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Central Nervous System Involvement of Natural Killer and T Cell Neoplasms

Ashley E. Aaroe[1] · Kathryn S. Nevel[2]

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Abstract

Purpose of Review Peripheral natural killer (NK) and T cell neoplasms comprise approximately 10–15% of non-Hodgkin lymphomas. There are 27 different subtypes of peripheral NK and T cell neoplasms, each of which is relatively uncommon. Treatment has been largely extrapolated from case series, retrospective reports, and paradigms developed for the aggressive B cell lymphomas. This review explores the current knowledge of the characteristics, outcome, and treatment of CNS T cell and NK neoplasms.

Recent Findings Primary and secondary CNS NK and T cell malignancies confer significant morbidity and poor prognosis. Despite clinical heterogeneity between the 27 subtypes, high-dose methotrexate–based regimens seem most effective overall. The role of prophylaxis against secondary CNS involvement remains controversial. Autologous stem cell transplant and immunotherapy are potential for promising future therapies.

Summary Current understanding of incidence, outcome, and optimal treatment strategies for CNS T cell and NK neoplasms is limited, in large part due to their diversity and rarity. Prognosis is poor, except in a few reports of long-term survival in patients most often treated with combination therapy including high-dose methotrexate. A future prospective study on treatment and outcome in CNS T cell and NK neoplasms is needed to better define these diseases.

Keywords T cell lymphoma · Brain metastasis · Central nervous system diseases · Leptomeningeal carcinomatosis · T cell leukemia · CNS

Introduction

In the World Health Organization (WHO) 2016 classification, there are 27 different subtypes of "mature T cell and natural killer (NK) cell neoplasms" [1] (Table 1). Unlike B cell neoplasms, these are organized by morphological, clinical, and immunophenotypical features, as many lack defining genetic alterations. The group is diverse and, as the category name describes, encompasses neoplasms of both T cell and NK cell origin.

These malignancies may either involve only the central nervous system (CNS) at diagnosis, as is the case in primary CNS T cell or NK cell lymphoma, or travel to the CNS secondarily in the form of associated metastatic disease or later relapse. Neurological symptoms do not vary by WHO classification of the underlying neoplasm, but rather arise from the location and compartment of the CNS affected. Manifestations range from subtle behavioral changes to gross neurologic deficits such as focal numbness, weakness or paresthesias, or cranial neuropathies (Table 2). Vision changes may come from direct ocular involvement, elevated intracranial pressure (ICP) and subsequent papilledema, or from mass lesions affecting various parts of the visual pathways. Altered levels of consciousness can be caused by severe elevations in ICP from either leptomeningeal disease or large focal parenchymal lesions, or by seizures.

Diagnosis of CNS involvement of NK and T cell neoplasms is made through clinical presentation and characteristic neuroimaging, supported by either brain biopsy or cerebrospinal fluid

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✉ Kathryn S. Nevel
knevel@iupui.edu

Ashley E. Aaroe
aea9009@nyp.org

[1] Department of Neurology, NewYork-Presbyterian Hospital, Weill Cornell Medicine, 528 East 68th Street, New York, NY 10065, USA

[2] Department of Neurology, Indiana University Health, Indiana University School of Medicine, 355 W. 16th St., Ste 3200, Indianapolis, IN 46202, USA

Table 1 Mature and NK neoplasms by WHO 2016 classification. Italic entities are discussed in this article

T cell large granular lymphocytic leukemia	*T cell prolymphocytic leukemia*
Aggressive NK cell leukemia	Systemic EBV+ T cell lymphoma of childhood
Hydroa vacciniforme-like lymphoproliferative disorder	*Adult T cell leukemia/lymphoma*
Extranodal NK−/T cell lymphoma, nasal type	Enteropathy-associated T cell lymphoma
Monomorphic epitheliotropic intestinal T cell lymphoma	*Hepatosplenic T cell lymphoma*
Subcutaneous panniculitis-like T cell lymphoma	*Mycosis fungoides*
Sezary syndrome	Primary cutaneous CD30+ T cell lymphoproliferative disorders
Primary cutaneous gamma-delta T cell lymphoma	*Peripheral T cell lymphoma, NOS*
Angioimmunoblastic T cell lymphoma	*Anaplastic large cell lymphoma, ALK+*
Anaplastic large cell lymphoma, ALK−	Indolent T cell lymphoproliferative disorder of the GI tract
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma	Primary cutaneous acral CD8+ T cell lymphoma
Primary cutaneous CD4+ small/medium T cell lymphoproliferative disorder	Follicular T cell lymphoma
Nodal peripheral T cell lymphoma with TFH + phenotype	Breast implant-associated anaplastic large cell lymphoma
Chronic lymphoproliferative disorder of NK cells	

(CSF) findings such as elevated protein, pathologic cells on cytologic analysis, or clonal populations identified via flow cytometry. In clinical practice, as in many of the case reports described later in this review, obtaining unequivocal pathological proof of CNS disease may not be feasible in all patients.

Here, we will review the presentation, evaluation, and management of both primary CNS lymphoma of T cell lineage and secondary CNS involvement of NK and T cell neoplasms. As no prospective studies exist on the treatment of CNS NK or T cell lymphoma, we will review retrospective reports on treatments of these diseases, as well as treatment and prophylaxis strategies in aggressive B cell malignancies, and their potential effectiveness when applied to NK/T cell populations.

Primary CNS Lymphoma of T Cell and NK-Cell Lineage

Secondary invasion of the CNS in these neoplasms is uncommon, but rarer still is primary CNS NK or T cell lymphoma. Primary CNS lymphoma (PCNSL) is defined as lymphoma involvement limited to the brain, spinal cord, leptomeninges, or eyes with no evidence of systemic disease. It represents 4–6% of all non-Hodgkin lymphoma, and 4% of newly diagnosed brain tumors [2]. Most cases are B cell in origin, specifically diffuse large B cell. Data suggests that approximately 2% of cases of PCNSL are of T cell derivation. One group noted T cell lineage in 8 out of 370 patients with PCNSL (2%) in 2003 [3], and a recent report using Surveillance, Epidemiology, and End Result (SEER) data found 64 of 4375 patients (1.5%) with stage IE PCNSL had disease of T cell origin [4].

A case series of 45 patients was published by the International Primary CNS Lymphoma Collaborative Group in 2005, summarizing clinical characteristics of primary CNS T cell lymphoma [5•]. In this series, the median age was 60 years (range 3–84) and 78% of cases occurred in males. The median progression-free survival was 22 months, and the overall disease-specific survival was 25 months. Multivariate analysis showed that both a better Eastern Cooperative Oncology Group (ECOG) performance status (< 2) and treatment with

Table 2 Signs and symptoms of CNS involvement

Brain parenchyma	Spinal cord	Leptomeningeal carcinomatosis	Symptom
x	x	x	Numbness, paresthesias
x		x	Diplopia, dysphagia, blurred vision, facial weakness
x		x	Cognitive dysfunction, personality change
x		x	Headache
	x	x	Bowel/bladder dysfunction

methotrexate-based regimens were associated with improved disease-specific survival (DSS). The hazard ratio for improved DSS in treatment with methotrexate was 0.4 (95% CI 0.2 to 0.8). However, details of morphologic, immunophenotypic, and treatment characteristics were limited.

Seeking to elucidate these characteristics, a group from the National Institutes of Health examined 18 patients with primary CNS T cell lymphomas in 2015 [6]. Of these, the most common histologic subtype was primary T cell lymphoma, not otherwise specified (NOS, 15 cases), followed by ALK-negative anaplastic lymphoma (2 cases) and ALK-positive anaplastic lymphoma (1 case). The median age at diagnosis was 58.5 years, similar to the previous case series, and there was also a male predominance (M:F ratio of 11:7). Most patients [7] had discrete supratentorial parenchymal lesions, with 3 demonstrating cerebellar involvement on neuroimaging. Other imaging findings included diffuse leptomeningeal enhancement [1], multiple meningeal lesions [1], and periventricular abnormalities [1]. Most cases had a cytotoxic phenotype as determined by staining with perforin, TIA1, and granzyme B. Next-generation sequencing revealed that 4 of 11 cases of primary T cell lymphoma NOS studied harbored somatic mutations, but that no mutation was common to multiple cases. CD3 was positive in all cases but one, and 10 of 17 cases were CD8 positive, and 5 of 17 cases were CD4 positive. Details regarding treatments strategies and their outcomes in this disease are sparse both in this study and in the literature at large.

A 2017 series of Japanese patients described 4 cases of primary CNS NK/T cell lymphoma [8]. Three patients were male, and one was female. Ages ranged from 21 to 77 years. Histology revealed angiocentric tumor growth and proliferation of blood vessels in two cases. The immunophenotype was consistent with typical markers of NK cell tumors. All four patients were treated with radiation, and methotrexate was given to two. In addition, ten cases from other published reports were reviewed by these authors. Of the immunocompetent patients in this group (9 of 10 patients), there was a slight male predominance (five males) and an age range from 25 to 68 years. Treatment information was only available for 7 of the 9 immunocompetent patients, who received various combinations of radiotherapy (five patients), chemotherapy (five patients, three of whom also received radiation), and surgery (two patients, both of whom were treated with methotrexate). The authors suggested that perhaps the SMILE regimen (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) used for extranasal NK/T cell lymphoma might have utility in primary CNS disease.

Overview of Secondary CNS Involvement in T Cell and NK-Cell Neoplasms

Secondary CNS involvement arises from either metastatic disease to the CNS discovered at diagnosis of systemic lymphoma or during relapse. The best-characterized entity among patients with CNS T cell lymphoma is secondary CNS involvement in relapsed peripheral T cell lymphoma (PTCL). The largest study to date analyzing the risk of CNS relapse in PTCL was done with the Swedish Lymphoma Registry, which found that 28 of 625 patients (4.5%) developed CNS relapse, which occurred at a median of 4.3 months (range 1–30) from diagnosis [9•]. Patients with known CNS involvement at diagnosis were excluded, although CSF sampling and neuroimaging were not undertaken for all patients during standard workup. Independent risk factors for CNS relapse included skin and gastrointestinal involvement, as well as the involvement of greater than one extranodal site. Fifty-one patients (8%) received intrathecal injections as part of the primary treatment strategy, which did not show an association with reduced risk of CNS relapse (HR 1.3 ($p = 0.7$)).

Yi and colleagues reported a higher incidence of CNS involvement (8.8%) in a 2010 study of 228 patients with PTCL, which notably included patients with CNS involvement at the time of diagnosis but excluded those with extranodal natural killer/T cell lymphoma (ENKTCL) and primary cutaneous T cell lymphomas [10]. The most common histologic subtype (57% of cases) represented in this study was PTCL-NOS, followed by 22.8% with angioimmunoblastic T cell lymphoma (AITL), 14% with anaplastic large cell lymphoma (ALCL), 3.5% with enteropathy-associated T cell lymphoma, and 2.6% with hepatosplenic T cell lymphoma. In multivariate analysis, elevated serum lactate dehydrogenase (HR 6.7, 95% CI 1.5–29.1, $p = 0.011$) and involvement of paranasal sinuses (HR 3.8, 95% CI 1.4–10.0, $p = 0.008$) were independently associated with CNS involvement. Five out of 21 patients with both risk factors (23.8%) developed CNS disease, whereas 14 out of 132 with one risk factor (10.6%) and 1 out of 75 with no risk factors (1.3%) did. Median overall survival from time of lymphoma diagnosis of patients with CNS involvement was 7.60 months versus 27.43 months in those without.

In an update of a retrospective study conducted at MD Anderson, the authors included 600 patients with systemic T cell lymphoma, of which 13 experienced relapse in the CNS. Median time to relapse was 6.4 months, and extranodal involvement > 1 site was the only significant factor associated with risk of CNS relapse (HR 4.9, 95% CI 1.6–15.0, $p = 0.005$) [11•]. In this study, all patients with CNS relapse (with the exception of one lost to follow-up) eventually died. The median OS duration from diagnosis of CNS relapse was 1.5 months (95% CI 0.5–7.4 months).

In 2016, Gurion and colleagues published a retrospective analysis from Memorial Sloan Kettering Cancer Center finding 6.5% of patients (15 of 231) with PTCL to have CNS involvement [12]. This includes four patients with CNS involvement at the time of diagnosis. Excluding these, as well as patients with adult T cell lymphoma/leukemia (ATLL), the incidence of CNS relapse was < 5%. The most common

histologic subtype with CNS involvement was also PTCL-NOS (6 patients), followed by ATLL with 4 patients, ENKTCL with 2 cases, AITL with 1 case, ALK-negative ALCL with 1 case, and hepatosplenic T cell lymphoma with 1 case. Extranodal involvement at greater than one site, high international prognostic index, and the histologic subtype of ATLL were all significantly associated with higher risk of CNS disease. Median overall survival from the time of CNS diagnosis was 2.63 months.

Combining the findings of these four large studies on secondary CNS involvement of PTCL, the commonly identified risk factor for CNS relapse was more than one extranodal site of disease at diagnosis. Most patients developed CNS relapse within about 6 months of diagnosis of primary disease, also indicating that when CNS relapse occurs, it usually occurs early in the disease course. While there was some variability in median overall survival between the studies, CNS relapse overall was associated with poor prognosis.

Reports of Secondary CNS Involvement by Subtype

Mycosis Fungoides

Cutaneous T cell Lymphoma (CTCL) is characterized by migration of T cells to the epidermis, causing an erythematous pruritic rash which can mimic eczema or psoriasis. The most common subtype is mycosis fungoides (MF) and its variants, with others including Sezary syndrome and primary cutaneous CD30+ T cell lymphoproliferative disorders [13]. In later stages of disease T cells become invasive and can migrate to lymph nodes and viscera, commonly the liver, spleen, and lungs. CNS manifestations of CTCL are rare, with an early retrospective analysis from 1994 noting a 4% overall incidence of direct neurologic complications [14].

Mycosis fungoides represents the most common subtype of CTCL. A 2006 paper estimated the incidence of developing CNS involvement in MF as 1.3%, by identifying a subgroup of 9 cases of CNS metastases from a cohort of 680 patients newly diagnosed with MF between 1963 and 2004 [15]. In this study, the estimated actuarial risk at 10 years was also 1.3%, as most cases developed CNS involvement within 3 years of diagnosis. Of the 9 reported cases, 3 were confirmed pathologically at autopsy. Other cases were determined to have CNS involvement through characteristic imaging findings of metastatic disease on computed tomography or magnetic resonance imaging of the brain, accompanied by appropriate clinical symptoms.

A recent review identified 77 patients with CNS metastases of MF from 40 case reports and 8 case series [7]. Of these patients, the median interval from MF diagnosis to the discovery of CNS disease was 36 months, and the time from known CNS involvement to death was 9 weeks. CNS involvement was determined radiographically, via cerebrospinal fluid (CSF) sampling, or at autopsy. Of 42 cases with CSF available, 34 were found to have either Sezary cells or lymphocytic pleocytosis. Other common CSF findings included elevated protein and elevated opening pressure. Fifty-three percent had metastatic disease to other extracutaneous sites at the time of identification of CNS metastases, and gait instability, cognitive deficits, and visual changes were the most common clinical manifestations. There have been case reports of brain metastasis following orbital involvement in MF [16, 17] but the exact concordance of ocular MF and CNS MF is not known.

A comparison of attempted treatments across case reports from Yang et al. did not yield a clearly superior therapy for CNS disease, though methotrexate, steroids, and radiation have all been used [18]. Experts have recommended manifold strategies for mitigating the risk of neurologic metastases in patients with MF. Approaches range from serial screening neuroimaging with orbital cuts [19], to consideration of prophylactic whole-brain radiation in high-risk patients (a group which this data suggests includes older males and those with extensive skin involvement) [15].

Gamma/Delta T Cell Lymphoma

Peripheral T cell lymphoma expressing gamma/delta T cell receptors was originally found in the liver and spleen, and as a result was referred to as "hepatosplenic" when first described [20]. Later cases of gamma/delta T cell lymphoma were described originating from other extranodal sites (most notably intestine and skin) [21]. Gamma/delta T cells represent only 1–5% of circulating lymphocytes, and only 2–4% of T cell lymphomas express gamma/delta receptors [22]. CNS involvement is rare, with few case reports in the literature.

One case report hypothesized that the variable expression of CD56 in T cell lymphoma of this type may play a role in CNS metastases; in their patient, flow cytology showed expression of this marker, which also plays a role in neural cell adhesion [23]. The primary omental lesion in this case was treated with multiple courses of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), and EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin), before the patient developed bilateral paraparesis and was found to have intracranial lesions. These showed a radiographic response to high-dose methotrexate, but ultimately the patient passed away due to the progression of the abdominal disease.

Cases have been described of CNS involvement from gamma/delta T cell lymphoma originating from ocular [24] and skin [25] primaries. There is also a report of primary CNS T cell lymphoma with gamma/delta receptor expression manifesting as an isolated cerebellar lesion, which was

resected. The patient was subsequently treated with high-dose methotrexate and cytarabine followed by autologous stem cell transplant and had no evidence of recurrence at 6-month follow-up at the time of the report [26].

Subcutaneous Panniculitis-Like T Cell Lymphoma

Subcutaneous panniculitis-like T cell lymphoma (SPTCL) is a cutaneous T cell lymphoma which is notable for indolent progression and typically favorable prognosis [27]. A case report exists of possible CNS relapse of SPTCL presenting as headache, blurred vision, and altered mental status which rapidly progressed to coma [28]. Contrast-enhanced magnetic resonance imaging (MRI) of the brain was unrevealing, but cerebrospinal fluid analysis showed elevated protein and lactate dehydrogenase. Flow cytometry was not performed. The patient was empirically treated with fotemustine, teniposide, and dexamethasone as well as intrathecal methotrexate, cytosine arabinoside, and dexamethasone, with a reported resolution of all neurological symptoms, sustained at 91 months at the time of publication.

Anaplastic Large Cell Lymphoma

The neoplastic cells in anaplastic large cell lymphoma (ALCL) are pleomorphic lymphoid blasts expressing CD30, which typically cause an aggressive disease associated with high fevers and frequent extranodal involvement. Most cases contain a chromosomal translocation involving the nucleophosmin gene on chromosome 5 and the anaplastic lymphoma kinase (ALK) gene on chromosome 2. This result in a fusion protein, ALK-1, and such lymphoma is referred to as primary systemic ALK+ ALCL. There is also primary systemic ALK− ALCL, and a third subtype referred to as primary cutaneous ALCL. A 2007 paper surmised that the 13 previously reported cases of CNS ALCL at that time (both ALK+ and ALK−) presented particular diagnostic challenges given a "reactive milieu" on histology which mimicked infectious, immunologic, or rheumatologic etiologies [29]. The apparent low incidence of CNS involvement of this neoplasm may be partially influenced by such diagnostic challenges. Leptomeningeal and dural involvement appears to be a common feature. While mortality was high overall, with 7 of 13 cases passing away after rapid clinical progression, some patients did well with surgery and radiation. In one case, a patient had no evidence of disease at 25 months following gross total resection and radiation [30], and another had no evidence of disease at 24 months following the same therapy [31]. The prognosis for ALK− ALCL in the CNS appears to be worse than that for ALK+ ALCL [32].

T Cell Prolymphocytic Leukemia

T cell prolymphocytic leukemia (TPLL) is an aggressive cancer which presents with hepatosplenomegaly, lymphadenopathy, leukocytosis, anemia, and thrombocytopenia. The median survival is usually less than 1 year. There are two notable case reports of CNS involvement of TPLL. One achieved hematologic remission from peripheral TPLL after fludarabine and cyclophosphamide treatment, followed by the development of confusion and dysarthria. Neuroimaging showed an infiltrative left frontal lobe lesion which was biopsied and found to be involved with leukemia. Treatment with the anti-CD52 monoclonal antibody alemtuzumab was planned, but the patient passed away before this could be initiated [33]. The second case was initially thought to be chronic lymphocytic leukemia (CLL) via clinical criteria by an outside institution [34]. After receiving cyclophosphamide, rituximab, vincristine, and prednisolone, the patient developed left facial weakness and ptosis of the left eye, followed by contralateral ptosis and extraocular movement abnormalities. MRI showed contrast enhancement of multiple cranial nerves, and the diagnosis of CNS TPLL was made via cytologic analysis of CSF. There is no clearly efficacious treatment strategy for this condition.

T Cell Large Granular Lymphocytic Leukemia

Granular lymphocytes are so named because they contain azurophilic granules. Some are NK cells, but a minority is cytotoxic T lymphocytes. Patients with T cell large granular lymphocyte leukemia (TLGLL) can have concomitant autoimmune disorders and may test positive for serologic abnormalities such as rheumatoid factor, antinuclear antibody, or monoclonal gammopathies [35]. Ocular involvement was associated with headache and gait ataxia in one patient found to have scattered punctate foci of enhancement on MRI, and TLGLL was confirmed on CSF cytology [36]. This patient was treated with intrathecal methotrexate followed by treatment with alemtuzumab. Significant neurologic improvement, with a clearance of cells from the CSF, was achieved but nevertheless, the patient passed away from pneumonia.

Adult T Cell Lymphoma/Leukemia (HTLV1+)

Adult T cell lymphoma/leukemia (ATLL) is associated with infection by human T-lymphotrophic virus type 1 (HTLV-1), and incidence of this neoplasm is higher in areas such as southern Japan, Africa, the Caribbean, and South America, where the virus is prevalent [37]. Approximately 4–5% of patients with chronic HTLV infection develop ATLL, and it may manifest as one of four different types—acute, lymphoma, smoldering, and chronic—based on a number of abnormal circulating lymphocytes, LDH, organ involvement, and clinical course.

The reported incidence of CNS involvement ranges from 2.5 [38] to 21% [39]. Radiographically, disease usually consists enhancement, and microscopic evidence of meningeal and perivascular invasion [40]. Neurologic complications may be under-recognized; 14% of ATLL cases in one report had evidence of CNS involvement on autopsy without clinical symptoms [41]. A review of 24 cases with detailed clinical and molecular features documented found that 62% of cases of ATLL with CNS involvement were associated with leukocytosis, 59% with hypercalcemia and 80% with elevated LDH levels [42]. The most common types of ATLL with CNS involvement were determined to be lymphoma and acute in this group. Some patients were successfully treated with high-dose methotrexate, carmustine, cytarabine, and methylprednisolone followed by whole-brain radiation therapy; treatment with interferon-alpha and the antiviral zidovudine may also be helpful [43].

Extranodal NK/T Cell Lymphoma

Extranodal natural killer T cell lymphoma (ENKTCL) is typically CD2+, surface CD3−, cytoplasmic CD3+, and CD56+, and almost invariably is Epstein-Barr virus positive. It is more common in Asian countries, representing 22% of cases than in the USA where it typically affects patients of Asian/Pacific, American Indian/Alaskan Native, and Hispanic White descent [44, 45]. CNS involvement is rare, occurring in an estimated 0–11% of patients with ENKTCL, with the primary site of involvement being the upper aerodigestive tract [9•, 12, 46]. Risk factors for CNS disease include Ann Arbor Stage III/IV disease, lymph node involvement and advanced NK prognostic index (a classification system based on disease stage, performance status, the presence of extranodal involvement, and non-nasal disease) [47•]. Pembrolizumab has been recently utilized in treating multiply refractory, relapsed, or advanced systemic ENKTCL, and there is hope it may be effective in CNS involvement as well [48].

Treatment and Prophylaxis

At this time, there is no standard treatment for CNS involvement of T cell or NK neoplasms, but general strategies mimic those used for CNS involvement in other aggressive lymphomas. Systemic chemotherapeutic agents with CNS penetration, or therapies instilled directly into the CSF space, are used frequently alone or in combination with whole-brain radiation.

Systemic treatment regimens most commonly include high-dose methotrexate. A retrospective analysis suggested that high-dose methotrexate–based regimens were associated with longer survival in T cell primary CNS lymphoma compared to patients who received other non-methotrexate-based chemotherapy regimens [5•]. In this report, methotrexate was dosed between 2 and 8 g/m^2 per month (with median 3. 75 g/m^2/month), and used in combination with other chemotherapy in 18 out of 29 patients. A multivariate analysis found that the hazard ratio for improved disease-specific survival was 0.4 (95% CI 0.2 to 0.8) in patients who received methotrexate compared with those who did not.

Methotrexate may also be administered intrathecally, as can cytarabine, in the case of leptomeningeal metastasis. Both have been used in the literature, and while there is no specific data to guide the use of intrathecal (IT) chemotherapy in NK and T cell neoplasms, general principles apply. For example, IT instillation of treatment (and therefore introducing additional volume into the CSF space) is contraindicated in patients with elevated intracranial pressure. IT chemotherapy may be administered either during lumbar puncture or via Ommaya (a device comprised of a catheter inserted into one of the lateral ventricles connected to a subcutaneous reservoir). With either procedure, risks of hemorrhage and infection are considerations [49].

Treatment of secondary CNS involvement may be more challenging, due to the effects of prior treatment and medical comorbidities. However, similar strategies as are used in primary CNS disease, mainly high-dose methotrexate–based regimens and intrathecal chemotherapy in the case of leptomeningeal disease [50]. Also, regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), ICE (ifosfamide, carboplatin, etoposide), and EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) have all been used in secondary CNS peripheral T cell lymphomas but there is not enough data to confirm definitive efficacy, and these regimens in general have less CNS penetration than high-dose methotrexate [11•].

While no prospective treatment trials have been conducted for patients with CNS T cell or NK lymphoma, one may extrapolate results from the CNS B cell lymphoma population. One group evaluated a high-dose methotrexate–based regimen followed by auto-SCT in a phase II trial of patients with secondary CNS involvement of aggressive B cell lymphomas (either at diagnosis or relapse) [51]. High doses of methotrexate (3 .5g/m^2) and cytarabine (2 g/m^2) with intrathecal liposomal cytarabine 50 mg were administered followed by rituximab plus high-dose sequential chemotherapy (R-HDS), and subsequent autologous stem cell transplant (ASCT). Patients with clinical remission were then followed, whereas those with residual parenchymal disease in the brain underwent irradiation. Five-year event-free survival was 40%, and there was no significant difference in survival outcome between those with CNS disease at presentation, and those with secondary CNS involvement thereafter. A separate group treated newly diagnosed PCNSL patients with 5 to 7 cycles of R-MVP—rituximab (500 mg/m^2), methotrexate (3.5 g/m^2), and procarbazine and vincristine (1.4 mg/m^2) [52]. Those who responded underwent subsequent consolidation with

thiotepa, cyclophosphamide, and busulfan, followed by ASCT. One year overall survival in the 26 of 33 patients transplanted was 88% (95% CI 70–95). While rituximab does not have utility in NK and T cell neoplasms, a similar approach with high-dose methotrexate–based therapy followed by consolidation with auto-SCT may be considered in selected patients.

In addition, in recent years, there have been promising responses reported to immunotherapy among patients with primary CNS B cell lymphoma [53]. Combined with early evidence that immunotherapy may be effective in the systemic ENKTCL population, there is hope that immunotherapy may also provide better outcomes for patients with CNS ENKTCL [54]. While chimeric antigen receptor T cells (CART) are now used in systemic B cell lymphoma, there is insufficient evidence at present to support utility in T cell lymphomas [55]. The use of CART in NK and T cell neoplasms is limited due to the challenges of identifying a target expressed on lymphomatous cells that are not also expressed on the CAR cells.

The incidence of CNS relapse in PTCL (with ATLL excluded) is generally low, less than 5% [9•, 12]. As such, ATLL, which is known to carry a high risk of CNS involvement, is the only entity in which intrathecal chemotherapeutic prophylaxis is currently recommended by the National Comprehensive Cancer Network (NCCN) guidelines [56]. In an investigation of 250 patients with PTCL at MD Anderson Cancer Center from 1996 to 2009, 14 patients received CNS prophylaxis at their treating team's discretion, based on the presence of bone marrow involvement, paraspinal masses, involvement of more than two extranodal sites, histology, or multiple factors [57•], and of these patients, only one experienced CNS relapse. Conversely, when the NCCN criteria for CNS prophylaxis for diffuse large B cell lymphoma (DLBCL) were applied to the PTCL population (paranasal sinus involvement, testicular involvement, epidural involvement, bone marrow involvement, involvement of more than two extranodal sites, or HIV-associated lymphoma), 99 patients had indications for prophylaxis, where only 6 experienced CNS recurrence. The authors surmised that CNS relapse was a rare, and often terminal event in patients with refractory disease, and that the guidelines for CNS prophylaxis in DLBCL did not generalize to PTCL.

Discussion

The challenges to clarify the behavior of T cell and/or NK neoplasms in the CNS, and to determine treatment strategies, are numerous. First, the low incidence of these conditions makes it difficult to gather sufficient data to power large-scale studies. Primary CNS T cell lymphoma is exceedingly rare. While secondary CNS involvement of T cell and/or NK lymphoma is slightly less rare, multiple subtypes of PTCL and NK lymphomas are often pooled in order to create large enough numbers to make any conclusions on incidence and management.

It is unclear if all subtypes should be considered equally in their management, treatment response, and prognosis. For example, it is unclear how generalizable recommendations for CNS involvement of MF are to CNS involvement of ENKTCL. If a randomized controlled trial was conducted studying treatments of secondary CNS T cell lymphoma, the results could hinge heavily on the proportions of each subtype included. Further, major advances in the understanding of these disorders continue at a blistering pace, which will undoubtedly necessitate more updates to the WHO classification. Such changes may ultimately render prior data, based on old classifications, no longer accurate, or complete enough to draw conclusions from. Successful future trials will therefore require careful identification and definition of the patient populations studied [33].

As another consequence of their rarity, the literature for most subtypes of T cell and NK neoplasms is at present largely comprised of case reports and series. In several of these reports, the diagnosis of CNS involvement is presumptive rather than definitive. While most case reports likely represent true CNS involvement of the primary malignancy, without tissue sampling at autopsy or via brain biopsy or CSF sampling, at least for some patients, there is a real possibility of "mimics" confounding the picture. Highlighting this possibility is a report of a patient with mycosis fungoides (MF) initially thought to have central nervous system metastasis of his disease, who was ultimately instead found to have multifocal epithelioid glioblastoma [58]. In Gurion study of PTCL, two patients with CNS lesions that were biopsied were subsequently diagnosed with concomitant primary diffuse large B cell lymphoma and glioblastoma [12]. It will be essential for future studies to carefully exclude mimics such as concomitant stroke, infection, alternate central nervous system malignancy, or neuroinflammatory condition.

Conclusion

In conclusion, primary and secondary CNS involvement of T cell and NK neoplasms is exceedingly rare. The true incidence of NK and T cell CNS involvement is further confounded by mimics. The outcome is usually poor, with most patients surviving months after diagnosis in the case of secondary CNS involvement to a few years in the case of primary CNS involvement. The role of CNS prophylaxis is unclear. Treatment strategies most commonly employed such as high-dose methotrexate, intrathecal chemotherapy, and radiation are based on small retrospective studies and case reports among patients with CNS T cell or NK malignancies, as well as prospective studies in the CNS B cell population. ASCT may be beneficial

as consolidative therapy, and immunotherapy holds exciting potential in the CNS ENKTCL population. A future prospective study is needed to determine best treatment practices for patients with CNS T cell and NK neoplasms.

Compliance with Ethical Standards

Conflict of Interest The authors declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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