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Primary CNS T-Cell Lymphomas: A Clinical, Morphologic, Immunophenotypic and Molecular Analysis

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Abstract

Primary central nervous system (CNS) lymphomas are relatively rare with the most common subtype being diffuse large B-cell lymphoma. Primary CNS T-cell lymphomas (PCNSTL) account for <5% of CNS lymphomas. We report the clinical, morphologic, immunophenotypic and molecular characteristics of 18 PCNSTLs. Fifteen cases were classified as peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS), 2 of which were of γδ T-cell derivation and 1 was TCR silent; there was 1 anaplastic large cell lymphoma (ALCL), ALK-positive and 2 ALCL, ALK-negative. Median age was 58.5 years (range 21-81), with M:F ratio of 11:7. By imaging 15 patients had supratentorial lesions. Regardless of subtype, necrosis and perivascular cuffing of tumor cells were frequently observed (11/18 cases). CD3 was positive in all cases but 1; 10/17 were CD8-positive and 5/17 were CD4-positive. Most cases studied had a cytotoxic phenotype with expression of TIA1 (13/15) and granzyme-B (9/13). PCR analysis of TRG rearrangement confirmed a T-cell clone in 14 cases with adequate DNA quality. Next Generation Sequencing (NGS) showed somatic mutations in 36% of cases studied; 2 had more than one mutation and none showed overlapping mutations. These included mutations in *DNMT3A*, *KRAS*, *JAK3*, *STAT3*, *STAT5B*, *GNB1* and *TET2* genes, genes implicated previously in other T-cell neoplasms. The outcome was heterogeneous; 2 patients are alive without disease, 4 are alive with disease and 6 died of disease. In conclusion, PCNSTL are histologically and genomically heterogeneous with frequent phenotypic aberrancy and a cytotoxic phenotype in most cases.

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Supplemental Digital Content.

SDC1. Further information regarding the methods used for Next Generation Sequencing and the complete list of the 38 targeted genes is found in the supplemental content.

SDC2 lists the genes Included in the Sequencing Panel

Keywords

T-cell lymphoma; central nervous system; next generation sequencing; gamma-delta T-cells; T-cell clonality; molecular diagnostics

INTRODUCTION

Primary central nervous system (CNS) lymphoma (PCNSL) is a relatively rare disease accounting for 2-6% of all primary brain malignancies and 1-2% of non-Hodgkin lymphoma (NHL) [1-5]. These lymphomas are defined as being confined to the brain, spinal cord or the eye without extra CNS or lymph node manifestations at presentation (1-6). However, late relapses outside the CNS can occur [3, 6] . While diffuse large B-cell lymphoma (DLBCL) is the most common type of PCNSL (with primary DLBCL of CNS enjoying a separate category in the current WHO classification), other lymphomas including Burkitt lymphoma, MALT lymphomas (dura), follicular lymphoma and T-cell lymphomas, can present with intracranial disease [2, 3, 7, 8]. The reported percentage of PCNSL of T-cell derivation (PCNSTL) varies from 3.6% (France), 8.5% (Japan) to 2% (8 cases out of 370 patients) in the largest PCNSL series from the western world [9]. Choi et al. described a somewhat higher percentage of T-cell lymphomas (16.7%, 7/42 cases) in their series of primary CNS lymphomas from Korea [10].

The most recently published large case series from the International Primary CNS Lymphoma Collaborative Group described 45 patients with PCNSTL[1]. In this series, 20 patients (44%) had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Twenty-six patients (58%) had involvement of cerebral hemispheres and 16 (36%) had lesions of deeper brain sites. The median disease-specific survival (DSS) was 25 months, and multivariate analyses demonstrated an association of better ECOG performance status and methotrexate use with longer survival. However, a detailed morphologic and immunophenotypic analysis is not available. In a separate study of primary CNS lymphoma other than DLBCL, outcomes for 7 patients with peripheral T-cell lymphomas (PTCL) were described; these T-cell lymphomas demonstrated similar or favorable clinical outcomes as compared to previously reported data on DLBCLs [7]. While several case series (referenced above) have made valuable contributions to the understanding of the clinical characteristics of PCNSTL, an extensive pathologic analysis/description is lacking. Several case reports and smaller case series have described the pathology and immunophenotype in varying detail[11-26].

The goal of this study was to describe in a comprehensive manner not only the clinical characteristics but also the histological, immunophenotypic and molecular characteristics of 18 PCNSTLs identified from the consultation files of the hematopathology division of the authors' institution.

MATERIALS AND METHODS

Case selection

Nineteen cases of PCNSTLs were identified from the pathology database of the Hematopathology Section, Laboratory of Pathology, National Cancer Institute, between 2000 and 2014. Eighteen cases were submitted in consultation as brain biopsies. One additional autopsy case was contributed by 1 of the coauthors (DCM). None of the patients had lymphadenopathy or evidence of extra CNS disease at the time of CNS presentation. One patient had a soft tissue mass involved by PTCL 3 months after diagnosis of the CNS lesion; given the close proximity of these lesions, this case was excluded. This study was approved by the Institutional Review Board of the National Cancer Institute.

Immunohistochemistry studies

Immunohistochemical studies were performed on available formalin-fixed paraffin-embedded tissue (FFPE) sections using the following antibodies: CD2, CD3, CD4, CD5, CD7, CD8, CD30, CD56, βF1, TCRγ, TIA1, granzyme-B, perforin, LMP1, MIB-1 and ALK1. The panel of antibodies, clone, dilution and source are listed in Table 1. A case was scored as positive if more than 50% of the atypical lymphoid cells expressed the antigen. MIB-1 was scored as low (< 33%), moderate (33-66 %), and high (67-100%) based the percent of lymphoid cells positive.

In situ hybridization for Epstein Barr virus (EBV) encoded RNA (EBER)

In situ hybridization was performed on FFPE tissue, using EBER1 DNP probe supplied by Ventana on an automated stainer (Ventana-Benchmark XT, Tucson, AZ). The ISH iView blue plus system with alkaline phosphatase and nitroblue tetrozolium and 5-bromo-4-chloro-3-indolyl phosphate substrate, with Fast Red contrast was used for visualization, with relevant controls.

Molecular studies

For T-cell receptor gamma (TRG) rearrangement, DNA was extracted from FFPE tissue blocks and either 1) single multiplexed PCR was done with primers directed against all known Vg family members, and the Jg1/2, JP1/2 and JP joining segments [27] or 2) three separate reactions were performed, one with primers Vg101, Vg11 and Jg12 (set 1), a second with primers Vg 101, Vg11 and Jp12 (set 2), and a third with primers Vg9 and Jg12 (set 3), the first 2 performed according to the method of Slack et al [28], and the third according to a validated in house method. Products were analyzed either via acrylamide gel electrophoresis or by capillary electrophoresis on an ABI 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA). The results were interpreted as polyclonal, restricted, or clonal. The “restricted” TRG category was defined as an abnormal rearrangement pattern with small peaks that did not meet criteria for monoclonality, as previously described[29].

Mutational analysis

DNA samples were analyzed for somatic mutations within genes previously implicated in the pathogenesis of mature T-cell lymphomas using a targeted next generation sequencing

(NGS) strategy[30]. The mutation panel includes targeted regions of 38 genes previously reported to be mutated in T-cell lymphomas as well as targeted regions of genes involved in T-cell signaling focused on the JAK/STAT signaling pathway. The amplicon libraries were generated with two custom primer pools (total 227 amplicons) and were sequenced on an Ion Torrent Personal Genome Machine (PGM) (Life Technologies). The paraffin-embedded tissue sections were macrodissected to enrich for tumor cells with at least 20% tumor content. DNA was extracted using the Qiagen QIAamp DNA FFPE Tissue Kit and performed on a QIAcube according to the instructions of the manufacturer. Further details regarding the NGS methods (SDC1) and a list of the genes analyzed (SDC2) are included in Supplemental Digital Content files.

RESULTS

Clinical features

Eighteen confirmed cases of PCNSTL were identified. The clinical features of these cases are summarized in Table 2. There were 11 males and 7 females; with a median age of 58.5 years (range 21-81). The clinical manifestations of patients ranged from headache, aphasia, facial paralysis, facial and upper limb sensory abnormalities, speech abnormalities, ataxia, leg weakness, and difficulties in short term memory etc. By imaging studies, 15 patients had supratentorial lesions, 3 had cerebellar involvement. Solitary tumor was seen in 9 cases, multiple masses in 8 and one showed diffuse enhancement of meninges. None of the patients presented with or developed lymphadenopathy at any time point. One case of ALCL, ALK-positive diagnosed at autopsy (Case 16), had extensive dural, leptomeningeal and spinal disease. At autopsy one out of several lymph nodes tested showed rare scattered CD30 and ALK positive cells, which were interpreted as secondary lymph node involvement by virtue of the high burden of the disease in the CNS and the lack of lymphadenopathy or histologically confirmed disease elsewhere.

Treatment information was available for 10 patients. 4 received chemotherapy and radiotherapy, 3 were treated with chemotherapy alone, 2 received only steroids and one patient did not received treatment due to a poor performance status. The outcome data was available for 12 patients. With a median follow-up of 5 months (range 1-64 months), 2 patients are alive without disease, 4 patients are alive with disease and 6 patients died of disease.

Morphologic findings

The PCNSTCL were classified as peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) (15 cases), anaplastic large cell lymphoma (ALCL), ALK-negative (2 cases), and ALCL, ALK-positive (1 case). The salient morphologic findings are summarized in Table 3. While most cases were submitted as small biopsies, detailed gross examination was available for one ALCL, ALK-positive diagnosed at autopsy (case 16). This case demonstrated tan-white nodules on the dural surface (mostly left-sided) with size ranging from 0.3-0.8 cm (Figure 1A). Leptomeningeal involvement was observed grossly in the lower thoracic and lumbar spinal cord with extension to the nerve roots of cauda equina. Overall, 5 cases had demonstrable leptomeningeal involvement.

Microscopically, most PTCL, NOS cases (11/15) were composed of atypical small and/or medium sized lymphocytes with dense, hyperchromatic nuclei, irregular nuclear outlines, occasional distinct nucleoli and scant cytoplasm (Figure 2). Medium to large cells (3 cases) or mostly large cells (1 case) were predominant in the remainder (Figure 3). Three cases showed features characteristic of ALCL, being composed of large cells with vesicular chromatin, evident nucleoli, and abundant cytoplasm; frequent “hallmark” cells were identified (Figure 1C). The tumor cells formed cohesive aggregates/sheets in two cases and were scattered throughout the white matter in one case.

Prominent perivascular infiltration was evident in most cases (11/18) (Figure 4), with tumor cells expanding the Virchow-Robin space. Areas of necrosis were visible in 11 cases. Several cases demonstrated significant background gliosis and abundant histiocytes probably related to necrosis.

Immunophenotype

The atypical lymphoid cells expressed CD3 in all cases except one (ALCL, ALK positive) (Table 3). 10/17 were CD8-positive and 5/17 were CD4-positive, with no case showing dual expression. Partial or total loss of T-cell antigens was seen in 4/15 cases for CD2, 11/18 cases for CD5 and 8/13 cases for CD7. No case expressed CD56, although high background staining for CD56 (as expected in CNS tissues) made interpretation difficult. 10/14 cases showed βF1 immunostaining. Among the 4 βF1-negative cases, a γδ T-cell derivation was confirmed in 2 by positivity for TCRγ (Figure 5); 1 case was TCR silent and 1 lacked material for TCRγ. Regardless of histological type, most of the cases showed a cytotoxic phenotype with expression of TIA1 in 13/15, granzyme-B in 9/13 and perforin in 4/7. Three (of 15) cases showed strong, uniform expression of CD30, corresponding to the diagnosis of ALCL, with one of these being positive for ALK, with both nuclear and cytoplasmic immunoreactivity. All 16 cases analyzed showed a brisk proliferation index as per Ki-67, with at least 50% of lymphoid cells positive. Rare EBV positive cells were present in 2/15 cases studied by EBER and/or LMP1. Stains for BCL6, CD10 and PD-1(CD279) were performed on a single CD4+ case (Case 5), and were negative.

T-cell Receptor Gene Rearrangement and Mutational analysis

The quality of DNA allowed for further analysis in 16/18 cases, with 2 cases showing no amplification products. A clonal rearrangement pattern was identified in 14 cases; one case showed a restricted pattern and 1 was considered suspicious for a significant clonal rearrangement.

Eleven of 18 cases (one of which was ALCL, ALK+) were analyzed with a custom NGS mutation panel targeting mutation hotspots in genes previously reported to be mutated in T-cell lymphomas, and in genes involved in T-cell signaling pathways. Four cases of PTCL-NOS were found to have somatic mutations (4/11, 36%); two had more than one mutation and none showed overlapping mutations. Case 3 displayed a *DNMT3A* (c.2207G>T; p.Arg736Leu) mutation. Case 9 was found to have *KRAS* (c.34G>A; p.Gly12Ser), *STAT5B* (c.1924A>C, p.Asn642His) and *JAK3* (c.1533G>T; p.Met511Ile) mutations. Case 14, PTCL, NOS of γδ T-cell derivation showed a TET2 (c.4034A>C; p.Tyr1345Ser) mutation

and Case 15, silent for TCR expression by immunostains, contained both *GNB1* (c.232A>G; p.Lys78Glu) and *STAT3* (c.1981G>C; p.Asp661His) mutations. All remaining cases were wild type at the targeted sites in the 38 genes included in the panel.

DISCUSSION

Through this study, we describe in detail the histopathologic, immunophenotypic and molecular characteristics of 18 cases of primary CNS T-cell lymphomas. Diagnosis of these lesions is often a challenge, with the main differential being an inflammatory process, as the neoplastic T-cells were small to medium in size in the majority of cases, most of which were classified as PTCL, NOS. The diagnosis was more readily made in three cases of anaplastic large cell lymphoma, one of which was positive for ALK. A helpful feature was prominent perivascular infiltration; perivascular cuffing is common feature among both primary CNS B-cell and T-cell lymphomas. Additionally, necrosis, gliosis and histiocytic infiltration were seen in a significant number of cases. In contrast, abundant plasma cells, neutrophils or eosinophils were absent; when present, these would favor an inflammatory process.

Given the small cell size in many cases, immunohistochemical studies and molecular analysis were key in diagnosis. The most common antigenic aberrancies included complete or partial loss of CD5 (61%) and CD7 (62%). Loss of CD3 was very uncommon, restricted to 1 case of ALCL. More than half were CD8 positive. While most cases appeared to be derived from αβ-T cells, 4 cases were βF1 negative, suggesting a γδ T-cell derivation. However, only two were positive for TCRγ by immunohistochemistry; one case was noted to be TCR silent, also a major aberrancy[31]. The majority of cases had a cytotoxic phenotype, irrespective of histological subtype, as determined by staining with granzyme B, perforin, and TIA-1. Prior studies have shown a high incidence of a cytotoxic phenotype in extranodal as opposed to nodal T-cell lymphomas[32].

Molecular testing for TCR γ chain gene rearrangement played an important role in the diagnosis of PCNSTL. A clonal process was confirmed in 14/16 cases with adequate DNA, while 2 others were either suspicious or showed a restricted pattern. PCNSTL have not previously been studied for molecular aberrations. Four of 11 PTCL, NOS studied (36%) had mutations involving, *STAT3, STAT5B, JAK3, DNMT3A, KRAS, TET2 and GNB1* genes. Interestingly, no mutation was common to multiple cases, suggesting molecular heterogeneity. However, the findings in 2 cases with mutations in STAT5B, STAT3 and JAK3 support the importance of the JAK/STAT pathway in T-cell malignancies. Activating mutations of STAT3, STAT5B and JAKs have been reported with high frequency in large granular lymphocytic leukemia[33, 34], γδ hepatosplenic T-cell lymphomas [30], T-prolymphocytic leukemia[35], non-hepatosplenic γδ T-cell lymphomas[36] and natural killer/T-cell lymphoma[37]. Other studies have demonstrated the importance of the JAK/STAT pathway in both ALK-positive and ALK-negative ALCL [38, 39]. Thus, our data suggest that JAK and/or STAT inhibitors might represent potential treatment options in patients with PCNSTLs.

DNMT3A and TET2 mutations have been recently reported as important events in the pathobiology of mainly nodal lymphomas of T_{LH} derivation[40, 41]. Interestingly, we found

evidence of these mutations in PCNSTLs; one case with a mutation in *DNMT3A* had a CD4-positive phenotype, whereas a second case with a *TET2* mutation was of γδ T-cell derivation. *TET2* has not previously been implicated in the pathogenesis of γδ T-cell lymphomas. Clinically, most of our cases of PCNSTL had supratentorial disease and at presentation had solitary masses. Most patients received some form of chemotherapy combined with steroids with or without intrathecal methotrexate and/or brain irradiation. 6 patients had expired at the time of this study. In the largest series of PCNSTCL of the western world (International Primary CNS lymphoma collaborative group)[1], the clinical characteristics were similar to those of primary CNS lymphomas in general [6, 9, 42] including the median age (approximately 60 years), propensity for supratentorial involvement, and male predominance. Similarly, primary CNS lymphomas of both B-cell and T-cell types are clinically aggressive, with median survivals of less than 2 years [1, 6, 9, 42].

Interestingly, a difference in prognosis based on morphology (i.e. small, medium versus large cells) was not present for PCNSTCL[1]. In a more recent study by Lim et al. [7], 9 patients with primary CNS PTCL were identified, and demonstrated relatively favorable clinical outcomes as compared to primary CNS DLBCL. However, other than CD3 positivity in these cases, further histologic, immunophenotypic and molecular data were not specified. Interestingly, a Korean study revealed a much higher percentage of PCNSTCL cases (16.7%) of all primary CNS lymphomas [10], significantly higher than that reported in western studies.

In a study by Levin et al [16], 5 patients out of a cohort of 100 patients with primary CNS lymphoma had T-cell lymphoma and all of them presented with isolated leptomeningeal involvement. However, in the study describing the largest primary CNS T-cell lymphoma cohort, only 1 out of 45 patients had leptomeningeal involvement [1]. In the other cases described in their study, the parenchyma of the cerebral hemispheres (cortex and white matter) were the most frequent site (64%) followed by deep brain structures. This is similar to the known manifestations of B-cell PCNSL.

In our study leptomeningeal involvement was present in 5 cases and was extensive in one (case 16, ALCL, ALK+). Involvement of the leptomeninges in ALCL is a common feature. Of the 24 cases of primary CNS ALCL that have been described [21, 25, 43-61], 10 cases demonstrated some degree of dural or leptomeningeal involvement. In addition, there are 2 documented cases of primary dural ALCL without CNS parenchymal involvement [44, 45]. In one case of ALCL from our series the bulk of the disease was in the leptomeninges, and the clinical syndrome was dominated by meningitic signs and symptoms. Of the reported ALCL cases, 13 were ALK positive, 10 were ALK negative, while data on three cases was unavailable. As expected, ALK positivity seems to correlate with a younger age and better prognosis (similar to that observed in systemic ALCL). Interestingly, leptomeningeal involvement does not seem to confer a worse prognosis (40). Secondary involvement of the CNS is very rare in most PTCL, being most often reported in ALCL in approximately 1% of cases[62]. The only PTCL that frequently involves the CNS is adult T-cell leukemia/lymphoma, which is a systemic disease in most patients[63].

In conclusion, the diagnosis of T-cell lymphomas in the CNS is challenging, especially considering that the vast majority of these lymphomas have small or intermediate size cells with variable cytologic atypia. These need to be differentiated from reactive T-cell infiltrates and encephalitis caused by infections and autoimmune diseases. A combination of morphologic assessment, immunophenotypic aberrancies and demonstration of clonal T-cell receptor rearrangement helps in establishing the diagnosis of a T-cell lymphoma. Preliminary genetic analysis identified mutations in genes involved in other mature T-cell malignancies, but no common recurrent genetic events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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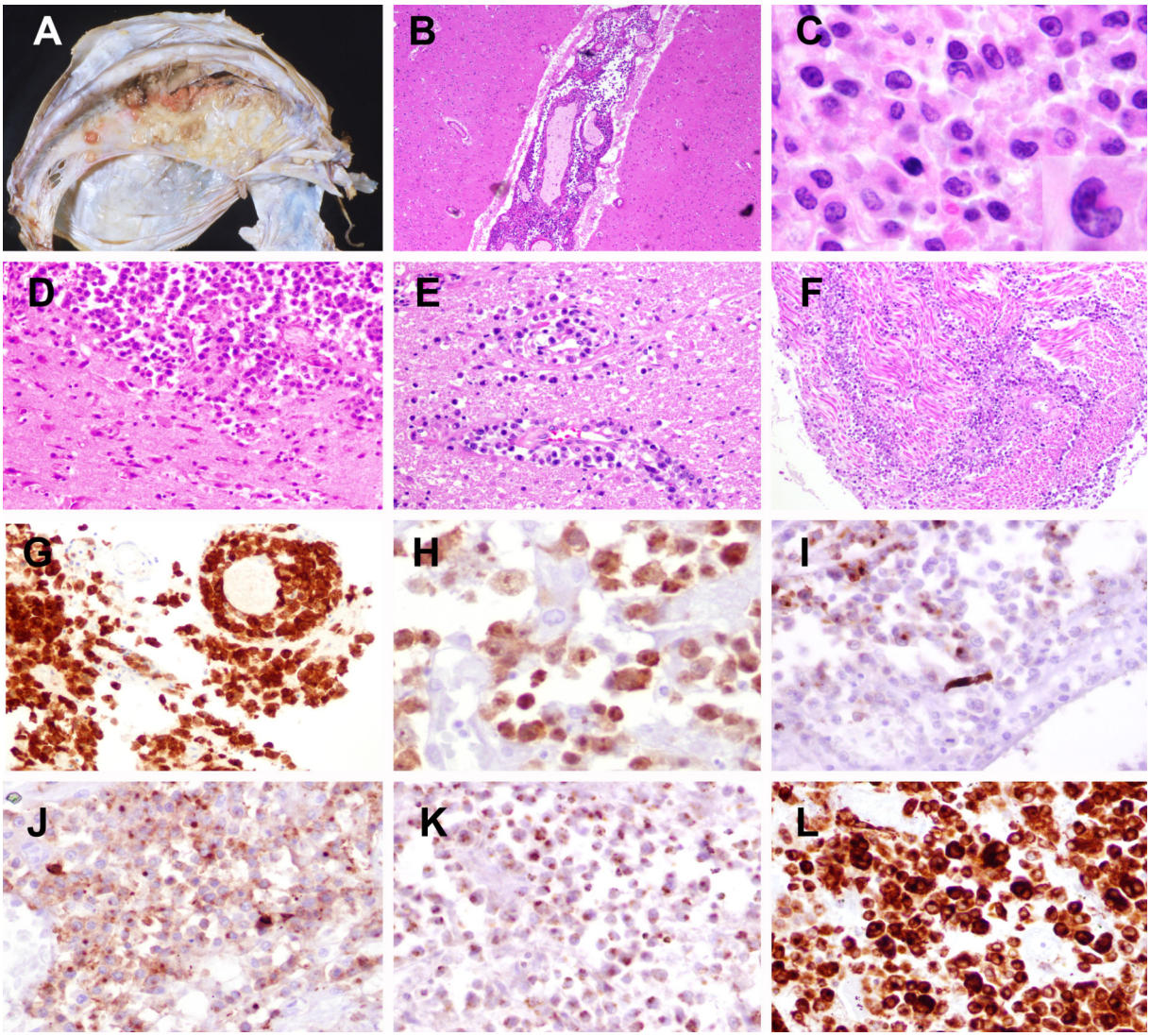

Figure 1. Anaplastic large cell lymphoma, ALK-positive (Case 16)

A) Multiple tan-white lesions are attached to the left side of falx dura. B) The leptomeninges are extensively involved. C) The cells are medium to large with irregular nuclei; occasional larger cells have eccentric kidney or horse shoe shaped nuclei and abundant cytoplasm consistent with “hallmark cells”. D) Parenchymal involvement was also seen along with perivascular infiltrates (E) as well as extensive spinal and nerve root involvement (F). The cells are positive for CD30 (G), ALK, nuclear and cytoplasmic (H), focal EMA (I), CD43 (J), TIA (K) and granzyme-B (L).

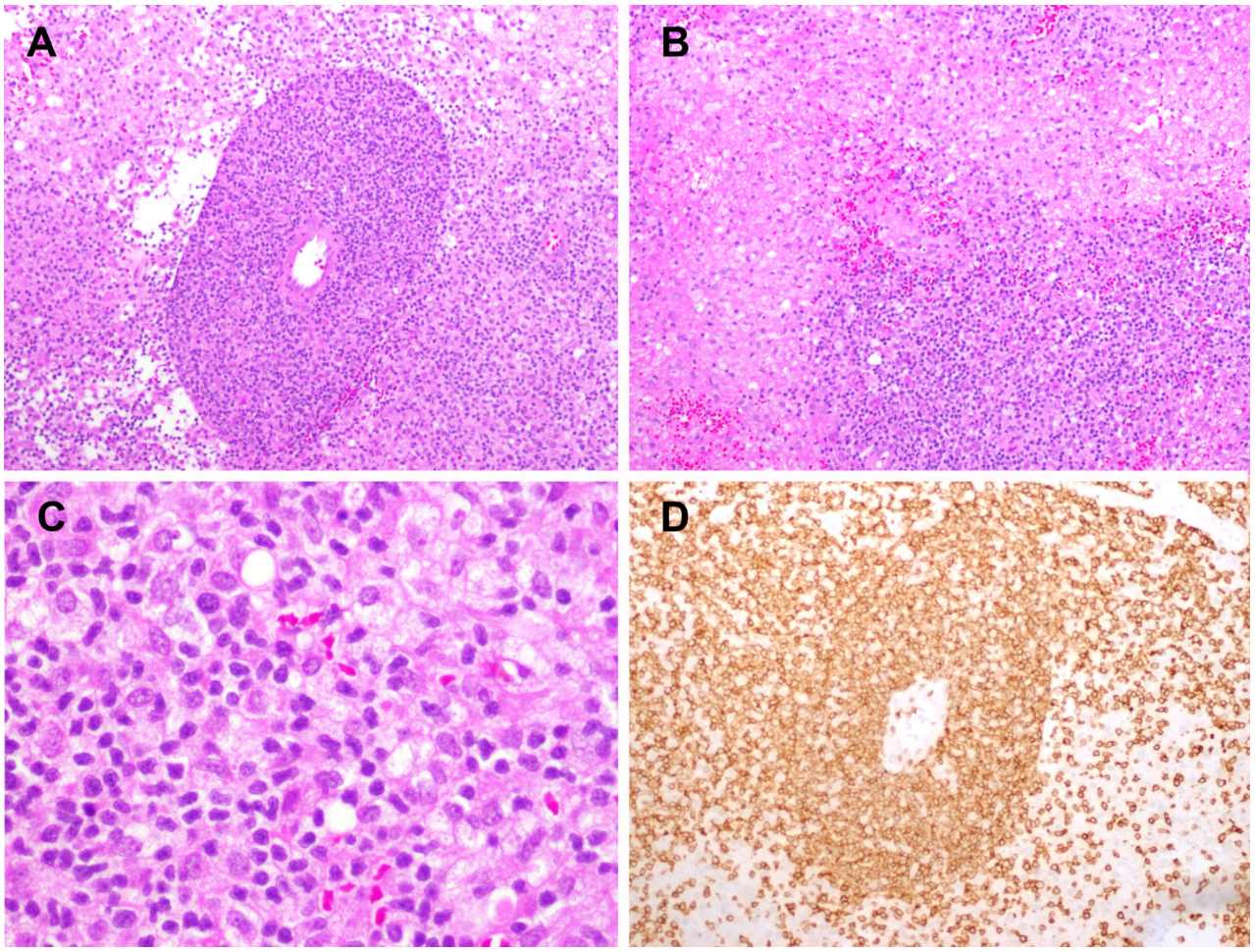

Figure 2. PTCL, NOS (Case 1)

A) Expansion of the Virchow-Robin space by an atypical lymphoid infiltrate. B) Broad areas of necrosis are visible. C) Neoplastic cells are small to medium in size with irregular nuclei; abundant admixed histiocytes are visible. D) The atypical cells are positive for CD3.

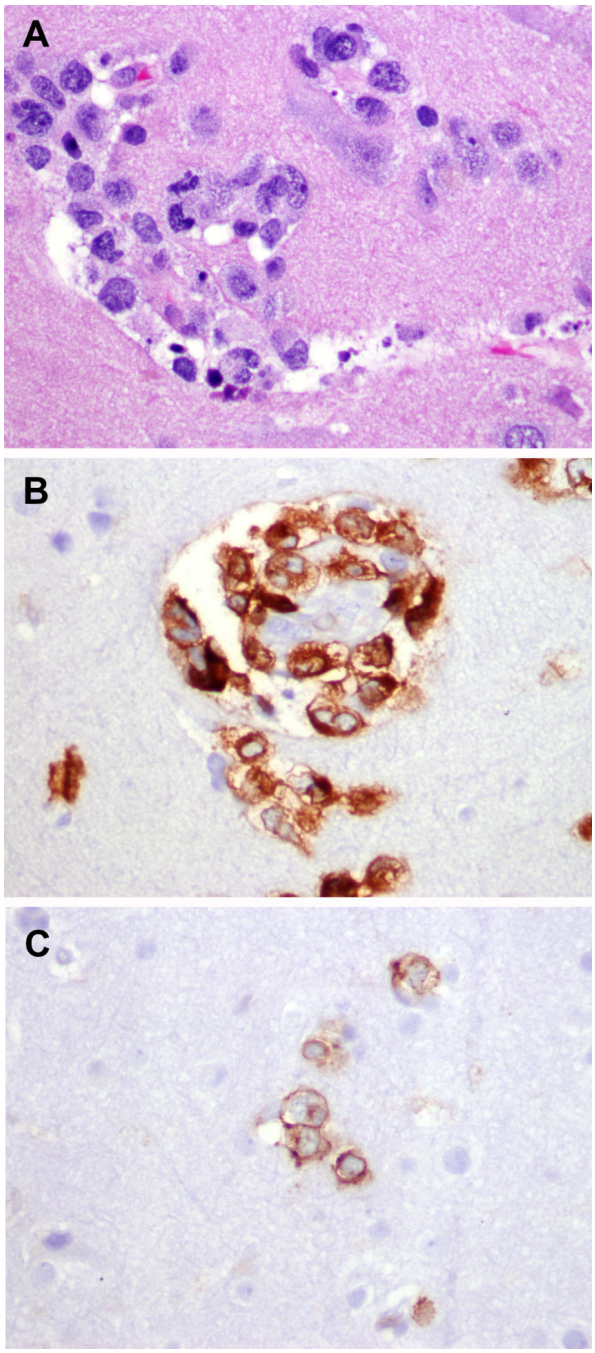

Figure 3. PTCL, NOS (Case 6)

A) A minority of cases, such as this one, contained large atypical cells with irregular nuclear contours, vesicular nuclei and basophilic nucleoli. The neoplastic cells are CD3-positive (B) and CD4-positive (C).

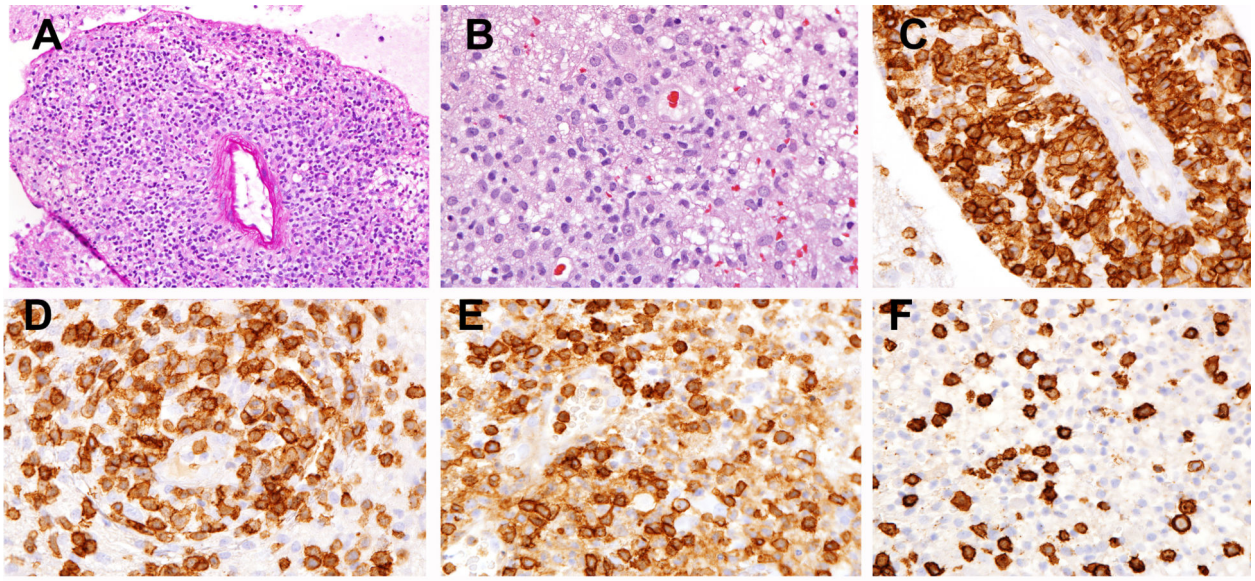

Figure 4. PTCL, NOS (Case 8)

(A) Marked perivascular infiltration is present. (B) The infiltrate is composed of small to medium atypical lymphocytes with significant background gliosis and abundant histiocytes. The atypical cells are strongly positive for CD2 (C), more variably positive for CD5 (D), positive for CD4 (E) and negative for CD8 (F).

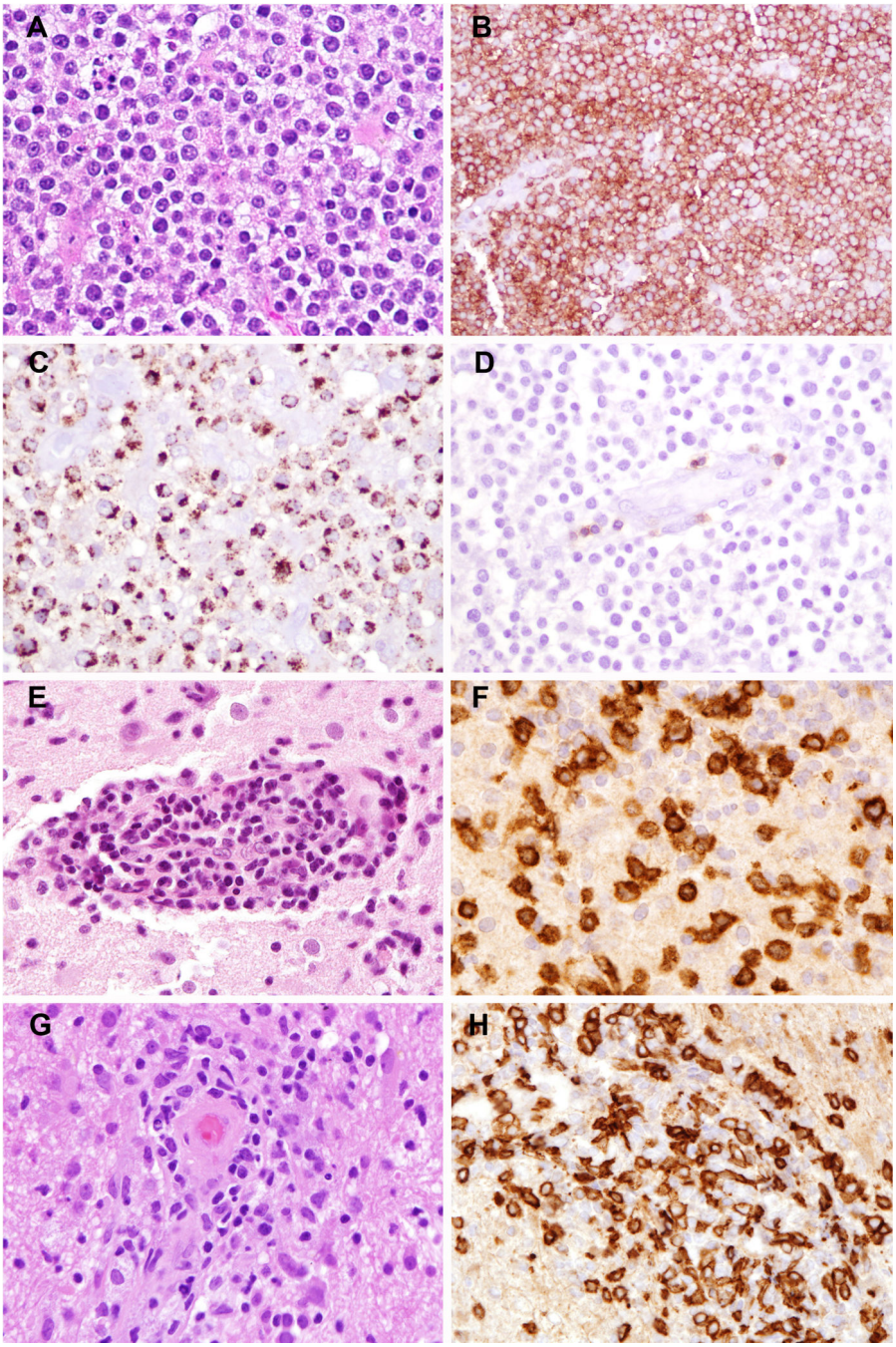

Figure 5. Phenotypic aberrancies in PCNSTCL

A-D, PTCL, NOS with TCR silent phenotype (Case 15). A) Monomorphic medium sized atypical lymphocytes with irregular nuclear contours, vesicular chromatin and occasional nucleoli. The neoplastic T-cells are CD8-positive (B), TIA-1-positive (C) and beta-F1 (D) negative. TCR gamma was also negative (not shown). **E-H) TCR gamma positive cases (Case 13 and 14)**. The cells are mostly small-medium with irregular nuclear contours,

admixed occasional larger cells and demonstrate prominent perivascular cuffing (E and G). The cells are strongly positive for TCR-gamma immunostain (F and H).

Table 1

Antibodies used in the immunophenotypic analysis

Antigen	Clone	Dilution	Source
CD3	Polyclonal	1:100	Dako
CD4	1F6	1:40	Novocastra
CD8	C8/144B	1:50	Dako
CD2	AB75	1:160	Novocastra
CD5	4C7	1:100	Novocastra
CD7	CD7-272	1:50	Novocastra
βF1	8A3	1:20	Endogen
TCRγ	γ3.20	1:100	Thermo Scientific
CD30	1G12	1:50	Novocastra
ALK1	ALK1	1:400	Dako
TIA1	2G9A10FS	1:1000	Immunotech
Granzyme-B	GrB-7+D170	1:100	Monosan
Perforin	KM585 PI-8	1:10	Vector
CD56	1B6	1:50	Novocastra
LMP1	CS1-4	1:400	Dako
Ki-67	MIB-1	1:50	Abcam

Table 2

Clinical Features, Imaging, Treatment and Outcome of PCNSTLs

Final No.	Age	Sex	Clinical presentation	Imaging	Treatment	Outcome
1	21	M	Headache	Solitary, right occipital mass (2 cm)	Steroids, Thiotepa+ HD MTX + XRT	na
2	61	M	NA	Solitary frontal mass	na	DOD
3	81	M	NA	Solitary, right occipital mass (2 cm)	Steroids	AwoD (64 mo)
4	54	M	Transient right facial and upper limb sensory symptoms, headaches, facial asymmetry and speech difficulties	Solitary, left frontal mass	HD MTX + XRT	AwD (47 mo)
5	60	M	Headache	Solitary, left cerebellar mass (2.2 cm)	Chemotherapy	DOD (3 mo)
6	57	M	Difficulties short term memory, ataxia, right leg weakness	Multiple lesions throughout the brain, largest left parietal lobe (3.5 cm)	na	na
7	69	M	na	Solitary, right parietal mass	MTX + AraC +Leucovorin + Procarbazine hydrocholoride	AwD
8	81	M	Altered mental status	Right occipital and temporal mass	2×MTX + bendamustine	AwD (4 mo)
9	63	F	Left sided weakness	Periventricular and striatocapsular abnormalities	no treatment	DOD
10	42	F	Seizures	Right frontal and temporal masses	Dexametasone + HD AraC + 3×MTX + 17 × XRT	AwD (5 mo)
11	21	F	Pregnant, headaches, behavior changes	Solitary parietal mass (7×7×5 cm)	na	na
12	67	F	Aphasia and facial paralysis	Multiple bilateral frontal and occipital masses	6× HD MTX + XRT	AwoD (56mo)
13	31	M	Seizure and slow (2 yrs) decline in mental function, weight loss, confusion	Bilateral temporal lobes enhancement	na	na
14	56	F	Headache	Solitary right frontal mass	na	na
15	57	M	Progressive neurologic decline	Multiple lesions in the basal ganglia, midbrain, brachium pontis and cerebellar hemispheres	na	DOD
16	43	M	Fever, nausea, vomiting (1 mo)	Multiple meningeal lesions (dural, leptomeningeal, spinal, superficial cortical parietal, right cerebellum and medulla involvement)	na	DOD
17	61	F	Weakness right superior extremity, paresthesia, mild paralysis	Diffuse enhancement	Dexamethasone	DOD (1 mo)
18	62	F	History multiple sclerosis, left lower extremity weakness (3 mo)	Solitary right frontal mass	na	na

Abbreviations: HD- high dose; XRT- radiation; IT- intrathecal; MTX- Methotrexate; DOD - died of disease, AwoD - alive without disease; AwD - alive with disease; na - not available

Table 3

rphology, Immunophenotype, TCR clonality and Mutation analysis

nal lo	Diagnosis	Size cells	Necrosis	Perivascular cuffing	Meningeal spread	CD2	CD3	CD4	CD8	CD5	CD7	CD56	BF1	TCRγ	TIA-1	GrB	Perf	CD30	ALK1	EBV	KI67	TRG PCR	Ion Torrent TCLP39
1	PTCL, NOS	small-medium	pos	pos	neg	na	pos	pos	neg	pos	na	equiv	na	na	na	na	na	na	na	neg (LPM1)	na	pos	na
2	PTCL, NOS	medium	pos	pos	pos	pos	pos	neg	pos	pos f	neg	neg	pos	na	pos	pos	na	neg	na	neg (LPM1)	na	pos	na
3	PTCL, NOS	small	neg	neg	neg	pos	pos	pos	neg	pos	pos f	neg	pos	na	pos	neg	neg	neg	na	neg	mod	susp	DNMT3A, c.2207G>T, p.Arg736Leu
4	PTCL, NOS	small-medium	pos f	pos	neg	pos f	pos	neg	pos	pos	pos	neg	pos	na	pos	neg	na	neg	neg	neg	high	pos	WT
5	PTCL, NOS	medium	pos	neg	neg	pos	pos	mix	mix	pos f	pos f	neg	pos	na	pos	neg	neg	neg	neg	rare	mod	rest	WT
6	PTCL, NOS	large	neg	neg	neg	pos	pos	pos	neg	pos f	pos f	not interp	pos	na	neg	neg	neg	neg	neg	neg	high	no amp	na
7	PTCL, NOS	medium-large	pos	pos	neg	pos	pos	pos	neg	pos	pos f	neg	pos	neg	pos	pos	pos f	neg	neg	neg	mod	pos	WT
8	PTCL, NOS	medium-large	pos	pos	neg	pos	pos	pos	neg	pos	pos f	neg	na	na	na	na	na	neg	na	neg	mod	pos	na
9	PTCL, NOS	small-medium	neg	neg	neg	neg	pos	neg	pos	neg	pos	neg	pos	neg	pos	pos	pos	neg	na	na	high	pos	KRAS, c.34G>A, p.Gly12Ser; STAT5B, c.1924A>C, p.Asn642His; JAK3, c.1533G>T, p.Met511Ile
10	PTCL, NOS	small-medium	pos	pos	pos	pos	pos	neg	pos	pos f	pos	neg	pos	neg	pos	pos	pos	neg	neg	neg	high	pos	WT
11	PTCL, NOS	medium-large	pos	pos	pos	pos	pos	neg	pos	pos f	na	na	pos	neg	pos	pos	na	neg	neg	neg	na	pos	WT
12	PTCL, NOS	small	pos	pos	pos	na	pos	neg	pos	pos f	na	neg	neg	na	pos	na	na	na	na	rare	high	pos	na
13	PTCL, NOS γδ	small-medium	neg	pos	neg	pos f	pos	neg	pos	pos	pos	na	neg	pos	pos	pos	na	neg	na	neg	mod	pos	WT
14	PTCL, NOS γδ	small-medium	neg	pos	neg	na	pos	neg	pos	neg	na	na	neg	pos	na	na	na	na	na	na	mod	pos	TET2, c.4034A>C, p.Tyr1345Ser
15	PTCL, NOS TCR silent	medium	neg	neg	neg	pos	pos	neg	pos	neg	pos	neg	neg	neg	pos	pos	na	neg	na	neg	high	pos	GNB1,c.232A>G, p.Lys78Glu; STAT3, c.1981G>C, p.Asp661His
16	ALCL, ALK pos	medium-large; “Hallmark” cells	pos	pos	pos*	neg	neg	neg	neg	neg	neg	neg	US	na	pos	pos	pos	pos	pos c	neg	high	pos	WT
17	ALCL, ALK neg	large, “hallmark” cells	neg	neg	neg	pos	pos	neg	pos w	pos	pos f	not interp	pos	neg	pos f	pos	na	pos	neg	na	mod	no amp	na
18	ALCL, ALK neg	large, “hallmark” cells	pos	neg	neg	na	pos w	na	na	neg	na	neg	na	na	neg	na	na	pos	neg	neg	high	pos	na

reviations: pos- positive; neg- negative; f - focal, w - weak, mix – mixed, both CD4 and CD8 positive cells present, na- not available; not interp - not interpretable, βF1- T-cell receptor beta F1; TCRγ- T-cell receptor gamma; GrB- Granzyme B; mod- moderate; TRG – T-receptor gene rearrangement; no amp- no amplification products; rest - restricted; susp - suspicious; EBV- Epstein-Barr virus; LMP1- EBV latent membrane protein, US – unsatisfactory.