogana, Sabina Capellari, Elena Sabattini, and Piero Parchi. Critical review of the manuscript and approval of the final version: all authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used and analyzed during the current study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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