Clinicopathologic and Genetic Features of Primary T-cell Lymphomas of the Central Nervous System
An Analysis of 11 Cases Using Targeted Gene Sequencing

Jeemin Yim, MD,* Jiwon Koh, MD, PhD,*† Sehui Kim, MD, PhD,*‡ Seung Geun Song, MD,*
Jeong Mo Bae, MD, PhD,*† Hongseok Yun, PhD,† Ji-Youn Sung, MD, PhD,‡
Tae Min Kim, MD, PhD,¶ Sung-Hye Park, MD, PhD,* and Yoon Kyung Jeon, MD, PhD*¶

Abstract: Primary central nervous system lymphoma (PCNSL) of peripheral T-cell lineage (T-PCNSL) is rare, and its genetic and clinicopathologic features remain unclear. Here, we present 11 cases of T-PCNSL in immunocompetent individuals from a single institute, focusing on their genetic alterations. Seven cases were subject to targeted panel sequencing covering 120 lymphoma-related genes. Nine of the eleven cases were classified as peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), of which one was of γδT-cell lineage. There was one case of anaplastic lymphoma kinase-positive anaplastic large cell lymphoma and another of extranodal natural killer (NK)/T-cell lymphoma (ENKTL) of γδT-cell lineage. The male to female ratio was 7 : 4 and the age ranged from 3 to 75 years (median, 61 y). Most patients presented with neurological deficits (n = 10) and showed multifocal lesions (n = 9) and deep brain structure involvement (n = 9). Tumor cells were mostly small-to-medium, and T-cell monoclonality was detected in all nine evaluated cases. PTCL-NOS was CD4-positive (n = 4), CD8-positive (n = 3), mixed CD4-positive and CD8-positive (n = 1), or CD4/CD8-double-negative (n = 1, γδT-cell type). Cytotoxic molecule expression was observed in 4 (67%) of the 6 evaluated cases. Pathogenic alterations were found in 4 patients: one PTCL-NOS case had a frameshift mutation in KMT2C, another PTCL-NOS case harbored a truncating mutation in TET2, and another (γδT-cell-PTCL-NOS) harbored NRAS G12S and JAK3 M511I mutations, and homozygous deletions of CDKN2A and CDKN2B. The ENKTL (γδT-cell lineage) case harbored mutations in genes ARID1B, FAS, TP53, BCOR, KMT2C, POT1, and PRDM1. In conclusion, most of the T-PCNSL were PTCL-NOS, but sporadic cases of other subtypes including γδT-cell lymphoma, anaplastic lymphoma kinase-positive anaplastic large cell lymphoma, and ENKTL were also encountered. Immunophenotypic analysis, clonality test, and targeted gene sequencing along with clinicoradiologic evaluation, may be helpful for establishing the diagnosis of T-PCNSL. Moreover, this study demonstrates genetic alterations with potential diagnostic and therapeutic utility in T-PCNSL.

Key Words: primary CNS lymphoma, primary CNS T-cell lymphoma, targeted gene sequencing, genetic analysis

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48% of patients. The majority of patients (64%) had cerebral hemisphere involvement and 36% had involvement of deep brain structures.\(^6\) The prognosis of T-PCNSL was comparable to PCNS-DLBCL, with a median disease-specific survival of 25 months and 2-year and 5-year disease-specific survival rates of 51% and 17%, respectively.\(^6\) However, the clinicopathologic characteristics of T-PCNSL have not been well elucidated.

Recently, a case series of 18 T-PCNSLs involving clinical, morphologic, immunophenotypical, and molecular analysis was reported.\(^7\) Those series included 15 cases of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), 2 cases of anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALCL), and 1 case of ALK-positive ALCL. Most of the PTCL-NOS cases (11/15) involved small and/or medium-sized lymphocytes, which might be diagnostically challenging for T-PCNSL. Similar to PCNS-DLBCL, perivascular cuffing was a characteristic and prominent feature in the majority of cases. In their series, the ratio of CD8 to CD4 lineage tumors was 2 : 1, and most cases showed a cytotoxic phenotype. The authors described genetic alterations of T-PCNSL and demonstrated mutations in DNMT3A, KRAS, JAK3, STAT3, STAT5B, GNB1, and TET2 genes for the first time using targeted next-generation sequencing.\(^7\)

However, the clinicopathologic, and particularly genetic, features of T-PCNSL remain unclear. Thus, the aim of this study was to demonstrate the clinicopathologic features of T-PCNSL and genetic alterations with potential diagnostic and therapeutic utility in T-PCNSL.

**MATERIALS AND METHODS**

**Case Selection**

Eleven cases of T-PCNSL were identified from the pathology database of Seoul National University Hospital (SNUH) between 2005 and 2021. The patients’ diagnoses were reviewed and classified according to the 4th World Health Organization classification.\(^1\) An experienced hematopathologist (Y.K.J.) and neuropathologist (S.-H.P.) evaluated the pathologic material. Clinical data including tumor location, initial symptoms, performance status, treatment modalities, and outcomes were obtained from medical records by a hemat-oncologist (T.M.K.). To exclude the presence of systemic disease, whole body positron emission tomography/computed tomography scan was performed in all the patients and the hemat-oncologist (T.M.K.) confirmed the primary central nervous system (CNS) origin of lymphoma in all patients. One patient (case 9) was previously reported as a single case.\(^8\) This study was approved by the Institutional Review Board (IRB) of SNUH (No. H-1807-070-958). Informed consent for participation in the study was waived by the IRB of SNUH.

**Immunohistochemistry and In Situ Hybridization for Epstein-Barr Virus-encoded RNA**

Immunohistochemical studies were performed for CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD15, CD20, CD30, CD56, Bel-2, Bel-6, C-MYC, MUM-1, PD-1, ICOS, ALK, TdT, TCRβF1, TCRγ, granzyme B, pHH3, and Ki-67 on available formalin-fixed paraffin-embedded tissue (FFPE) sections. Information on the antibodies and staining methods are summarized in Supplementary Table S1 (Supplementary Digital Content 2, http://links.lww.com/PAS/B299). Epstein-Barr virus (EBV) in situ hybridization was performed using the Bond Ready-to-Use ISH EBV-encoded RNA (EBER) probe (Leica Biosystems, Newcastle, UK) or INFORM EBER Probe (Ventana Medical Systems, Tucson, AZ), in conjunction with the Bond-Max autostainer (Leica Microsystems) and Ventana Benchmark XT automated system (Ventana Medical Systems), respectively, according to the manufacturer’s protocol.

**T-cell Clonality Test**

T-cell monoclonality was detected using the Identicleone TCRG Gene Clonality Assay (Invivosecribe Technologies Inc., San Diego, CA) or multiplex-PCR for the T-cell receptor (TCR)γ gene, followed by heteroduplex analysis as previously described.\(^9\)

**Targeted Gene Sequencing**

We created a customized panel composed of 120 genes important in the pathogenesis of lymphoid neoplasm (Supplementary Table S2, Supplementary Digital Content 3, http://links.lww.com/PAS/B300). At least 50 ng genomic DNA was extracted from each FFPE sample using the Maxwell FFPE Purification Kit (Promega, Madison, WI). Library preparation was performed using the SureSelect XT-HS Target Enrichment System (Agilent Technologies, Santa Clara, CA). Library concentrations were quantified and assessed by the 4200 TapeStation System (Agilent Technologies). Paired-end sequencing was performed on the Illumina NextSeq 550Dx Platform (Illumina Inc., San Diego, CA).

**Sequencing Data Analyses**

Sequencing reads were mapped against the reference genome (GRCh37/hg19) using Burrows-Wheeler Aligner (BWA) (version 0.7.17) and GATK Best Practice (version 4.0.2.1). SNVVer (version 0.5.3) and LoFreq (version 2.1.2) were used to call single nucleotide variants (SNVs) and small insertions and deletions (INDELs). A CNVkit was used to identify and visualize copy number variations (CNVs). SnpEff (version 4.3) was used for variant annotation. To exclude possible germline variants in the general population, only variants with allele frequency <0.1% in the Genome Aggregation Consortium East Asian database, Korean Reference Genome Database, and Korean Variant Archive were retained for further analyses.

**RESULTS**

**Clinical Features of Patients With T-PCNSL**

The clinical features of the 11 patients with T-PCNSL are summarized in Table 1, and the clinicopathologic features of the cases are briefly described in the Supplementary Information (Supplementary Digital Content 1, http://links.lww.com/PAS/B298). The age of the patients ranged from 3 to 75 (median, 61 y), and the male to female ratio was 7 : 4. None of the patients had a history of immune deficiency. Patients visited the hospital with neurological deficits, visual disturbance, headache, and/or dizziness. Most of the patients showed involvement of deep brain structures (ie, periven-
### TABLE 1. Clinical Features of the T-PCNSL Cases

| No. | Age/Sex | Dx                  | Initial Sx             | KPS | LDH | Location                                      |
|-----|---------|---------------------|------------------------|-----|-----|-----------------------------------------------|
| 1   | 40/M    | PTCL-NOS            | Neurologic deficit     | 90  | WNL | Temporal, parietal, occipital                 |
| 2   | 69/F    | PTCL-NOS            | Neurologic deficit     | 60  | Elev.| Both cerebral hemispheres, cerebellum         |
| 3   | 69/F    | PTCL-NOS            | Neurologic deficit     | 60  | Elev.| Parieto-occipital                             |
| 4   | 16/M    | ALK(+) ALCL         | Headache, dizziness, diplopia | 90  | Elev.| Frontal                                       |
| 5   | 68/F    | PTCL-NOS            | Neurologic deficit     | 90  | Elev.| Frontal                                       |
| 6   | 62/M    | PTCL-NOS            | Visual deficit         | 90  | Elev.| Frontal                                       |
| 7   | 61/M    | PTCL-NOS            | Visual deficit         | 90  | WNL | Rt periventricular WM, Lt cerebral peduncle   |
| 8   | 26/M    | PTCL-NOS            | Neurologic deficit     | 30  | WNL | Basal ganglia                                  |
| 9   | 75/F    | PTCL-NOS (γδT-cell) | Neurologic deficit     | 30  | NA  | Spine, Lt lateral periventricular WM          |
| 10  | 3/M     | PTCL-NOS            | Neurologic deficit     | 60  | Elev.| Thalamus                                      |
| 11  | 61/M    | ENKTL (αβT-cell)    | Intermittent headache  | 90  | Elev.| Lt parietotemporal WM, Rt thalamus, midbrain, and pons, Rt frontoparietal subcortical WM |

*Viterous fluid involvement.
†Neurological deficit with cough, sore throat, fever.

ALCL indicates anaplastic large cell lymphoma; autoPBSC, autologous peripheral blood stem cell transplantation; COPADM, cyclophosphamide, vincristine, prednisolone, doxorubicin, and high-dose methotrexate; CRu, unconfirmed complete response; CT Rx, chemotherapy regimen; CT, chemotherapy; Dx, diagnosis; Elev., elevated; ENKTL, extranodal NK/T-cell lymphoma; IMEP, ifosfamide, methotrexate, etoposide, prednisone; KPS, Karnofsky Performance Score; LDH, lactate dehydrogenase; Lt, left; MA, high-dose methotrexate and cytarabine; mCR, metabolic complete response; modified COP, cyclophosphamide, vincristine and prednisone; MVP, high-dose methotrexate, vincristine, and procarbazine; NA, not available; No., case number; Op, operation; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; RT, radiotherapy; Rt, right; SD, stable disease; Sx, symptoms; Tx, treatment; WNL, within normal limit.

### TABLE 2. Morphology, Immunophenotype, TCR Clonality, and Mutational Status of the T-PCNSL Cases

| No. | Dx                  | Cell size | PVL | CD3 | CD4/8 | CTM | EBV | TCRβF1 | TCRγ |
|-----|---------------------|-----------|-----|-----|-------|-----|-----|--------|------|
| 1   | PTCL-NOS            | Small     | Present | (+) | CD4 | NA | (−) | NA | NA |
| 2   | PTCL-NOS            | Small/medium | Present | (+) | CD8 | (+) | (+) | NA | NA |
| 3   | PTCL-NOS            | Small/medium | Present | (+) | CD4 | NA | (−) | (+) | NA |
| 4   | ALK(+) ALCL         | Large/anaplastic | Present | (−) | NA | NA | (−) | NA | NA |
| 5   | PTCL-NOS            | Small     | Present | (+) | CD4 | (+) | (−) | (+) | NA |
| 6   | PTCL-NOS            | Small     | Present | (+) | CD4 | (−) | (−) | (+) | NA |
| 7   | PTCL-NOS            | NA        | NA     | (+) | NA | NA | (−) | NA | NA |
| 8   | PTCL-NOS            | Small     | Present | (−) | Mixed | NA | (−) | (+) | NA |
| 9   | PTCL-NOS (γδT-cell) | Medium/large | Absent | (+) | DN* | (+) | (−) | (−) | (+) |
| 10  | PTCL-NOS            | Small     | Absent | (+) | CD8 | (−) | (−) | (+) | (−) |
| 11  | ENKTL (αβT-cell)    | Large     | Present | (+) | CD8 | (+) | (+) | NA | NA |

*CD8-positive in <10% of tumor cells.

ALCL indicates anaplastic large cell lymphoma; CTM, cytotoxic molecules (granzyme B or TIA-1); DN, double negative; Dx, diagnosis; ENKTL, extranodal NK/T-cell lymphoma; f+, focal positive; GR, gene rearrangement; IHC, immunohistochemistry; NA, not available; No., case number; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; PVL, perivascular lymphocytic cuffing.
### TABLE 1. (continued)

| Deep Structure Involvement | Multi-focality | Vitreoretinal/CSF Involvement | Tx detail | Upfront CT Rx | CT/RT Response | Outcome | PFS, m | OS, m |
|---------------------------|---------------|-------------------------------|-----------|---------------|----------------|---------|--------|-------|
| Yes                       | Yes           | No                            | OP/CT/RT  | MA(×6)       | CRu            | Alive   | 122.7  | 122.7 |
| Yes                       | Yes           | Yes                           | OP/CT     | MVP(×2)      | NA             | Death   | 6.5    | 6.5   |
| Yes                       | Yes           | Yes                           | CT        | MVP(×1)      | NA             | Death   | 1.1    | 20.0  |
| Yes                       | No            | NA                            | CT/RT/autoPBSCT | COPADM(×2) | Alive | 70.4  |      |       |
| No                        | No            | Yes                           | CT/RT     | MVP(×6)      | SD→mCR         | Alive   | 57.0   | 57.0  |
| No                        | Yes           | Yes*                          | CT/RT     | MVP(×6)      | CRu            | Alive   | 55.7   | 55.7  |
| Yes                       | Yes           | No                            | CT/RT     | MVP(×2)      | CRu            | Death   | 27.2   | 31.6  |
| Yes                       | Yes           | No                            | OP        | NA           | NA             | Death   | 3.0    | 3.0   |
| Yes                       | Yes           | Yes                           | CT        | Modified COP | NA             | Alive   | 1.3    | 33.2  |
| Yes                       | Yes           | No                            | OP/CT     | IMEP+Pegasparagase | PD | Alive | 0  | 3.3 |

### TABLE 2. (continued)

| Other IHC | TCG GR | IGH GR | Pathogenic Mutations | VUS Mutations |
|-----------|--------|--------|----------------------|---------------|
| CD30(a few +), TdT(−), CD5(+) | Monoclonal | Polyclonal | NA | NA |
| CD30(−) | Monoclonal | NA | KMT2C p.Arg380fs | None |
| CD30(+), CD15(−), ALK(+) | Monoclonal | NA | TET2 p.Leu371* | FAS p.Glu272Gly |
| CD2(−), CD5(−), CD7(f+), TdT(−) | Monoclonal | Polyclonal | None | None |
| CD2(f+), CD5(f+), CD7(f+) | Monoclonal | Polyclonal | NA | NA |
| CD103(−), CD56(−), CD30(−) | Monoclonal | Polyclonal | NRAS p.Gly12Ser | POT1 p.Lys33Glu |
| ALK(−), TdT(−) | Monoclonal | NA | JAK3 p.Met511Ile | KMT2C p.Pro335Ser |
| CD56(+), CD30(−), PD-1(−), ICOS(−) | Monoclonal | NA | CDKN2A homozygous deletion | SMARCA2 p.Gln230_Gln231delinsPro |
|                |                |                | CDKN2B homozygous deletion | BCL2 p.Ser70Leu |
|                |                |                | None | KMT2C p.Gly908Cys |
|                |                |                | JAK3 p.Met511Ile | FAS p.Glu272Gly |
|                |                |                | EGR2 p.Pro169Leu | None |
|                |                |                | NFRKB p.Val786Ile | None |
|                |                |                | TET2 p.Asn697Ile | None |
|                |                |                | BRAF heterozygous deletion | None |
|                |                |                | EZH2 heterozygous deletion | None |
|                |                |                | FYN heterozygous deletion | None |
|                |                |                | GATA3 heterozygous deletion | None |
|                |                |                | IDH2 heterozygous deletion | None |
|                |                |                | JAK3 copy number gain | None |
|                |                |                | MEF2B copy number gain | None |
|                |                |                | MYD88 copy number gain | None |
|                |                |                | NOTCH1 copy number gain | None |
|                |                |                | NFRKB copy number gain | None |
|                |                |                | PLCG1 copy number gain | None |
|                |                |                | RELA copy number gain | None |
|                |                |                | RHOA copy number gain | None |
|                |                |                | UBR5 copy number gain | None |
tricular regions, basal ganglia, brain stem, and/or cerebellum) (9/11, 81.8%) and multifocal sites (9/11, 81.8%) on initial brain magnetic resonance imaging. The major locations of the lesions included the brain cerebral hemispheres, deeper brain sites, and spine. Cerebrospinal or vitreoretinal involvement was observed in 4 (44.4%) of the 9 patients, including 1 patient (case 6) with vitreoretinal involvement. The majority of patients received high-dose methotrexate in combination with vincristine and procarbazine (n = 6); the others received high-dose methotrexate and cytarabine (n = 1), cyclophosphamide, vincristine, prednisone, doxorubicin, and high-dose methotrexate (n = 1), cyclophosphamide, vincristine, and prednisone (n = 1), or ifosfamide, methotrexate, etoposide, and prednisone (n = 1) as the initial chemotherapy, followed by radiotherapy (n = 6). Two patients (cases 2 and 9) died of disease within 1 year of diagnosis, 1 patient (case 3) after 20 months of diagnosis, and another (case 7) after 31.6 months of diagnosis. One patient (case 10) was referred to hospice care. The median progression-free survival time was 27.2 months, and the median overall survival time was 33.2 months.

**Pathologic Features of T-PCNSLs**

Pathologic features of the 11 cases with T-PCNSL are summarized in Table 2. The histologic and immunophenotypical features of the cases are described in the Supplementary Information (Supplementary Digital Content 1, http://links.lww.com/PAS/B298). Representative pathologic images are shown in Figures 1–4 and Supplementary Figures S1–S3 (Supplementary Digital Contents 4–6, http://links.lww.com/PAS/B301, http://links.lww.com/PAS/B302, http://links.lww.com/PAS/B303). Nine of the 11 cases were classified as PTCL-NOS (Figs. 1, 2 and 4; Supplementary Figs. S1–S3, Supplementary Digital Contents 4–6, http://links.lww.com/PAS/B301, http://links.lww.com/PAS/B302, http://links.lww.com/PAS/B303) and 1 patient (M/61 y) was diagnosed with ALK-positive ALCCL (Figs. 3A–F). Case 11 (M/61 y) was diagnosed with primary CNS extranodal natural killer (NK)/T-cell lymphoma (ENKTL) of αβ T-cell lineage; no other extracranial sites of origin (Figs. 1J–L), the clinicopathologic features of which were previously reported in detail.5 Tumor cells were small or small-to-medium in the majority of patients (n = 7) (Figs. 1A–1, 2, and 4; Supplementary Figs. S1–S3, Supplementary Digital Contents 4–6, http://links.lww.com/PAS/B301, http://links.lww.com/PAS/B302, http://links.lww.com/PAS/B303), medium-to-large in the patient with PTCL of γδ T-cell origin (Figs. 1J–L), large in the patient with ENKTL (Figs. 3G–L), and large-to-anaplastic in the patient with ALK-positive ALCCL (Figs. 3A–F). Perivascular lymphocytic infiltration was observed in the majority of cases (8/10, 80%) with 6 cases showing prominent perivascular infiltration (cases 1 [Supplementary Fig. S1B, Supplemental Digital Content 4, http://links.lww.com/PAS/B301], 3, 5, 6 [Fig. S3A, Supplemental Digital Content 6, http://links.lww.com/PAS/B303], 8 (Fig. 2I), and 11 (Fig. 3H).

Detailed morphologic features of representative cases were as follows: in case 1 (PTCL-NOS), small lymphoid cells with mild atypism were infiltrating perivascular area and parenchyme with strong perivascular lymphocytic infiltration (Supplementary Fig. S1, Supplemental Digital Content 4, http://links.lww.com/PAS/B301). In 2 (PTCL-NOS), geographic necrosis and focal microscopic hemorrhage were observed. At the interface between necrotic area and brain parenchyme, many small-to-medium-sized atypical lymphoid cell were observed. Atypical lymphoid cells were also diffusely infiltrating adjacent brain parenchyme along with perivascular and involvement of Virchows Robin spaces (Figs. 1B, C). The lymphoid cells had nuclear atypia with irregular or angulated nuclear contour and coarse chromatin and scanty clear cytoplasm (Figs. 1B, C). In microscopic examination of case 3 (PTCL-NOS), the biopsied tissue was hypercellular and densely infiltrated by small-to-medium-sized atypical lymphoid cells and histiocytes (Fig. 2B). Perivascular lymphocytic infiltration was frequently observed and the lymphoid cells showed nuclear atypia with irregular or angulated nuclear contour and scanty clear cytoplasm. In case 9 (PTCL of γδ T-cell origin), removed spinal tumor was hypercellular and composed of diffuse and dense infiltration of atypical monomorphic lymphoid cells (Figs. 1J–L). The atypical lymphoid cells were medium-to-large in size and had round nuclei, condense or finely dispersed chromatin, small inconspicuous nuclei, and pale-toeosinophilic moderate amount of cytoplasm (Figs. 1J–L). In the patient with ALK-positive ALCCL (case 4), microscopic examination revealed diffuse infiltration of large atypical cells with an anaplastic morphology admixed with small lymphocytes, histiocytes, and reactive astrocytes (Figs. 3B–F). CD30 immunostaining highlighted occasional cohesive arrangement of lymphoma cells along with perivascular and diffuse infiltration of ENKTL case was CD8-positive. CD30 immunostaining highlighted occasional cohesive arrangement of lymphoma cells along with perivascular and diffuse infiltration of ENKTL and negative in the other cases. The ALCCL of γδ T-cell lineage (case 11), microscopic examination revealed large atypical lymphoid cells infiltration predominately in Virchows Robin spaces and perivascular area along with perineuronal satellitosis (Figs. 3G, H). The atypical lymphoid cells had large atypical nuclei with finely dispersed chromatin, irregular nuclear membrane, occasional nuclear grooves and multiple small distinct nucleoli. Apoptotic cells were easily detected in any high power field.

Among the cases of PTCL-NOS, 4 (4/8, 50%) were predominantly infiltrated by CD4-positive cells, and 3 (3/8, 37.5%) by CD8-positive cells; 1 case (1/8, 12.5%) showed a mixed pattern with both CD4-positive and CD8-positive cell infiltration. The PTCL of γδ T-cell origin was CD4/CD8-double-negative and the ENKTL case was CD8-positive. Cytotoxic molecules (granzyme B or TIA-1) were expressed in the majority (4/6, 66.7%) of evaluated cases. EBV in situ was diffusely positive in ENKTL and negative in the other cases. T-cell monoclonality was detected in all 9 evaluated cases.

**Genetic Features of T-PCNSLs**

A total of 40 mutations in 28 genes were found in 6 patients; no recurrent mutations were observed (Table 2, Fig. 5). KMT2C was the most frequently mutated gene (5/7, 71%) with missense, splicing, and frameshift mutations and copy number alterations, followed by TET2, FAS, POT1, and
FIGURE 1. Representative images of case 2 (PTCL-NOS) (A–I) and case 9 (PTCL-NOS of γδT-cell lineage) (J–L). In case 2, brain magnetic resonance imaging showed an irregular peripheral enhancing lesion involving the left temporal, parietal, and right occipital lobes (A). Atypical lymphoid cells were infiltrating brain parenchyma with perivascular cuffing (B, C). In immunohistochemistry, tumor cells were positive for CD3 (D, E), CD8 (F), TCRβF1 (G) and granzyme B (H). T-cell monoclonality was observed in a TCRG gene rearrangement study (I). Case 9 (PTCL-NOS of γδT-cell origin) showed diffuse infiltration of atypical medium-to-large lymphoid cells (J), which expressed CD3 (K) and TCRγ (L). PTCL-NOS indicates peripheral T-cell lymphoma, not otherwise specified.
FIGURE 2. Representative images of case 3 (PTCL-NOS) (A–F) and case 8 (PTCL-NOS) (G–L). A, Brain magnetic resonance imaging of case 3 showed multiple enhancing lesions in both cerebral hemispheres (A) and the cerebellum (not shown). Brain parenchyme was diffusely infiltrated by small-to-medium-sized atypical lymphoid cells (B), which expressed CD3 (C), TCRβ1 (D), and CD4 (E). Scattered suspected reactive cells were positive for CD8 (F). G, Brain magnetic resonance imaging of case 8 showed ill-defined T2 high SI lesions in both basal ganglia, the internal capsule, and adjacent white matter. Small-sized lymphoid cells infiltrated brain parenchyme along with perivascular cuffing (H, I). Infiltrating cells were positive for CD3 (J, K) and negative for CD20 (L). PTCL-NOS indicates peripheral T-cell lymphoma, not otherwise specified.
FIGURE 3. Representative images of case 4 (anaplastic lymphoma kinase-positive anaplastic large cell lymphoma) (A–F) and case 11 (extranodal natural killer/T-cell lymphoma of αβT-cell lineage) (G–L). A, Brain magnetic resonance imaging of case 4 showed a solid and cystic mass involving the right cingulate, corpus callosum body and parieto-occipital region. Large pleomorphic anaplastic cells were infiltrating brain parenchyma (B, C). Most of the anaplastic cells were negative for CD3 (D), but positive for CD30 with a strong membranous and Golgi pattern (E), and for anaplastic lymphoma kinase with strong cytoplasmic and nuclear pattern (F). In case 11 (extranodal natural killer/T-cell lymphoma of αβT-cell lineage), large atypical lymphoid cells were infiltrating brain parenchyma along small vasculature or in a perineuronal satellitosis pattern (G). Clear perivascular cuffing of atypical cells was observed (H). Tumor cells were diffusely positive for CD3 (I), CD8 (J), TCRβF1 (K), and Epstein-Barr virus (L).
Pathogenic mutations were found in 4 cases. Case 2 had KMT2C frameshift mutation (c.1139delG; p.Arg380fs), and case 3 had nonsense mutation in TET2 (c.1112T>A; p.Leu371*). Case 9 had missense mutations in NRAS (c.34G>A; p.Gly12Ser) and JAK3 (c.1533G>A; p.Met511Ile), and homozygous gene copy deletions in CDKN2A (CN=0) and CDKN2B (CN=0). Case 11 harbored a nonsense mutation in ARID1B (c.1274C>A; p.Ser425*), frameshift mutation in BCOR (c.472dupA; p.Ser158fs), splicing mutation in FAS (c.652-2A>G), and multiple missense mutations in TP53 (c.404G>T; p.Cys135Phe, c.482C>T; p.Ala161Val, c.524G>A; p.Arg175His). This case also harbored copy number deletions in KMT2C, POT1, and PRDM1.

DISCUSSION

This study identified the clinical, pathologic, and genetic features of 11 rare cases of T-PCNSL, including 9 of
PTCL-NOS, 1 of ALK (+) ALCL and 1 of ENKTL. Most of the cases with PTCL-NOS were characterized by small or small-to-medium-sized cells; the cases of PTCL-NOS of γδT-cell lineage and ENKTL were characterized by medium-to-large or large cells. Perivascular lymphocytic infiltration of variable intensity was observed in most cases, similar to PCNS-DLBCL. The majority of cases showed cytotoxic molecule expression, and the proportions of cases with the CD4 and CD8 phenotype were similar. Although our study includes only a limited number of cases, our study reveals that the genetic alterations found in T-PCNSL are similar to that of systemic T-cell lymphomas. The molecular study demonstrated frequent KMT2C alterations in T-PCNSL cases, and NRAS G12S and JAK3 M511I mutations, and homozygous deletions of CDKN2A and CDKN2B, in the case of PTCL with γδT-cell subtype. In one of the cases of PTCL-NOS, truncation mutation of TET2 was observed. In the case of PCNS-ENKTL, genetic alterations similar to systemic ENKTL were observed.

We confirmed 4 cases (cases 2, 3, 9, and 11) with interesting pathogenic alterations. Case 2 (PTCL-NOS) harbored the frameshift mutation of KMT2C. KMT2C (mixed-lineage leukemia 3) is a member of the mixed-lineage leukemia family of histone methyltransferase and methylates histone 3 tail at lysine 4 (H3K4).10 KMT2C was one of the most frequently mutated genes in a targeted sequencing study of PTCL-NOS,11 with nonsynonymous somatic mutations in 32% (23/71 cases) of samples.

Case 3 (PTCL-NOS) had a nonsense mutation of TET2. As TET2 is an epigenetic regulator and somatic mutations driving aging-associated clonal hematopoiesis readily occur in TET2,12 we additionally performed targeted gene sequencing using the patient’s peripheral blood sample. The patient’s peripheral blood did not reveal the TET2 L371* mutation found.
in the patient’s brain lesion, confirming that it is a mutation of the tumor rather than clonal hematopoiesis. 

*References*
