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Diagnosis, prevention and treatment of central nervous system involvement in peripheral t-cell lymphomas

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ABSTRACT

Non-Hodgkin lymphomas with T-cell immunophenotype encompass a heterogeneous group of infrequent neoplasms that follow variable clinical courses but prevalently include aggressive behavior and high mortality rates. The involvement of the central nervous system (CNS) is an uncommon event in T-cell lymphomas, with wide variability among the different disease entities. CNS can be affected either at initial diagnosis or at recurrence, and both forms are considered "secondary CNS T-cell lymphoma". Given the low incidence of secondary CNS T-cell lymphoma, related literature is sparse, contradictory, and primarily constituted by small case series and single case reports. However, reported studies uniformly suggest high mortality rates related to this event. Therefore, to improve our ability to identify high-risk patients and offer them successful CNS prophylaxis or timely and effective treatment once the event has occurred may prevent CNS-related T-cell lymphomas deaths. For example, some entities like aggressive adult T-cell leukemia/lymphoma, extranodal natural killer/T-cell lymphoma, and other peripheral T-cell lymphomas with involvement of two or more extranodal organs are prone to CNS dissemination and should be considered for personalized CNS prophylaxis. The level of evidence suggesting an increased risk of CNS recurrence for other T-cell lymphomas and for other risk factors is lower. Published case series show that, following the example of aggressive B-cell lymphomas, patients with T-cell lymphomas and putative increased CNS risk receive different forms of prophylaxis, mostly methotrexate and cytarabine delivered by intrathecal and/or intravenous routes, with varied success. To date, achievements in the treatment of CNS involvement in patients with aggressive B-cell lymphoma were not replicated in secondary CNS T-cell lymphomas, and identification of effective therapies remains an urgent research target. This review is focused on clinical findings, diagnosis, treatment, and prognosis of patients with T-cell lymphoma experiencing CNS dissemination either at presentation or relapse. It aims to provide logical and, oftentimes, evidence-based answers to the most common questions on the most probable risk factors to CNS involvement in patients with T-cell lymphoma, the indications and strategies to prevent this life-threating event, and the management of patients with CNS disease.

1. Introduction

Non-Hodgkin lymphomas with T-cell immunophenotype are a heterogeneous group of neoplasms with variable clinical courses; however, they often show aggressive behavior and are associated with high mortality rates. The involvement of the central nervous system (CNS) is an uncommon event in T-cell lymphomas, with a wide incidence rate among the different disease entities. Tumor cells can infiltrate the brain

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parenchyma, leptomeninges, spinal cord, cranial nerves, and eyes at different time points in the course of these malignancies (Lim et al., 2011). Given the low incidence of this event, related literature is sparse and contradictory, being mostly constituted by small case series and single case reports. Moreover, results and conclusions of reported studies vary significantly among different geographical areas, mostly due to different incidence of some T-cell lymphoma entities among countries. Nevertheless, reported studies uniformly show poor survival rates after CNS dissemination in patients with T-cell lymphomas. This discouraging prognosis may be addressed by implementing a few main strategies: 1) establish predictors of an increased risk of CNS involvement with high diagnostic sensitivity; 2) offer patients with a high risk of CNS recurrence an effective CNS prophylaxis; and 3) establish effective options for treating patients with T-cell lymphoma and active CNS disease. Validated recommendations for these strategies are lacking, mostly because of the paucity of high-level studies; consequently, there is widespread use of palliative care for these patients, and high mortality rates are common. This review is focused on the biology, risk factors, prevention, clinical features, and treatment of secondary CNS involvement in peripheral T-cell lymphomas, as an effort to summarize available evidence and provide recommendations for the diagnosis and treatment of these challenging conditions.

2. Nomenclature, definitions and search strategy

Two main variants of CNS lymphoma should be distinguished: the primary form that includes lymphomas exclusively involving the CNS at presentation, and the secondary CNS lymphomas. Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma entity primarily arising in the CNS. The last World Health Organization (WHO) classification has recognized a new disease entity termed “primary diffuse large B-cell lymphoma of the CNS (PCNSL)” (Swerdlow et al., 2016), which exhibits some peculiar biological, molecular, and clinical characteristics and involves the CNS as an exclusive site of disease both at presentation and relapse, with rare cases of relapsing disease outside the CNS. Other lymphoma subtypes arising primarily in the CNS are the marginal zone lymphoma and some uncommon T-cell lymphoma entities (Swerdlow et al., 2016; Rubenstein et al., 2008; Chihara et al., 2018; Chihara and Oki, 2018; Levin et al., 2008). Nearly 2% of all lymphomas primarily arising in the CNS have T-cell immunophenotype (Shenkier et al., 2005), with some small case series suggesting a higher incidence of this condition in Eastern countries (Choi et al., 2019). These primary CNS lymphomas should be distinguished from the “secondary CNS lymphomas,” forms diagnosed in patients with systemic lymphoma where CNS involvement can occur at presentation or relapse as an isolated site of recurrence or associated with systemic disease (Chihara et al., 2018; Levin et al., 2008; Gurion et al., 2016). Lymphoblastic lymphoma, Burkitt lymphoma, DLBCL, peripheral T-cell lymphomas, and mantle cell lymphoma are the most common lymphoma entities with CNS tropism.

Data for this review was derived from articles found on PubMed, MEDLINE, Current Contents, and from references from relevant articles, which were searched for using the keywords "CNS", “central nervous system”, "meningeal", and "brain" combined with “dissemination”, “infiltration”, “involvement”, and “recurrence”, among others. Names and abbreviations of the most relevant T-cell lymphoma entities, terms like “peripheral T-cell”, “anaplastic T-cell”, “angioimmunoblastic”, “extranodal NK/T-cell”, “adult T-cell leukemia/lymphoma”, “cutaneous T-cell” in combination with “lymphoma”, were used to identify papers related to each entity. Articles published in English between 1990 and 2020 were reviewed. As some T-cell lymphomas show relevant geographical variations (a.e., NK/T lymphomas are more common in Eastern countries), publications in non-English languages with abstracts in English were also considered. Abstract only data from international meetings during the last three years were considered.

“CNS dissemination” indicates both brain intraparenchymal lesions and leptomeningeal infiltration, at diagnosis (“presentation” or “initial diagnosis”) or at failure (“relapse”, “recurrence” or “progressive disease”). The terms “disseminated disease”, “advanced stage”, and “systemic disease” were used to define stage III-IV lymphoma.

3. Epidemiology

Peripheral T-cell lymphomas encompass a heterogeneous group of mature T-cell and natural killer (NK)-cell neoplasms that represents 10–15 % of non-Hodgkin’s lymphomas (Gurion et al., 2016; Zing et al., 2018). Its incidence is variable worldwide, depending on the ethnicity and epidemiology of some viruses related to T-cell lymphomagenesis. In particular, geographical variations in the prevalence of human T-lymphotropic virus type 1 (HTLV-1) and Epstein-Barr virus (EBV) infections result in relevant differences in incidence of related T-cell lymphomas (Zing et al., 2018).

The reported incidence of CNS involvement in T-cell lymphomas is quite variable. CNS involvement is present at the time of initial lymphoma diagnosis in 1–2 % of patients with T-cell lymphomas (Chihara et al., 2018; Ellin et al., 2015), ranging between 2.4 % and 25 % of patients with peripheral T-cell lymphomas (Gurion et al., 2016; Ellin et al., 2015). This wide range is due to variability in the T-cell lymphoma entities considered, the geographical area, as well as by the inclusion or not of patients with CNS disease at initial lymphoma diagnosis (Gurion et al., 2016; Yi et al., 2011). In the largest case series reported in Western countries (Chihara et al., 2018; Ellin et al., 2015), 2–4 % of T-cell lymphomas patients experienced CNS recurrence, with a 1- and 5-year cumulative incidences of 1.5 % and 2.1 %, respectively (Chihara et al., 2018). In a study on 228 Korean patients with peripheral T-cell lymphomas other than extranodal natural killer/T-cell lymphoma (ENKTCL) and cutaneous T-cell lymphomas, 9% of patients experienced CNS recurrence at a median follow-up of 14 months, with a CNS recurrence rate of 15 % among patients with anaplastic large T-cell lymphoma (ALCL) (Yi et al., 2011). In a series of 208 patients with ENKTCL, nasal type, CNS recurrence has been detected in 10 % of cases (Kim et al., 2010).

The peak of incidence of secondary CNS T-cell lymphomas occurs in the sixth decade, with a slight male predominance (Gurion et al., 2016; Kim et al., 2020). Although CNS dissemination can occur at any time of the disease course, this event is more commonly diagnosed within the first two years after the initial lymphoma diagnosis, with a median of 3–6 months (Gurion et al., 2016; Ellin et al., 2015; Yi et al., 2011). One-quarter of CNS relapses occur as second or third recurrence of T-cell lymphomas; in particular, this event is often detected in patients with T-cell lymphoma refractory to first-line treatment who receive salvage therapy with drugs with limited CNS penetration (Ruf et al., 2018). Comprehensively, these figures are different from those reported for DLBCL, where nearly all CNS recurrences are detected at first relapse (Gurion et al., 2016; Ellin et al., 2015).

4. Incidence of CNS dissemination by T-cell lymphoma entity

Some T-cell lymphoma entities, like adult T-cell leukemia-lymphoma (ATLL), peripheral T-cell lymphomas-no other specified (PTCL-NOS), ALK-positive ALCL (ALK + ALCL), and ENKTCL seem to be associated with an increased risk of CNS dissemination (Table 1), an event rarely reported in patients with angioimmunoblastic T-cell lymphoma (Chihara et al., 2018; Gurion et al., 2016; Ellin et al., 2015; Kim et al., 2020; Pro and Perini, 2010). CNS involvement occurs in 10–25% of patients with ATLL (Rubenstein et al., 2008; Gurion et al., 2016; Yi et al., 2011; Kim et al., 2010; Teshima et al., 1990), but it is very rare initial diagnosis (Ma et al., 2014); higher risk of CNS relapse is reported in the forms with disseminated disease, such as lymphomatous and acute forms, especially the former, which represents almost half the ATLL patients (Kitajima et al., 2002; Hsi et al., 2014). However, the rate of CNS dissemination in ATLL patients may be underestimated; this is suggested by a study

Table 1
Risk factors for CNS involvement at presentation or relapse in T-cell lymphomas according to the reviewed literature.

Lymphoma entities	
	Aggressive Adult T-cell Leukemia Lymphoma*
	Extranodal natural killer/T-cell lymphoma with a CNS-PINK = 2#
	Enteropathy-associated T-cell lymphoma
	Monomorphic epitheliotropic intestinal T-cell lymphoma
Risk factors	
	Involvement of >1 extranodal site
	Involvement of gastrointestinal tract or skin
	Involvement of nose or paranasal sinuses
	Advance disease (Ann Arbor stage III or IV)
	International Prognostic Index score ≥3
	Elevated serum lactate dehydrogenase level
Other conditions	
	AIDS/HIV patients, mainly with low CD4 counts, unresponsive to antiretroviral treatment

* This category includes the "lymphoma type of ATL, extranodal primary cutaneous variant" (Cook et al., 2019).

CNS-PINK score of 2 consists of intermediate-high PINK score (B symptoms, stage III or IV, distant lymph-node involvement, and non-nasal type) and involvemnt of two or more extranodal organs (Kim et al., 2020).

showing that 14 % of ATLL patients without neurological symptoms had evidence of CNS involvement on autopsy (Teshima et al., 1990). In addition, CNS relapse seems to be more common in ATLL patients with leukocytosis, hypercalcemia, or elevated serum lactate dehydrogenase (LDH) levels (Hsi et al., 2014). In ENKTCL, nasal type, CNS dissemination was strongly related to the natural killer prognostic index (NKPI includes B symptoms, stage III or IV, elevated serum LDH concentration, and lymph node involvement), with a CNS relapse rate of 1.8 % for patients with NKPI score 1–2 and 10.2 % for patients with NKPI 3–4 (Kim et al., 2010). In a recent retrospective study on two cohorts of 399 and 253 patients with ENKTL treated with non-anthracycline–based chemotherapy (Kim et al., 2020), researchers demonstrated that the combined analysis of PINK score (age >60 years, stage III/IV, distant lymph-node involvement, and non-nasal type) and number of involved extranodal organs were independently associated with the risk of CNS dissemination. In fact, patients with an intermediate-high PINK score and involvement of two or more extranodal sites exhibited a 2-year CNS relapse rate of 23 % versus 4% for the other patients (Kim et al., 2020).

CNS recurrence occurs anecdotally in intestinal T-cell lymphomas. This event has been reported in 7% of patients with enteropathy-associated T-cell lymphoma (Ellin et al., 2015), and in 10 % of patients with monomorphic epitheliotropic intestinal T-cell lymphoma (Yi et al., 2019); however, these rates must be confirmed in other, larger case series. Mycosis fungoides rarely disseminate to the CNS, an event reported in 1.3 % of cases (Stein et al., 2006). CNS recurrence is a late event in mycosis fungoides, with a median interval from initial diagnosis to the detection of CNS disease of 3 years (Yang and Wickless, 2017), which is remarkably later than medians reported for other T-cell lymphomas. CNS involvement is exceptionally rare in gamma-delta T-cell lymphomas (Harada et al., 2004) and T-cell prolymphocytic leukemia (Göçmen et al., 2014). However, CNS relapse rate in these highly aggressive tumors may be underestimated because most of the affected patients could have died before the CNS event could be detected.

5. Other risk factors

Factors associated with a higher risk of CNS dissemination remain to be defined in patients with peripheral T-cell lymphomas. Some risk factors related to disease and patient characteristics have been suggested (Table 1), mostly in case reports and small retrospective cohorts (Rubenstein et al., 2008; Ma et al., 2014; Amano et al., 2011; Marshall et al., 1998). The presence of more than one involved extranodal organ at initial lymphoma diagnosis was found to be an independent risk factor for CNS relapse (Chihara et al., 2018; Gurion et al., 2016). This association was recently reported in a large case series of patients with ENKTCL (Kim et al., 2020). Besides the number of extranodal organs involved (>1 site), the lymphomatous involvement of some specific extranodal organs, such as gastrointestinal tract and skin, is also independently associated with higher risk of CNS relapse, which was three times higher when at least one of these three factors is recorded (Chihara et al., 2018; Chihara and Oki, 2018; Gurion et al., 2016; Ellin et al., 2015; Kim et al., 2020; Nevel et al., 2019; Zhao et al., 2014). The association with testis and kidney, two sites of disease traditionally associated with CNS involvement in aggressive B-cell lymphomas, remains to be addressed because the infiltration of these organs is very rare in peripheral T-cell lymphomas (Ellin et al., 2015). The involvement of nose and paranasal sinus is related to increased risk for CNS dissemination due to the porous structure of adjacent bones (Yi et al., 2011; Kim et al., 2010). Nevertheless, this association was not confirmed in patients with ENKTCL of nasal type (Kim et al., 2010), which should be considered with caution because most of these patients receive high-dose methotrexate (HD-MTX) as part of primary chemotherapy, a drug currently used to prevent and treat CNS recurrence in aggressive lymphomas (Ellin et al., 2015).

Ann Arbor stage III/IV, International Prognostic Index (IPI), and elevated serum LDH, among others, have been proposed as risk factors, but further studies that confirm this finding are needed (Gurion et al., 2016; Ellin et al., 2015; Yi et al., 2011; Kim et al., 2010; Pro and Perini, 2010; Nevel et al., 2019). Regarding patient characteristics, immunological status is considered an important predictor of CNS involvement (Rubenstein et al., 2008; Chiavazza et al., 2018; Matinella et al., 2015; Cook et al., 2019).

6. Diagnosis

The CNS involvement usually results in a different therapeutic program and poorer prognosis in B and T-cell lymphomas. Accordingly, any effort to confirm CNS involvement early should be made. Exams aimed to diagnose the involvement of the CNS in patients with T-cell lymphomas are the same currently used in aggressive CNS B-cell lymphomas, and consist of physicochemical exams, cytological examination and flow cytometry of cerebrospinal fluid (CSF), ophthalmological exams (direct ophthalmoscopy, slit-lamp exam, fluoroangiography) and gadolinium-enhanced Magnetic Resonance Imaging (MRI) of the brain +/- spinal cord. These exams should be indicated in patients with neurological and/or visual symptoms, whereas the role of the routine use of these exams in asymptomatic patients remains to be defined.

Relapse sites in the CNS vary among the reported studies; this is mostly related to confounding effects of prior treatments and the use of different CNS prophylaxis strategies, as well as to different prevalence of T-cell lymphoma subtypes within the reported series. Some studies seem to suggest specific CNS dissemination patterns for some T-cell lymphoma entities. For instance, in Korean series with a prevalence of PTCL-nos, ALCL and angioimmunoblastic T-cell lymphoma, CNS recurrence has been associated with systemic relapse in 90 % of patients, and CNS disease was limited to leptomeninges in 70 % of cases, whereas 25 % have brain parenchymal lesions and only 5% of patients had both (Yi et al., 2011). In a European case series, half of CNS recurrences have been isolated, with brain parenchymal lesions in one-third of patients (Ellin et al., 2015). In an American case series, leptomeninges were the exclusive CNS relapse site in every case, which was detected by MRI, CSF cytology, or both (Chihara et al., 2018). In a Western case series of ENKTCL, 90 % of cases had meningeal recurrence, concomitant with persisting systemic disease in all cases (Nevel et al., 2019).

In patients presenting with expansive brain lesions, the overall strategy is similar to those recommended for PCNSL: a systemic site of

disease should be rapidly excluded by contrasted whole-body CT scan (Kitajima et al., 2002) and FDG-PET (Ferreri et al., 2019a). In patients with primary involvement of the CNS, suspicion should be confirmed with histological or cytological examination of brain biopsy, CSF and/or vitrectomy samples (Zhao et al., 2014). In patients with concomitant CNS and systemic lesions, histological assessment should be performed on tissue sampled from extra-CNS organs, lymph nodes in particular. In these patients, histological confirmation of brain lesions might be superfluous if suspicion of CNS involvement is strongly supported by modern neuroimaging and is consistent with tumor behavior (i.e., fast infiltrating tumor growth parallel to systemic disease progression). Importantly, patients with ocular involvement at presentation have often concomitant systemic disease (Chaput et al., 2017). Confirmation of intraocular infiltration, which is usually bilateral, by cytological examination is not mandatory in patients with histopathological diagnosis of T-cell lymphoma performed on brain or extra-CNS tissue. In the near future, the assessment of molecular and biological markers in the vitreous and aqueous humors could be an alternative, conservative diagnostic tool in this scenario (Chaput et al., 2017).

6.1. *Presenting symptoms*

The vast majority of patients with T-cell lymphoma and CNS disease have symptoms and signals at presentation; diagnosis can be difficult in the rare cases of asymptomatic CNS disease. In the latter, CNS involvement can be detected incidentally after a lumbar puncture for intrathecal prophylaxis or only via autopsy. (Nevel et al., 2019) Presenting symptoms and signals vary according to the affected areas and compartments of the CNS, are not specific for T-cell lymphomas, and are similar in patients with primary or secondary CNS involvement (Lim et al., 2011; Kim et al., 2020). Manifestations range from subtle behavioral changes to gross neurologic deficits such as focal numbness, weakness or paresthesia, or cranial neuropathies. Headache, vomiting, paresthesia, diplopia, aphasia, and cognitive defects are the most commonly reported. Cognitive abnormalities such as confusion and amnesia, lethargy, fatigue and somnolence are also reported (Lim et al.,

Table 2
Published case series on CNS involvement in PTCL.

Author	Year	No of Pts	Subtype	Ann Arbor Stage	Primary CNS involvement	Secondary CNS involvement	Site	Treatment	OS (months)
Kim	2010	12	ENKTL (12)	I/II (2) III/IV (10)			Parenchyma (6) Leptomeninges (6)	HD-MTX	6
Yi	2011	20	PTCL-NOS (11); ALCL (5); AITL (3); EATL (1)	I/II (3) III/ IV (17)	2	18	Leptomeninges (14) Parenchyma (5) Both (1)	HD-MTX	7.6
Mak	2013	19	ALCL (5); AITL (3); EATL (1)	III/IV (17) I/II (2)	7	12	Parenchyma (5) Leptomeninges (6) Both (1)	NA	NA
Ellin	2015	28	PTCL-NOS (15); EATL (4); AITL (3); ALCL ALK+ (3); ALCL ALK- (2); ALCL (1)	II (8) III (5) IV (15)		28	Leptomeninges (18) Parenchyma (10)	NA	1.1
Gurion	2016	15	PTCL-NOS (6); ATLL (4); ENKTCL (2); AITL (1); ALCL ALK- (1); HSTCL (1)	NA		15	NA	NA	2.63
Chaput	2017	7	PTCL-NOS	I (3) III (2) IV (2)	3	4	Eyes (vitreous) Parenchyma (2) Leptomeninges (1) Both (1)	IT & IV MTX; intravitreal MTX; RDT	21.7
Miyata-Takata	2017	4	NK cell	I	4		NA	HD-MTX; RDT	NA
Nevel	2019	10	ENKTCL	I (1) III/IV (8) N/A (1)	1	9	Leptomeninges (8) Parenchyma (1) Both (1)	HD-MTX ± IT-MTX	8.5
Lewis	2019	1	HSTCL	IV		1	Leptomeninges	HD-MTX and IT-MTX + ARAC	NA
Wang	2018	1	ENKTCL nasal type	III/IV		1	Parenchyma	l- asparaginase, MTX, gemcitabnine, oxaliplatin	6
Wu	2018	1	HSTCL	IV		1	Multifocal	GDP + liposomal doxorubicin, IT-MTX	NA
Imataki	2018	1	PTCL-NOS	III		1	Multifocal	HD-MTX	2
Gupta	2017	1	PTCL-NOS	I	1		Parenchyma	Rituximab, vincristine and HD-MTX	1
Afrantou	2017	1	ALCL ALK-	III		1	Parenchyma	CHOP	NA
Jones	2017	1	Gama-delta	III		1	Parenchyma	CODOX-M/IVAC	10
Major	2017	1	ALCL ALK-	IV		1	Parenchyma	HD-MTX	7
Qiu	2016	1	SPTCL	III		1	Multifocal	FTD	91

ALCL: anaplastic large cell lymphoma; AITL: angioimmunoblastic T-cell lymphoma; ALK: anaplastic lymphoma kinase; ALK u: anaplastic lymphoma kinase status unknown; ARAC: Cytarabine; Auto SCT: autologous stem cell transplantation; CNS: Central nervous system; EATL: enteropathy-associated T-cell lymphoma; ENKTL: extranodal NK/T-cell lymphoma, nasal type; FTD: Fotemustine, teniposide and dexamethasone; HD-MTX: high dose of metotheraxate; HSTCL: hepatosplenic T-cell lymphoma; IT: intrathecal; IV: intravenous; PTCL-NOS: peripheral T-cell lymphoma not otherwise specified; SPTCL: Subcutaneous panniculitis-like T-cell lymphoma.

2011; Yang and Wickless, 2017; Nevel et al., 2019; Menon et al., 2015; Miyata-Takata et al., 2017). Neuropathy due to neural and spinal infiltration is less common and mimics immune diseases (eg. as vasculitis), which explains the frequent misdiagnosis (Levin et al., 2008). Seizures are less frequent than in other CNS tumors (Nevel et al., 2019; Chiavazza et al., 2018). Vision disturbance may be related to elevated intracranial pressure, intraocular disease, and direct infiltration of the optic radiations or occipital cortex (Kim et al., 2020). Intraocular lymphoma in peripheral T-cell lymphomas is less common than in B-cell lymphomas (Chaput et al., 2017; Jun et al., 2007); the vitreous and the retina are the most commonly involved structures, with vitritis, anterior uveitis, and serous retinal detachment as the most frequent clinical signs (Chaput et al., 2017). One third of patients with T-cell lymphoma and intraocular disease has concomitant infiltration in other areas of the CNS (Rubenstein et al., 2008; Chaput et al., 2017).

Rare cases of *lymphomatosis cerebri* (LC) with T-cell immunophenotype have been reported (Li et al., 2018). This is a neoplasm diffusely infiltrating the CNS, characterized by rapidly progressive dementia in the elderly, and varied contrast-enhancement patterns on MRI (see "*Imaging*").

6.2. Imaging

Neuroimaging shows a good diagnostic sensitivity but a low specificity to distinguish secondary CNS T-cell lymphomas. There are no radiological findings specific for this condition because cumulative experience is still limited (Table 2). Brain computed tomography (CT) is usually the first image tool since it is cheaper and more readily available. However, brain MRI is the method of choice to better investigate these patients (Yi et al., 2011; Kim et al., 2010; Pui and Thiel, 2009; Bühring et al., 2001). White matter involvement is recorded in around two-thirds of all the patients with T-cell CNS lymphomas, followed by infiltration of deep grey matter structures, whereas leptomeningeal disease is detected by neuroimaging in very few cases, as part of relapsing disease (Ellin et al., 2015), often in association with systemic dissemination (Shenkier et al., 2005). CNS T-cell lymphomas imaging findings are slightly different from the most common PCNSL (Fig. 1). Usually, the parenchymal mass lesions show a rim enhancement after the gadolinium administration with mild to severe peritumoral edema. The mass presents iso to high-signal intensity on T2/FLAIR sequences and focus of hemorrhage are most frequently noted in those cases (Figs. 1 and 2). Single and multiples lesions have been related and the subcortical white matter is the most common location observed (Kim et al., 2010).

MRI of rare cases of *lymphomatosis cerebri* with T-cell immunophenotype has shown diffusely infiltrated CNS white matter along the corticospinal tract, possible involvement of the gray matter, a slight mass effect and varied contrast-enhancement patterns (Li et al., 2018). Non-enhancement or non-mass-like enhancement on MRI may be a special form of *lymphomatosis cerebri* during disease development and progression (Li et al., 2018). Importantly, MRI findings in the leptomeninges show a high concordance with detection of lymphomatous cells in the CSF (Ellin et al., 2015).

Advanced imaging techniques such as perfusion MRI and proton spectroscopy do not increase diagnostic specificity. However, somehow they could be useful in distinguishing a lymphomatous mass from metastases, glioblastoma multiform and infections (Chiavazza et al., 2018; Menon et al., 2015; Bühring et al., 2001; Küker et al., 2005).

The ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) PET-CT, widely used in lymphoma's staging, exhibits some sensitivity limitations to evaluating CNS masses, due to the high uptake of normal brain grey matter (Chiavazza et al., 2018; Hoang-Xuan et al., 2015). Other tracers, like methionine, could improve diagnostic sensitivity of brain PET, which may be used to assess response to treatment.

MRI is not specific in detecting ocular involvement but it could help to improve diagnostic sensitivity when used in combination with ocular examination by slit-lamp and funduscopy (Chaput et al., 2017; Gao et al., 2019). The optical coherence tomography can provide more information about retinal infiltration, and should be considered as part of the diagnostic work-up (Chaput et al., 2017; Gao et al., 2019).

6.3. Pathology

Radiological and clinical findings as well as dissemination patterns in the CNS are not specific for T-cell lymphomas. Therefore, it is essential to confirm diagnosis with histopathological examination of an appropriate tissue specimen (Rubenstein et al., 2008; Gurion et al., 2016; Zhao et al., 2014). In patients affected by a histopathologically diagnosed systemic T-cell lymphoma with a lesion in the CNS, indication for a confirmatory biopsy should be considered due to the rarity of this condition. However, strong suspicion of CNS recurrence based on modern imaging (evaluated by expert neuroradiologists), if consistent with clinical behavior of the neoplasm, may be sufficient evidence to make the diagnosis of secondary CNS T-cell lymphoma. It is important to emphasize that CNS lymphomas are highly sensitive to steroids, routinely used to reduce perilesional edema and related symptoms, and that the use of these drugs can interfere with the correct histological diagnosis due to fast tumor shrinkage. Mass regression or clearance of tumor cells from CSF samples support the diagnostic suspicion of CNS lymphoma, but, at the same time, can lead to false negative results at histopathological examination (Rubenstein et al., 2008; Levin et al., 2008; Chiavazza et al., 2018; Menon et al., 2015; Hoang-Xuan et al., 2015; Imataki et al., 2018; Shaw et al., 2014). For this reason, when possible, steroids should be avoided before biopsy.

Histopathological examination of sample tissue collected by stereotactic biopsy is the gold standard for diagnosing lymphomatous lesions in the brain parenchyma (Gurion et al., 2016; Hoang-Xuan et al., 2015). Histopathological examination associated with clinical and radiological findings are essential to differentiate primary and secondary CNS lymphoma (Ma et al., 2014). As in nodal lymphomas, PTCL-NOS is the most common T-cell subtype diagnosed in the CNS, followed by ALCL and ENKTCL (Kim et al., 2020; Chiavazza et al., 2018; Menon et al., 2015; Miyata-Takata et al., 2017; Hoang-Xuan et al., 2015). ENKTCL of nasal type commonly occurs in the upper respiratory and digestive tracts, and in spite of its localization and aggressive behavior, it rarely infiltrates the CNS (Yi et al., 2011; Kim et al., 2010; Wang et al., 2018). This may be explained by the frequent use of HD-MTX as part of therapeutic combinations, which should act as CNS prophylaxis (see below) (Yamaguchi et al., 2011).

T-cell lymphoma is always a challenging diagnosis, in particular in the CNS, which requires the involvement of an expert hematopathologist. As demonstrated by the International T-Cell Project, up to 10.3 % of T-cell lymphomas have been reclassified after a centralized pathology review (Bellei and Federico, 2019). Distinguishing clonal and reactive T cells is difficult because of the limited amount of tumor tissue in stereotactic biopsy samples, the presence of high amounts of inflammatory cells, and the wide variety of rare T-cell lymphoma entities (Rubenstein et al., 2008; Shaw et al., 2014; Liu et al., 2003).

Perivascular lymphocytic infiltrates are usually seen in CNS lymphoma, but it is not specific; other conditions like encephalitis, viral infections and autoimmune diseases also show this histopathological finding. Necrosis, gliosis, histiocytic infiltration, hypervascularization, and vascular damage are often observed (Menon et al., 2015; Ponzoni et al., 2002). The morphology is not specific. Lymphoma cells are usually small to medium size (in particular in PTCL-NOS) and are present along the perivascular spaces, which supports the hypothesis that the tumor cells spread through this route, resulting in the leptomeningeal infiltration (Amano et al., 2011).

Immunohistochemistry is mandatory to define the cell lineage using T-cell surface markers, and polymerase chain reaction (PCR) can be used to identify T-cell receptor (TCR) gene rearrangements (Chaput et al., 2017; Menon et al., 2015; Hoang-Xuan et al., 2015; Shaw et al., 2014; Liu et al., 2003; Ogura et al., 2013). Tumor T cells often express CD2,

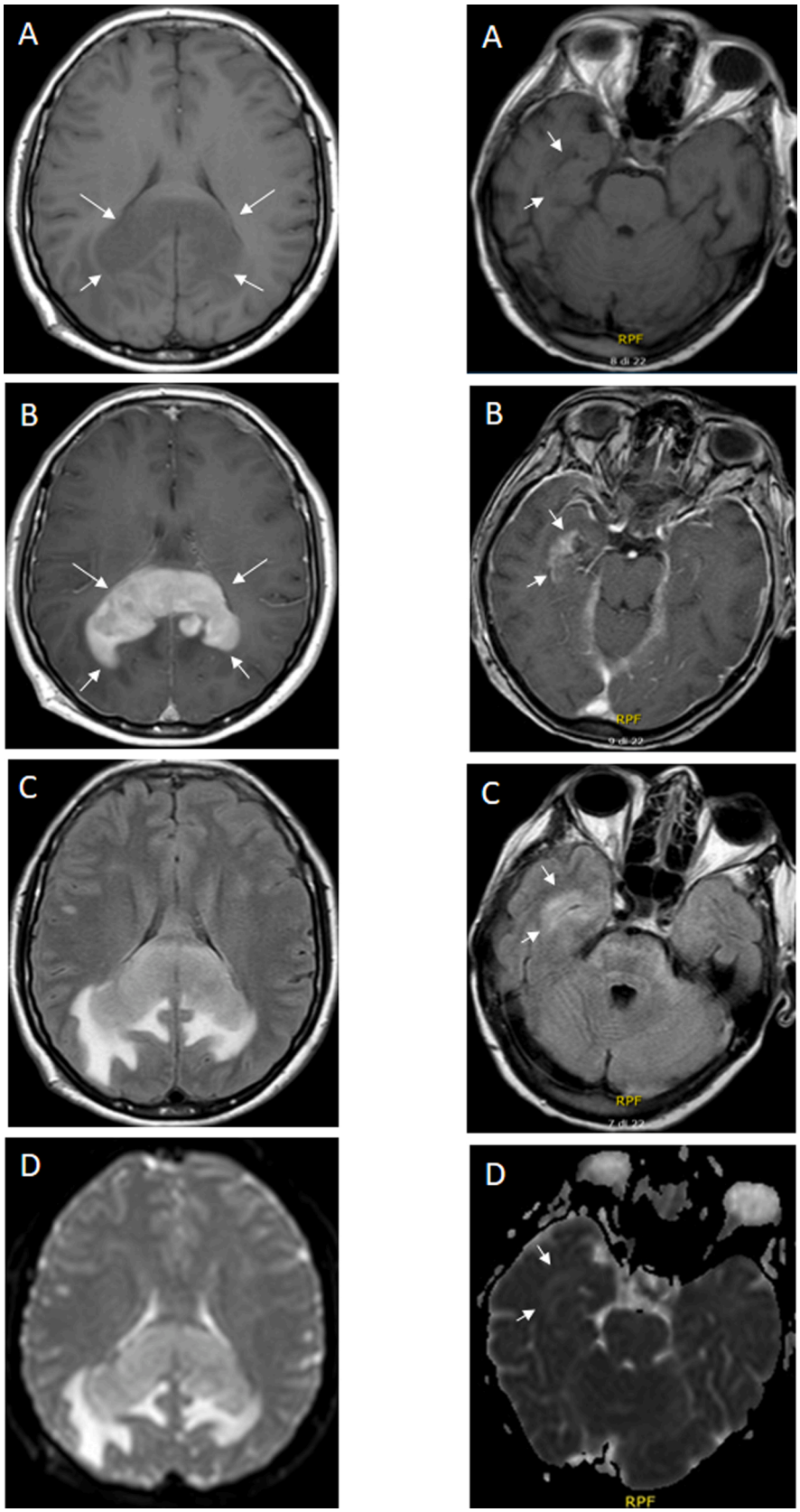

Fig. 1. MRI findings of primary diffuse large B-cell lymphoma of the central nervous system (PCNSL) and secondary CNS involvement of peripheral T-cell lymphoma not otherwise specified (SCNSTCL).
Photos on the left side regards a patient with PCNSL with infiltration of the splenium of the corpus callosum, forceps maior, hypocampus and neighbor white mater (arrows in A and B). Photos on the right side regards a patient with SCNSTCL with a lesion infiltrating periventricular areas at the right temporal lobe (arrows in A and B).
Pre-contrast T1 weighted MRI scans (A) showed an hyperintense mass infiltrating in the case of PCNSL and an isointense lesion in the SCNSTCL. Contrast enhancement after Gadolinium injection at the T1 weighted scan (B) was intense and homogeneous in the PCNSL, and irregular in the SCNSTCL. Abnormal signal at FLAIR scan (C) was recorded in both cases, whereas the diffusion weighted imaging (D) showed reduced diffusion in the PCNSL and only modest changes in the SCNSTCL.

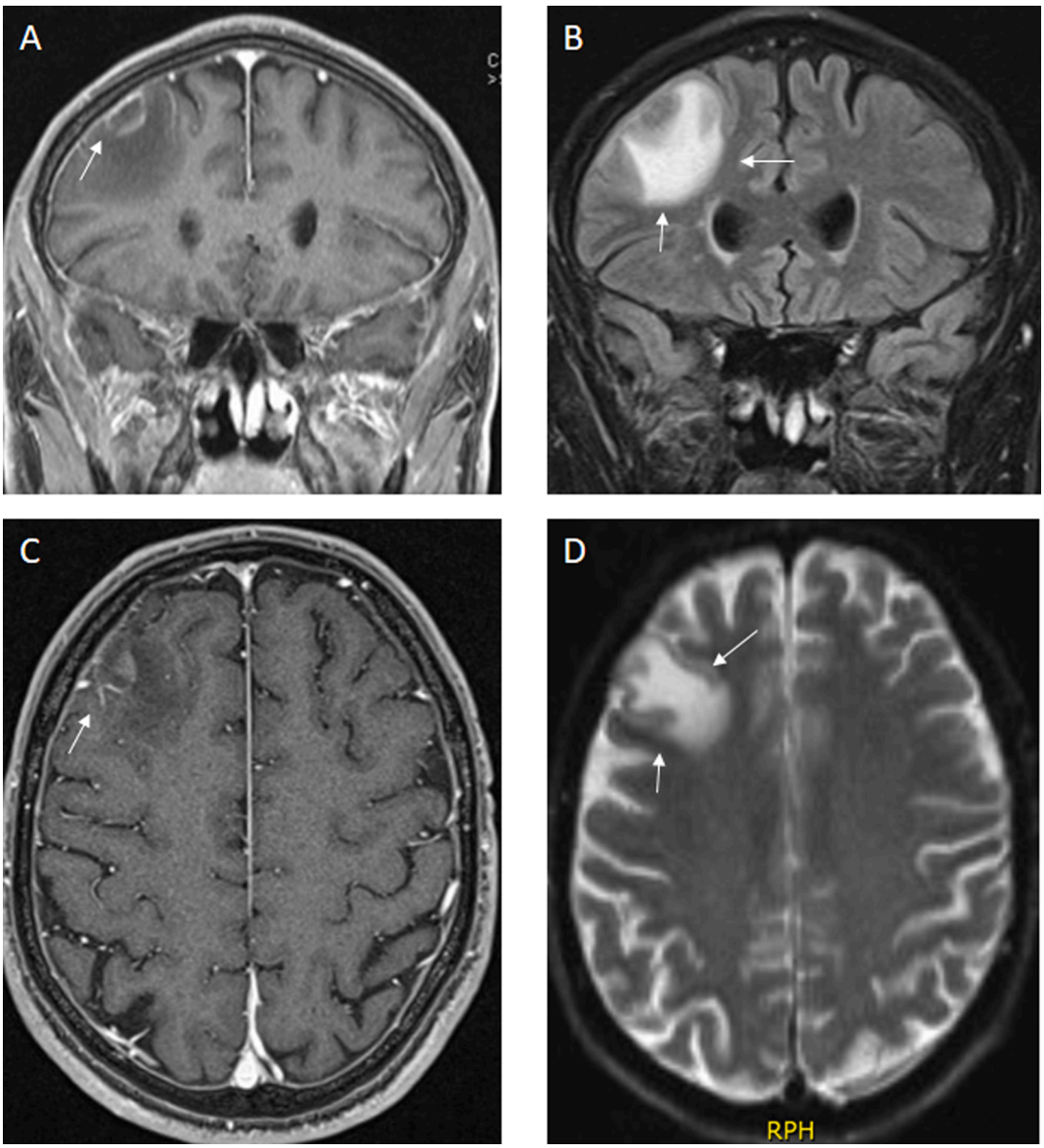

Fig. 2. Secondary CNS dissemination of ALK-negative anaplastic large T-cell lymphoma.
Irregular contrast enhanced area in T1 weighted MRI scans (arrows in A and C), related to extensive signal abnormalities both in FLAIR (B) and diffusion (D) scans. Please compare with Fig. 1.

CD3 (except by ALCL, ALK-positive), CD5, CD4 or CD8, and CD30. Most cases are αβ-T cells; nevertheless, γδ-T cells are also found. CD56 is usually positive in ENKTCL. Cytotoxic molecules like T cell-restricted intracellular antigen (TIA1) and granzyme B are expressed in more than 70 % of T-cell lymphomas (Chihara and Oki, 2018; Menon et al., 2015; Miyata-Takata et al., 2017; Wang et al., 2018). ALK-positivity is a helpful finding to distinguish large tumor cells from reactive cells in cases of ALCL (Menon et al., 2015). Ki-67 is usually over 50 % (Menon et al., 2015; Miyata-Takata et al., 2017; Wang et al., 2018).

The detection of EBV infection is an important diagnostic tool in T-cell lymphomas. This virus-lymphoma association shows a variable incidence depending on the lymphoma entity (a.e., 31 % of PTCL-NOS, 100 % of ENKTCL) (Miyata-Takata et al., 2017; Wang et al., 2018; Ogura et al., 2013). The assessment of EBV RNA by EBER in situ hybridization is the gold standard for establishing the EBV tissue state considering the low sensitivity of LMP1 immunohistochemistry.

CSF analysis is an important tool to confirm the presence of lymphomatous cells and to exclude differential diagnosis (i.e., infections), and should be performed in any patient with suspected or confirmed CNS lymphoma unless there is a formal contraindication (i.e., severe intracranial hypertension, bleeding) (Ellin et al., 2015; Zhao et al., 2014; Chiavazza et al., 2018). Three to 10 ml of CSF collected by lumbar puncture are necessary to perform the minimum physical and chemical assessments, in particular, protein and glucose concentration, cytological examination, immunocytochemistry, flow cytometry, and other evaluations. In patients with cerebral masses, a high protein concentration is detected in the CSF, which is an indicator of blood-brain barrier damage. In patients with lymphomatous meningosis, reduction of glucose levels may be observed, especially in cases with high tumor cells counts. Cytomorphology and immunocytochemistry are useful to confirm lymphoma diagnosis, and are part of staging work-up to confirm or exclude meningeal dissemination in lymphoma patients. Cytology examination should be combined with flow cytometry. Lymphoma cells are fragile, and should be analyzed within a few hours of collection, and the exam should be performed by expert cytologists and pathologists (Rubenstein et al., 2008; Kim et al., 2010; Ponzoni et al., 2002). In case

of suspicion of CSF/meningeal disease as first abnormal finding, T and B lymphocytes, NK, monocytes, granulocytes, and red cells should be counted; clonality should be demonstrated; and flow cytometry with a panel including CD2, CD3, CD4, CD8, CD14, CD16, CD19, CD45, and light chains should be performed. In patients with a histological or cytological diagnosis of T-cell lymphoma, a more specific panel should include CD2, CD3, CD4, CD5, CD7, CD8, CD16, CD19, CD45, and CD56.

Diagnosis of intraocular involvement is challenging in lymphomas in general due to the small number of cells present in most samples, the frailty of cells present in the vitreous (that necessitate analysis to be performed soon after sample collection), and the confounding effect of reactive lymphoid cells. This is even more difficult in T-cell lymphomas (Chaput et al., 2017), where anaplastic lymphoid cells of large size are often recorded, but small sized and pleomorphic cells are also reported (Chaput et al., 2017). The vitreous cells could be analyzed by flow cytometry, but reliable results are achieved only in large centers with suitable experience (Chaput et al., 2017; Hoang-Xuan et al., 2015). Clonality by assessment of T-cell receptor rearrangement can help to complete the diagnosis of intraocular lymphomatous involvement (Chaput et al., 2017).

Recurrent genetic abnormalities are uncommon in T-cell lymphomas. Moreover, peripheral T-cell lymphomas associated with secondary CNS exhibit ample clonal heterogeneity, which makes it challenging to track reliable abnormalities, and changes in distribution of clones within the same tumor could change during diagnosis and treatment (Menon et al., 2015). *G*ene rearrangements were identified in a number of T-cell lymphomas, but with wide molecular heterogeneity among lymphoma subtypes, including overlapping mutations, resulting in difficulties to incorporate them in routine practice (Chihara and Oki, 2018; Menon et al., 2015; Koo et al., 2012). Novel techniques like molecular methods, cytogenetics and next-generation sequencing, among others, are currently used to diagnose and characterize T-cell lymphoproliferative disorders. These important tools have been used in a few recently reported cases of SCNSTCL, but specific recommendations for SCNSTCL cannot be provided. These methods should be applied to diagnose and characterize SCNSTCL following suggested algorithms currently used for systemic T-cell lymphomas. Circulating tumor DNA, or liquid biopsy, generally identified by next generation sequencing or real-time PCR is a new, promising technology used in B-cell lymphoma. This method can be used in plasma and CSF samples for diagnostic, prognostic, and response assessment purposes (Bobillo et al., 2021; Hickmann et al., 2019; Rimelen et al., 2019). This may also be used in the assessment of T-cell lymphomas with CNS involvement in the near future.

7. CNS prophylaxis

7.1. Indications

CNS prophylaxis was initially indicated for acute leukemia in children in the early 1970s and, subsequently, for high-grade lymphomas such as Burkitt lymphoma, and more recently for DLBCL, in combination with systemic chemotherapy. The rarity of secondary CNS T-cell lymphoma and the heterogeneity of T-cell lymphomas have hampered the establishment of reliable recommendations on the indications and type of CNS prophylaxis in this setting. Conversely to that which is reported in B-cell lymphomas, prognostic indexes to predict CNS involvement in T-cell lymphoma patients do not exist. Moreover, when the CNS-IPI, the prognostic index most commonly used in aggressive B-cell lymphomas, is used in peripheral T-cell lymphomas, the diagnostic sensitivity is only 6% (Pro and Perini, 2010). Therefore, variables and related prognostic scores currently used to distinguish patients with aggressive B-cell lymphomas and increased CNS risk should not be used routinely in patients with T-cell lymphomas.

Although supported by only low-level evidence, a few types of patients with T-cell lymphoma should be considered for personalized CNS prophylaxis (Table 1): patients with aggressive ATLL (Cook et al., 2019); patients with ENKTCL with a CNS-PINK of 2 (Kim et al., 2020); patients with other peripheral T-cell lymphomas and involvement of two or more extranodal organs, in particular gastrointestinal tract, skin and/or paranasal sinus (Chihara et al., 2018; Gurion et al., 2016); and AIDS/HIV patients, mainly with low CD4 counts, unresponsive to antiretroviral treatment should be considered at high risk of CNS. This risk may be even higher when these patients present with advanced-stage disease and/or high IPI scores. Finally, although supported by a low level of evidence, the pros and cons of CNS prophylaxis should be discussed with patients with enteropathy-associated T-cell lymphoma (Ellin et al., 2015) or monomorphic epitheliotropic intestinal T-cell lymphoma (Yi et al., 2019) and other risk factors.

7.2. Modalities

Following the example of aggressive B-cell lymphomas, three CNS prophylaxis options are available: the whole-brain irradiation, which has already been abandoned, intrathecal chemotherapy, and intravenous HD-MTX-based chemotherapy (Pui and Thiel, 2009; Ferreri et al., 2015). None of these strategies can be recommended to patients with aggressive T-cell lymphoma in routine practice because supporting literature is lacking. The retrospective analysis of 625 cases of T-cell lymphoma treated between 2000 and 2009 and recorded in the Swedish Lymphoma Registry demonstrated that CNS prophylaxis with drugs delivered by intrathecal route is not associated with reduced risk of CNS recurrence; interestingly, a high incidence of leptomeningeal relapses after intrathecal chemotherapy alone was reported (Chihara and Oki, 2018; Ellin et al., 2015). Similar results have been described in a single-center experience, where three (13 %) of 24 patients with peripheral T-cell lymphomas who received intrathecal MTX and 12 (6%) of 204 who did not receive prophylaxis experienced CNS recurrence (Gurion et al., 2016). Moreover, intrathecal MTX did not play any role when the analysis was limited to the 91 patients with high-intermediate or high IPI score (Chihara and Oki, 2018; Gurion et al., 2016).

In contrast, intravenous delivery of drugs with good-moderate CNS bioavailability, used at conventional or high doses, did prevent CNS dissemination in patients with high-risk hematological malignancies (Leppä et al., 2020). MTX delivered at $\geq$3 g/m^2 was the most frequently adopted approach, mainly in lymphoblastic and Burkitt lymphomas, two neoplasms that exhibit a high sensitivity to this drug. In the last decade, HD-MTX was used extensively in high-risk patients with DLBCL, a lymphoid malignancy where MTX does not represent a first-choice drug (Gurion et al., 2016; Pui and Thiel, 2009; Ferreri et al., 2015; McMillan et al., 2013). The use of high-dose cytarabine has been associated with a lower CNS recurrence rate in DLBCL (Holte et al., 2013); however, its role in T-cell lymphomas should be better investigated. Since it has good CNS bioavailability, etoposide may be another candidate for CNS prophylaxis in T-cell lymphomas. However, the level of evidence suggesting a benefit when it is used in combination with the CHOP regimen in patients with T-cell lymphomas is low and only applies to some subgroups of patients (Schmitz et al., 2010), and the study of the Swedish Lymphoma Registry failed to demonstrate a positive effect of this drug on the CNS relapse risk (Ellin et al., 2015). Presently, there is no evidence supporting the use of other drugs other than MTX as CNS prophylaxis in patients with T-cell lymphomas.

Despite the good preventive effect reported in several retrospective series of DLBCL patients treated in the rituximab era, the role of MTX as CNS prophylaxis in T-cell lymphomas remains to be addressed. Probably, the prophylactic effect of this drug, if any, is not uniform among the varied subgroups of T-cell lymphomas. This effect can be analyzed separately in patients with T-cell lymphoma entities who are currently treated with HD-MTX as part of standard chemotherapy (a.e., ENKTCL, enteropathy-associated T-cell lymphoma). HD-MTX seems to play an important role in preventing CNS recurrence in patients with high-risk ENKTCL. CNS involvement has been detected in 10 (17 %) of 60

patients with ENKTCL treated without high doses of MTX or cytarabine in Western countries, whereas this event has occurred in only gtwo (8%) of 26 patients with advanced-stage ENKTCL treated with SMILE regimen in Japan (Nevel et al., 2019; Yamaguchi et al., 2019). Interestingly, both CNS recurrences reported after SMILE treatment have occurred in patients with extra-nasal-type form (Nevel et al., 2019; Yamaguchi et al., 2019). In a comprehensive analysis of 208 Korean patients with high-risk ENKTCL nasal type managed without intrathecal prophylaxis, CNS recurrence has been detected in 9% of patients treated with upfront CHOP or similar, whereas no patient treated with SMILE or other HD-MTX-containing regimens have experienced CNS relapse (Kim et al., 2010). In a recent study on 652 ENKTCL patients from South Korea and Japan (Kim et al., 2020), the use of combinations including MTX at $\geq$2 g/m^2 (i.e. SMILE or SMILE-like regimens) was associated with a significantly lower CNS relapse rate. This effect was observed in patients with a CNS-PINK score of 2 (high risk), whereas no benefit was observed among low-risk patients (Kim et al., 2020). Enteropathy-associated T-cell lymphoma is another entity often treated with combinations including HD-MTX alternated with regimens containing anthracycline and/or high-dose ifosfamide (Sieniawski et al., 2010). CNS involvement is an exceptional event in patients with enteropathy-associated T-cell lymphoma both when treated with or without intermediate-dose MTX, which makes it difficult to establish the role of this drug (Sieniawski et al., 2010). Overall, patients with T-cell lymphomas at high risk of CNS dissemination, who receive HD-MTX as part of first-line treatment do not need for additional prophylaxis.

Among T-cell lymphomas currently treated without HD-MTX as part of first-line approach, ATLL is that associated with the highest risk of CNS involvement; 10–20 % of patients with aggressive ATLL experience CNS dissemination (Teshima et al., 1990), with the CNS being affected in more than one half of relapses after chemotherapy in patients without an initial involvement of these organs (Tsukasaki et al., 1993). Despite the use of prophylaxis with intrathecal chemotherapy, CNS recurrence has been reported in 8% of patients treated with CHOP-14 regimen and between 4% and 6% of patients treated with VCAP-AMP-VECP (LSG15) or similar regimens (JCOG9303 and JCOG9801 trials), which is worse than the 1.6 % CNS relapse rate reported with a combination of vincristine, doxorubicin, etoposide, and pentostatin without intrathecal chemotherapy (JCOG9109 trial) (Tsukasaki et al., 2007). The higher CNS relapse rate in patients treated with intrathecal prophylaxis is explained by the per-protocol CSF examination in all patients even without neurological symptoms. Overall, CNS prophylaxis in patients with ATLL is advised; however, the best strategy remains to be defined, with the only clear suggestion that intrathecal chemotherapy is insufficient as exclusive prophylaxis measure.

Recent retrospective studies suggested that CNS recurrence occurs in 10 % of patients with monomorphic epitheliotropic intestinal T-cell lymphoma treated with CHOP or similar regimens (Yi et al., 2019); more intensified combinations including drugs with good CNS availability deserve to be assessed in this neoplasm.

In the case HD-MTX prophylaxis is added to conventional chemotherapy, questions on the best dose, schedule and timing remain open, in particular in T-cell lymphomas. A recent retrospective study was focused on the effect of the timing of delivery of 1–4 courses of MTX at a dose $\geq$3 g/m^2 (Swerdlow et al., 2016) as CNS prophylaxis in 334 high-risk patients with DLBCL (Wilson et al., 2020). Effects on toxicity, CNS relapse, and survival of delivering HD-MTX intercalated with primary chemoimmunotherapy (i.e., R−CHOP) vs. after chemoimmunotherapy completion were analyzed. Early delivery was associated with significantly increased toxicity, mucositis and febrile neutropenia in particular, as well as treatment delay, with no improvement in CNS relapse or survival (Wilson et al., 2020). A better tolerability was recorded when HD-MTX was delivered before day 10 of R−CHOP cycles. This hypothesis-generating study deserves to be reproduced on a larger DLBCL series, but seems to be impractical in T-cell lymphomas. However, it may support individualized decisions on CNS prophylaxis in selected patients with high-risk T-cell lymphomas.

8. Treatment and prognosis

Although limited to case reports and small case series, available literature uniformly suggests that, with current treatments, the prognosis of patients with secondary CNS T-cell lymphoma is poor, with rare, short-lived responses, a median survival shorter than 6 months, and only 10 % of patients alive at one year from CNS relapse (Chihara and Oki, 2018; Gurion et al., 2016; Ellin et al., 2015; Menon et al., 2015; Miyata-Takata et al., 2017). In a large retrospective case series of patients with peripheral T-cell lymphomas, CNS recurrence was associated with a median OS of 7.6 months, while patients without CNS disease had a median OS of 27.4 months (Yi et al., 2011). However, CNS recurrence seems to play a marginal effect on OS of patients with relapsed/refractory T-cell lymphoma as it is currently associated with systemic disease dissemination, which is the foremost cause of death in this setting (Yi et al., 2011). Moreover, as demonstrated by the large Swedish Lymphoma Registry study, the median OS from lymphoma relapse/progression was 1.1 months for the 28 patients with CNS dissemination and 3.8 months for the 369 patients with failure without CNS involvement (Ellin et al., 2015). Taken together, these notions clearly reflect the overall poor prognosis of the whole population of patients with T-cell lymphomas and inefficacy of salvage options, which is independent from CNS involvement.

Treatment of CNS recurrence has been rarely described in detail in reported case series. However, it is clear that a proportion of these poor-prognosis patients have received only supportive care, while some others have received whole-brain irradiation alone, with some cases of durable responses in patients with isolated brain relapse (Yi et al., 2011). Surgical debulking is not recommended, but it is indicated in selected patients to reduce intracranial hypertension quickly, allowing fast performance status improvement and timely chemotherapy. For patients with intraocular involvement, intravitreal MTX injection is an option, with or without local radiotherapy, in combination with systemic treatment (Chaput et al., 2017; Miyata-Takata et al., 2017). When used alone, intravitreal MTX permits good intraocular disease control, but treated patients experience invariably systemic or cerebral progressive disease.

Most young and fit patients with secondary CNS T-cell lymphoma have been treated following the example of aggressive B-cell lymphomas (Ferreri et al., 2019a). These patients have received polychemotherapy with high doses of anti-lymphoma drugs like MTX, cytarabine and ifosfamide. However, CNS-driven chemotherapy has been associated with a median survival after CNS relapse of <2 months (Table 2), with durable clinical benefit only in a few patients (Chihara et al., 2018; Gurion et al., 2016; Yi et al., 2011). Nevertheless, some case-series studies seem to support the use of drugs with good CNS bioavailability in selected patients with CNS recurrence from specific T-cell lymphoma entities. For instance, survival of patients with mycosis fungoides and CNS disease is particularly poor, especially when these patients are managed without CNS-driven therapies (Yang and Wickless, 2017); conversely, some cases of long-lasting responses when HD-MTX was combined with specific anti-mycosis fungoides therapies were reported (Zhao et al., 2014). Similarly, a recent, international good practice paper suggested including HD-MTX into combination chemotherapy regimens, such as CHOP or high-dose cytarabine, in patients with ATLL and active CNS disease at initial diagnosis, whereas no recommendations on salvage therapy for CNS relapse were provided (Cook et al., 2019). Importantly, CNS-driven approaches should be considered with caution in patients with secondary CNS T-cell lymphoma, because they are fragile and exposed to an increased risk of lethal complications when managed with high-dose, intensified treatments. This is particularly evident in patients with secondary CNS ENKTCL (Nevel et al., 2019).

In a tumor where CNS prophylaxis remains a matter of debate and available drugs exhibit a poor efficacy even on extra-CNS disease, the

identification of new active drugs is a priority. Among target therapies currently used in T-cell lymphoma patients, brentuximab vedotin, an anti-CD30-antibody, anti-tubulin drug conjugate currently used in patients with relapsed CD30 + PTCL, and crizotinib, an ALK tyrosine kinase inhibitor, exhibit poor CNS penetration and relevant limitations in controlling CNS disease (Ruf et al., 2018; Younes et al., 2010; Yoshida et al., 2016; Costa et al., 2011). Histone deacetylase inhibitors, like vorinostat, romidepsin, panobinostat, and belinostat, are used in different forms of T-cell lymphomas, but these molecules show low CNS bioavailability (Seo et al., 2014). New CNS-penetrant histone deacetylase inhibitors are being investigated (Choi et al., 2019). Preliminary data seem to suggest that immune checkpoint inhibitors are active in patients with ENKTCL who did not respond to L-asparaginase regimens (Kwong et al., 2017). Pembrolizumab is able to induce complete remission in patients with ENKTCL and CSF relapse (Ferreri AJM, personal observation). Following the example of PCNSL, the development of strategies aimed to enhance BBB penetration of the active drugs may result in improved CNS disease control even in T-cell lymphomas (Ferreri et al., 2019b).

Few data is available on the role of stem cell transplantation in cases of CNS T-cell lymphoma. Transplant indications and modalities in reported cases of secondary CNS T-cell lymphoma followed the example of aggressive B-cell lymphomas. Accordingly, consolidative high-dose chemotherapy with autologous stem cell rescue should be offered to patients with secondary CNS T-cell lymphoma responsive to induction chemotherapy. However, it is important to highlight that the mortality risk is high in these patients, mainly associated with infection complications related to the immunosuppression (Nevel et al., 2019; Korfel et al., 2013). It is known that better outcomes are achieved in patients who are transplanted in complete remission, but it is possible that patients with partial response could also benefit from this approach (Nevel et al., 2019; Sieniawski et al., 2010). Alkylating agents able to achieve therapeutic concentrations in the CNS tissues, like thiotepa, carmustine and busulfan, should be considered as part of conditioning regimens (Korfel et al., 2013; Ferreri and Illerhaus, 2016). Consolidation with allogeneic stem cells transplantation was anecdotally used in this setting, in particular in ATLL patients with CNS disease (Fukushima et al., 2011), sometimes with encouraging efficacy but high transplantation-related mortality (Fukushima et al., 2011; Bittencourt et al., 2007). Its indication remains controversial; however, if this strategy were to be used, drugs with high CNS bioavailability (e.g., nitrosoureas, thiotepa) should be considered.

9. Future perspectives

Due to its rarity, secondary CNS dissemination in patients with T-cell lymphoma remains a challenging event, with several uncertainties in diagnosis and treatment. The establishment of biomarkers predicting high risk of CNS dissemination will be an important step forward to distinguish the best candidates for prophylaxis. The identification of reliable molecular and radiological features useful for detecting CNS relapse early and for monitoring disease behavior should be investigated in the near future. Modern neuroimaging techniques may be an important means of generating early suspicion of CNS involvement, resulting in timely and accurate diagnosis. The application of advanced technologies to design novel drugs with activity against T-cell lymphoma and good availability in the CNS tissues is urgently needed to improve the prognosis of this often fatal condition.

Author Contributions

Natalia Zing, Thais Fischer, Massimo Federico, Carlos Chiattone, Andrés J. M. Ferreri: Conceptualization; Data curation; Investigation; Methodology; Resources; Validation; Writing - original draft; Writing - review & editing.

Declaration of Competing Interest

No conflict of interest are disclosed.

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