Clinical Case Report

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Richter's syndrome of the central nervous system diagnosed concurrently with chronic lymphocytic leukaemia

A case report and literature review

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Abstract

Rationale: Central nervous system (CNS) infiltration of Richter's syndrome (RS) is rare and only a few cases were discussed. Of these published cases, either they were accompanied with lymph node involvement or with a history of chronic lymphocytic leukemia (CLL). To our knowledge, this is the first published case of RS of the brain and meninges diagnosed concurrently with CLL in the absence of any evidence of lymphoma outside of the CNS.

Patient concerns: A 67-year-old female presented with slurred speech, headache, and left-sided hemiparesis. Magnetic resonance imaging of the brain revealed an irregular lesion 30 mm in diameter in the right parietal lobe. The mass was totally removed and pathology revealed diffuse large B-cell lymphoma (DLBCL) of non-germinal center type by Hans' classification. The patient's leukocyte count was 12.1 × 109/L (76.9% lymphocytes), and fluorescence-activated cell sorting (FACS) analysis of blood revealed a clonal B-cell population (36.75% leukocytes) corresponding to the immunological CLL profile (Matutes score of 5/5). Bone marrow (BM) aspiration and biopsy also indicated CLL. The analysis of immunoglobulin heavy chain gene (IGH) and kappa chain gene (IGK) in the patient's BM and CNS tissue indicated that the DLBCL of the brain was derived from the CLL clone.

Diagnoses: RS of the CNS diagnosed concurrently with CLL.

Interventions: The patient received intravenous chemotherapy (6.0 g methotrexate) and intrathecal chemotherapy (10 mg methotrexate, 50 mg cytarabine, 5 mg dexamethasone).

Outcomes: The patient returned to our department with left-sided hemiparesis and headache 2 weeks after the chemotherapy. Repeat MRI showed progression of the brain lesion. Her general condition deteriorated significantly with confusion and high fever, and she died within a few days at only 10 weeks after the onset of symptoms.

Lessons: The survival of CNS-RS patients is very poor and and is always complicated with multiple and different genetic alterations. Because of chemotherapy insensitivity, a multidisciplinary treatment including surgery and radiotherapy together with novel agents may be an option to improving patient outcomes.

Abbreviations: BM = bone marrow, CLL = chronic lymphocytic leukemia, CNS = central nervous system, CSF = cerebrospinal fluid, DLBCL = diffuse large B-cell lymphoma, FACS = fluorescence-activated cell sorting, IGHV = immunoglobulin heavy chain variable region, MRI = magnetic resonance imaging, PET = positron emission tomography, RS = Richter's syndrome, RT = Richter's transformation, SUVmax = maximum standardized uptake value.

Keywords: central nervous system, chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), immunoglobulin heavy chain variable region gene, Richter's syndrome, Richter's transformation

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The datasets supporting the conclusions of this article are included within the article.

The institutional review board of Second Affiliated Hospital of Dalian Medical University approved this report.

Written informed consent for publication of this case report and any accompanying images was obtained from the patient. A copy of this written consent is available for review by the Editor-in-Chief of this journal.

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1. Introduction

In 1928, Maurice N. Richter first reported the transformation of B cell chronic lymphocytic leukemia (CLL) into diffuse large B-cell lymphoma (DLBCL), which became known as Richter's syndrome (RS), or Richter's transformation (RT). We now know that although DLBCL is the most common type of RS, occurring in approximately 5–10% of CLL patients, other rarer types such as Hodgkin and composite lymphoma also can occur.[1] The reported incidence of RS has varied from 2% to 10% with a median time from CLL diagnosis to RT of 23.0 months.[2] RS is typically characterized by an aggressive presentation, chemotherapy-resistance, and poor survival, with reported median survival times of 8 months and a 5-year survival rate less than 5%.[3,4] The majority of RS cases occur in lymph nodes, but other primary sites such as the gastrointestinal system, eye, nose, skin, bone, bronchus, and even face have been reported.[5] Central nervous system (CNS) infiltration RS is quite rare. Here we report an unusual case of patient who initially presented with the simultaneous occurrence of CLL in the blood and bone marrow (BM) and DLBCL in the brain and meninges. To our knowledge, this is the first published case of RS of the brain and meninges diagnosed concurrently with CLL in the absence of any evidence of lymphoma outside of the CNS.

2. Case presentation

A 67-year-old female presented with slurred speech, headache, and left-sided hemiparesis in March 2017. Upon admission, she had a white blood cell (WBC) count of 22.2×10^9/L and lymphocyte count of 14.5×10^9/L, with a normal hemoglobin level and platelet count. Magnetic resonance imaging (MRI) of the brain revealed an irregular lesion with a diameter of 30 mm in the right parietal lobe (Fig. 1A). The mass was completely removed via surgical resection and pathological evaluation revealed a diagnosis of DLBCL (Fig. 2), of a non-germinal center type by Hans' classification. The immune phenotype was CD20 (+), BCL-2(+, 70%), BCL-6(+, 40%), CD10 (–), CD21 (–), CD23 (–), CD3 (–), CD5 (+, a few cells), MUM-1(+), p53(+, 80%), C-myc (+, 30%), Ki-67 index of 80%, and EBER(–). The patient's symptoms disappeared after the surgery.

The patient attended to our department in April 2017 for chemotherapy, without night sweats, fever or body weight loss.

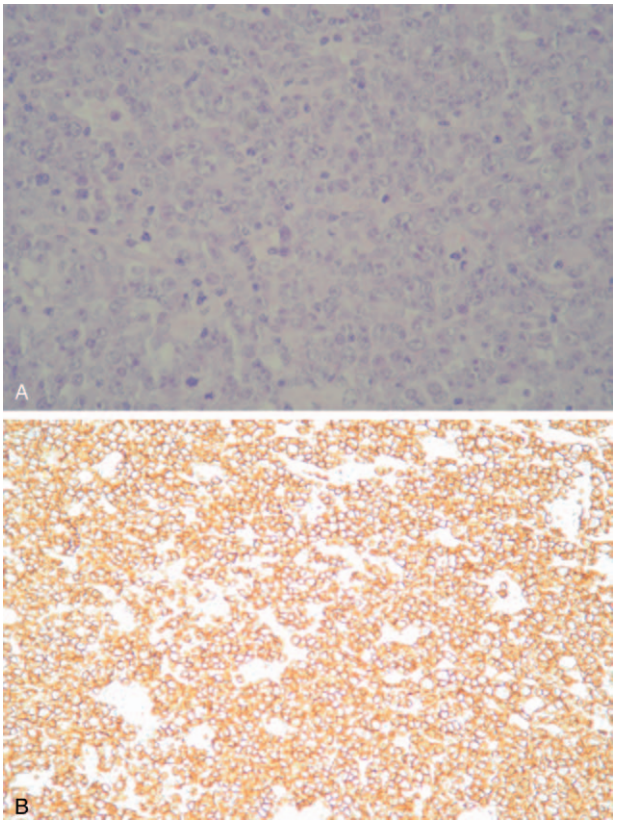

Figure 2. Brain tumor histology showed infiltration consistent with DLBCL on hematoxylin-eosin (H&E) staining (40 × 10) (A). Immunocytochemical staining for CD20 within the brain mass was positive (20 × 10) (B). DLBCL = diffuse large B-cell lymphoma.

Peripheral blood examination revealed a hemoglobin level of 120 g/L, a platelet count of 257×10^9/L, and a leukocyte count of 12.1×10^9/L (76.9% lymphocytes). Fluorescence-activated cell sorting (FACS) analysis of the blood revealed a clonal B-cell population (36.75% leukocytes) co-expressing CD5, CD19, CD23, CD43, CD79b, surface lambda, CD20 (dim), and CD22 corresponding to the immunological profile of CLL (Matutes

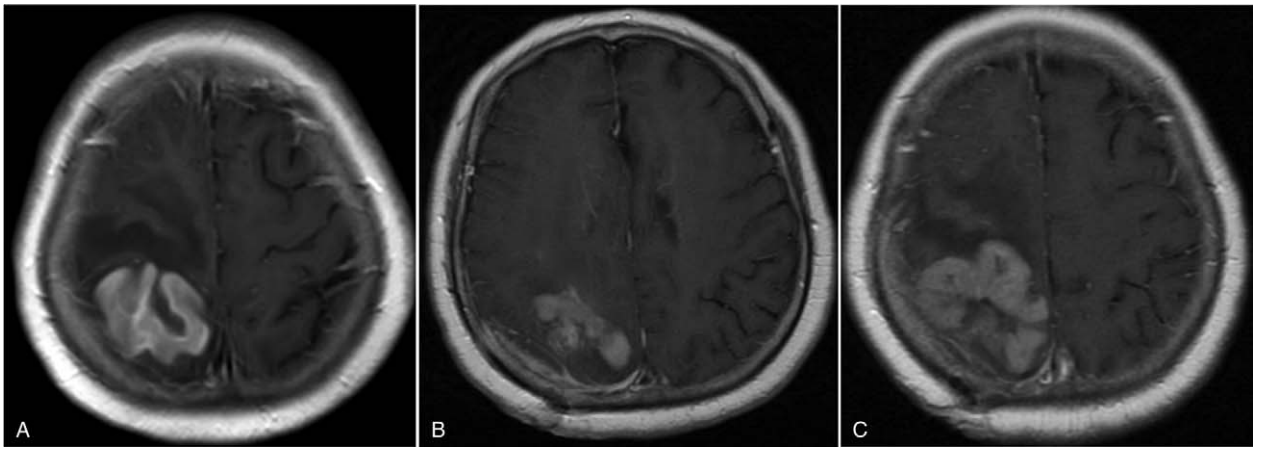

Figure 1. Magnetic resonance images of the tumoral lesion in the right parietal lobe before surgery (A); recurrence of the tumor mass at 1 month after surgery (B); and progression of the brain lesion after chemotherapy (C).

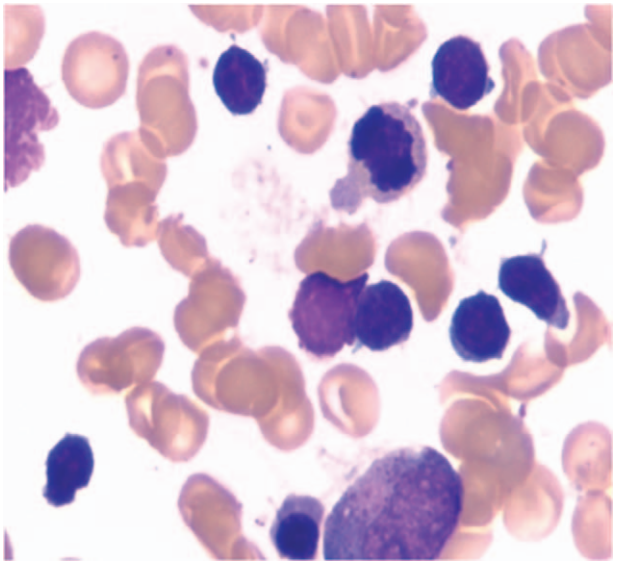

Figure 3. Bone marrow aspiration showing mature lymphocytoid cells with a condensed circular nucleus.

score of 5/5). Staining results for CD38, CD13, FMC-7, cKappa, and CD10 were negative. BM (BM) aspiration revealed 46.5% mature lymphocytes and 2% prolymphocytes (Fig. 3). FACS analysis of BM also confirmed the diagnosis of CLL. BM biopsy revealed nodular BM infiltration by small lymphocytes, and the immune phenotype was CD20 (+), CD23 (+), CD5 (+), CD3 (–), p53 (+), CyclinD1 (–), and CD10(–), also consistent with CLL. No lymph node enlargement or hepatosplenomegaly was observed on enhanced computed tomography. Testing for human immunodeficiency virus (HIV) was negative, and the lactase dehydrogenase level was 155 IU/L (normal range: 120–250 IU/L). A patchy, locally enhanced lesion was found in the right parietal lobe of brain on MRI (Fig. 1B). No abnormalities were found on ophthalmological examination. The cerebrospinal fluid (CSF) was turbid, with an elevated protein concentration of 804 mg/L and normal glucose level of 2.9 mmol/L. Cytological analysis of the CSF revealed many lymphocytes, and some were lymphoma cells. Specifically, we counted 463 lymphocytes, and 200 were B lymphocytes found to express CD20, CD22 and CD19 but not CD5 or CD23 on FACS analysis of the CSF. These FACS results indicated the cells were DLBCL cells. Simultaneous diagnosis of CLL and DLBCL of the CNS was established (RS). However, the relationship between the CNS lesion and peripheral CLL cells was not definite, and thus, we analyzed the expression of immunoglobulin heavy chain gene (IGH) and kappa chain gene (IGK) in the patient's BM and CNS tissue. The observed amplified segments (monoclonal peaks at 330 bp for IGH and 144 bp for IGK) seemed to be identical and indicated that the DLBCL in the brain was derived from the CLL clone. (Due to copyright issues, we could not present images from the IGH analysis).

The patient received intravenous chemotherapy (6.0 g methotrexate) and intrathecal chemotherapy (10 mg methotrexate, 50 mg cytarabine, 5 mg dexamethasone). Unfortunately, she returned to our department with left-sided hemiparesis and headache after 2 weeks. Repeat MRI showed progression of brain lesion (Fig. 1C). The patient's condition was too poor for her to receive the planned radiotherapy, and it continued to decline significantly with the development of confusion and high fever. She died within a few days at just 10 weeks after the onset of symptoms.

3. Discussion

RS within the CNS tissue is very rare, and we could identify only a few published cases (Table 1).[6–17] Of the 16 cases described in

Table 1

Reported cases of RS isolated within the CNS.

Reference	Age (years)	Gender	Stage of CLL at RS diagnosis	Received chemotherapy	Time from CLL diagnosis to RS (months)	Lesion location	Treatment regimen	Follow-up duration	Alive at last follow-up	Symptoms
O'Neill et al[3]	64	Male	NA	No	36	Left thalamic	Brain irradiation	24 months	Yes	Headache, confusion
	70	Male	NA	Yes	96	Left frontal lobe	Neurosurgery, brain irradiation	2 months	No	Language dysfunction, right hemiparesis
Mahe et al[6]	64	Male	NA	NA	NA	Right occipital	Chemotherapy, brain irradiation	17 months	Yes	NA
	70	Male	NA	NA	NA	Right frontal	Brain irradiation	13 months	Yes	NA
Resende et al[7]	74	Male	NA	Yes	72	Right frontal	Neurosurgery, chemotherapy, brain irradiation	14 days	No	Confusion, gait disturbance
Bayliss et al[8]	78	Male	NA	No	Concurrent	Right temporal, left frontal	No treatment	22 days	No	Confusion
Agard et al[9]	61	Female	Binet A	Yes	48	Meninges	Chemotherapy	2 months	No	NA
Bagic et al[10]	58	Female	Binet B	Yes	40	Both hemispheres	Brain irradiation, rituximab	NA	NA	Left leg weakness
Robak et al[11]	60	Female	Binet A	Yes	84	Right parietal lobe	Neurosurgery, brain irradiation	3 months	Yes	Left-sided hemiparesis
Floisand et al[12]	58	Male	Binet B	Yes	14	Left cerebellum	Neurosurgery, rituximab, chemotherapy, brain irradiation	12 months	Yes	Nausea, vomiting, dizziness
Stuplich et al[13]	56	Male	Binet A	No	1	Right basal ganglia and brainstem	Chemotherapy, brain irradiation	9 months	No	Psychomotoric deficits, left-sided hemiparesis
	71	Female	Binet A	No	12	Both thalami	Rituximab, chemotherapy, brain irradiation	NA	No	Double vision, vertigo, gait disturbance
Ishida et al[14]	66	Male	Binet A	Yes	24	Right putamen caudate nucleus	Rituximab, brain irradiation	12 months	Yes	Left hemiplegia
Jain et al[15]	67	Female	Binet A	Yes	120	Posterior pons deep white matter	Rituximab, chemotherapy, brain irradiation	10 days		Gait disturbance, tremors, slurred speech, confusion, visual impairment
Schmid et al[16]	75	Male	NA	No	36	Pons and medulla	Chemotherapy	NA	No	Tachypnea
Ghofrani et al[17]	64	Male		Yes	60	Left occipital	Rituximab, chemotherapy, brain irradiation	3 months	No	Headaches, vomiting, blurry vision

CLL = chronic lymphocytic leukaemia, CNS = central nervous system, NA = not available, RS = Richter's syndrome.

the literature, 9 patients received treatment after CLL was found. The median age among the 16 cases was 64 years, and the male to female ratio was 11: 5. None of the cases were classified as Binet stage C. The median transformation time for RS was 38.0 months, with the longest duration being 10 years from the initial diagnosis of CLL. This transformation time was longer than that for RS occurring outside of the brain (mean transformation time for RS outside the CNS, 23.0 months).[2] Survival among these patients ranged from 10 days to more than 2 years, and the median survival time of 6.0 months was shorter than the median survival time of 8.0 months for RS occurring in other sites.[4] All 16 published cases of RS infiltration of the CNS had either lymph node involvement or a history of CLL. Thus, the case described in the present report is unusual and the first published case to be simultaneously diagnosed with CLL and DLBCL in the brain and meninges without evidence of lymphoma outside of the CNS.

Among the reported cases, the clinical presentation of CNS-RS was headache, hemiparesis, vomiting, and confusion and lacking specific symptoms. Whether the use of chemotherapy as treatment for CLL will increase the risk of RS has remained controversial. Traditional chemotherapy was reported to double the risk of RT to a rate of 1% per annum for those treated with chemotherapy from the rate of 0.5% per annum among those not treated with chemotherapy.[18] However, others have concluded that the evidence for an increased risk of Richter's transformation in CLL patients treated with chemotherapy in combination with rituximab is inadequate.[19,20] Multiple factors have been linked to an increased risk of RS in CLL patients, including Rai stages III–IV, lymph node size >3 cm, deletion of the p53/Rb/p27genes, mutations of the SAMHD1/XPO1/MED12/NOTCH1/MYC genes, loss of cell cycle inhibitors CDKN1A/CDKN2A/CDKN1B, CD38 expression (CD38 ≥30%), stereotyped B-cell receptor, telomere length <5000 base pairs, absence of del13q14/11q23, overexpression of ZAP70/BCL2/LRP4 genes, decreased expression of MYBL1, immunoglobulin heavy chain variable region (IGHV) homology >98%, and IGHV gene usage (B-cell receptor subset 8 using IGHV4–39/IGHD6–13/IGHJ5), trisomy 12, and chromosome 11 abnormalities.[4,5,21] Notably, 95% of DLBCL cases resulting from Richter's transformation display an ABC phenotype, in which staining for CD20 expression is generally positive and that for CD5 and CD23 expression may be dim to negative as in the present case, which is similar to the phenotype of de novo DLBCL. However, molecular profiles including genetic alterations and immunoglobulin gene mutations are found more frequently among patients with RS than those with de novo DLBCL,[22] and these abnormalities may increase the proliferation of CLL cells. In other words, the genetic abnormalities resulting from combinations of multiple, different genetic lesions may promote the development of RS in CLL patients. Importantly, positron emission tomography (PET) can be helpful for identifying RS in CLL patients at high risk. With a maximum standardized uptake value (SUVmax) cut-off of 5.0, PET was shown to detect RT of CLL to DLBCL with a high sensitivity (91%) and high negative predictive value (97%).[23] Papajik et al reported a median SUVmax for suspected or confirmed RT of 16.5.[24] Unfortunately, our patient did not undergo PET-CT scanning for economic reasons. Without the results from such examination, she underwent surgical resection first, which could significantly impact her performance status and which also delayed the administration of chemotherapy and radiotherapy to possibly negative influence her survival.

It is believed that RS cells will express the same surface light chain restriction as its derived CLL clones.[4] In order to definitively determine the clonal relationship of the CNS lesion with the CLL cells in the present case, we examined the sequences of IGH and IGK with the patient's BM and CNS tissue. Monoclonal peaks at 330 bp for IGH and 144 bp for IGK were observed for both the brain DLBCL and BM samples, indicating the gene sequences were identical in the 2 tissue types and that the CLL and DLBCL cells originated from the same B-cell clone. Mao et al found in a study of 23 patients, that RS cells were clonally related to the original CLL (as in our case) in 78% of cases, while the RS cells were clonally unrelated in 22% of cases.[25] The clonally related cells show a higher prevalence of tumor p53 disruption (60.0% versus 23.1% for clonally unrelated cells),[26] which will lead to expression of p53. The expression of p53 by 80% of cells in the brain lesion in the present case indicated that the cancer was aggressive and would be difficult to treat. Hence, it is important to detect p53 expression within lesions as a potential risk factor for poor prognosis among CLL patients. An additional study reported that the clonally related type of RS is characterized by rapid deterioration of performance status, chemotherapy-resistance, immunosuppression, and a poor survival with a median overall survival of 14.2 months versus 62.5 months for the cohort with clonally unrelated RS.[27]

Although rare, RS within the CNS has consistently presented with rapid development, and the optimal treatments remain unknown. Therapeutic regimens established for primary CNS lymphoma have been applied, with chemotherapy combined with rituximab often being used to treat RS. Unfortunately, the results have been generally disappointing due to the chemotherapy-resistance and poor performance status of the patients.[28] Allogeneic stem cell transplantation has been found to improve survival in select patients.[29] Multidisciplinary treatment including surgery and radiotherapy together with stem cell transplantation and novel agents may be an option for chemoresistant RS in patients whose physical condition permits such treatments.

4. Conclusions

To our knowledge, this is the first published case of RS of the brain and meninges that lacked evidence of lymphoma outside of the CNS and was diagnosed concurrent with CLL. Thus, the clinical and pathological descriptions of this case expand the literature related to RS of the CNS. Based on our review of the available but limited literature on RS of the CNS, recognition of risk factors is important for early diagnosis. So far, survival has remained very poor, with RS being insensitive to chemotherapy due to multiple different genetic alterations. Further research is needed to explore the pathogenic mechanism of RS in the CNS and to develop the optimal treatment strategy.

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Author contributions

LYX and JCS were involved in patient care and data collection and were major contributors in writing the manuscript. XHS and JCS were involved in the study concept and design of the study. JZ performed flow cytometry. ZFG and LL performed the pathological analysis and IGHV analysis. JCS was involved in manuscript editing. All authors read and approved the final manuscript.

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