Radiology Case Reports 19 (2024) 2168–2182

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Case Report

Primary central nervous system post-transplantation lymphoproliferative disorder: A case report and systematic review of imaging findings ☆

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ARTICLE INFO

Article history:
Received 7 September 2023
Revised 7 February 2024
Accepted 9 February 2024

Keywords:
Primary central nervous system post-transplant lymphoproliferative disorder
MRI
CT
FDG PET-CT

ABSTRACT

Primary central nervous system post-transplant lymphoproliferative disease (PCNS-PTLD) is a rare subset of post-transplant lymphoproliferative disorder (PTLD) isolated to the CNS without nodal or extra-nodal organ involvement [1,2]. PCNS-PTLD occurs primarily in patients following either solid organ transplants or hematopoietic stem cell transplants and tends to be monomorphic DLBCL. The development of PCNS-PTLD is commonly associated with EBV infection [3]. Many intracranial pathologies can resemble the imaging appearance of PCNS-PTLD, including primary CNS lymphoma, glial tumors, metastatic disease, and intracranial abscesses. The purpose of this systematic review is to identify the most common imaging characteristics of PCNS-PTLD. Our review included 97 sources that describe the imaging appearance of PCNS-PTLD. Based on our review, PCNS-PTLD lesions are typically multifocal, ring-enhancing and diffusion-restricting. PCNS-PTLD lesions typically demonstrate focal FDG avidity. Despite advancement in medical imaging, PCNS-PTLD remains a diagnostic challenge due to its rare incidence. Limited data is available on advanced imaging

Abbreviations: PTLD, post-transplant lymphoproliferative disorder; PCNS-PTLD, primary central nervous system post-transplant lymphoproliferative disorder; SOT, solid organ transplant; HSCT, hematopoietic stem cell transplantation; DLBCL, diffuse large B-Cell lymphoma; EBV, Epstein-Barr virus; CT, computed tomography; MRI, Magnetic resonance imaging; PCR, polymerase chain reaction; FDG PET-CT, Fluorodeoxyglucose positron emission tomography-computed tomography; ADC, apparent diffusion coefficient; DCE, dynamic contrast enhancement; rCBF, relative cerebral blood flow; fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging.

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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https://doi.org/10.1016/j.radcr.2024.02.030

with regards to PTLD, but techniques including DCE-MRI and fMRI demonstrate promising results that may help further delineate PCNS-PTLD.

Introduction

Primary central nervous system post-transplant lymphoproliferative disease (PCNS-PTLD) is a rare subset of post-transplant lymphoproliferative disorder (PTLD) isolated to the CNS without nodal or extra-nodal organ involvement [1,2]. Secondary central nervous system-PTLD (CNS-PTLD) refers to PTLD outside the CNS with concomitant or subsequent CNS involvement. PCNS-PTLD most frequently occurs in immunosuppressed patients following solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT). It encompasses 5-15% of all PTLD diagnoses and is most commonly monomorphic diffuse large B-cell lymphoma (DLBCL) due to Epstein-Barr virus (EBV) infection [4,5]. PCNS-PTLD is most associated with renal transplants, and presents with symptoms such as headache, confusion, dizziness, and focal neurological deficits (including hemiparesis, ataxia, and aphasia) [2,3,6]. Due to its rarity and nonspecific presentation, it is often a challenge to distinguish PCNS-PTLD from other intracranial processes [1]. Herein, we report a case of PCNS-PTLD and provide a review of literature focusing on imaging, clinical, and pathologic characteristics.

Case report

A 25-year-old male presented to the emergency department with headaches and dizziness. His past medical history was significant for congenital renal hypoplasia, requiring renal transplant at age 13, and an immunosuppressive regimen of tacrolimus and mycophenolate mofetil. A CT head in the emergency department revealed multiple intracranial lesions (Fig. 1).

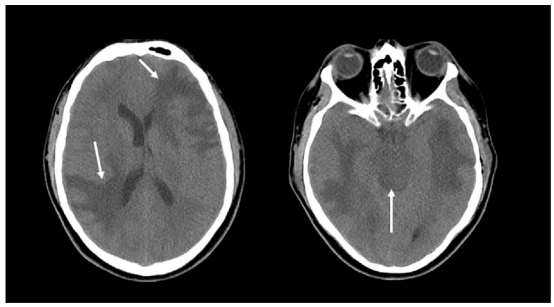

Fig. 1 – Axial sections of a non-contrast CT head exam reveal ill-defined intracranial lesions with surrounding edema, the largest in the right temporal lobe, left frontal lobe, and pons (white arrows).

MRI with and without intravenous contrast showed numerous intra-axial enhancing supratentorial and brainstem lesions (Fig. 2). Biopsy of a right frontal lesion revealed EBV-positive diffuse large B-cell monomorphic post-transplant lymphoproliferative disorder (Fig. 3). CSF cytology was negative for malignant cells, and FISH high grade lymphoma panel was negative. EBV was not detected in peripheral blood or in the cerebrospinal fluid by PCR. CT chest abdomen pelvis revealed no additional tumors.

Mycophenolate mofetil was discontinued, and tacrolimus was continued at a minimal dose. The patient was ini-

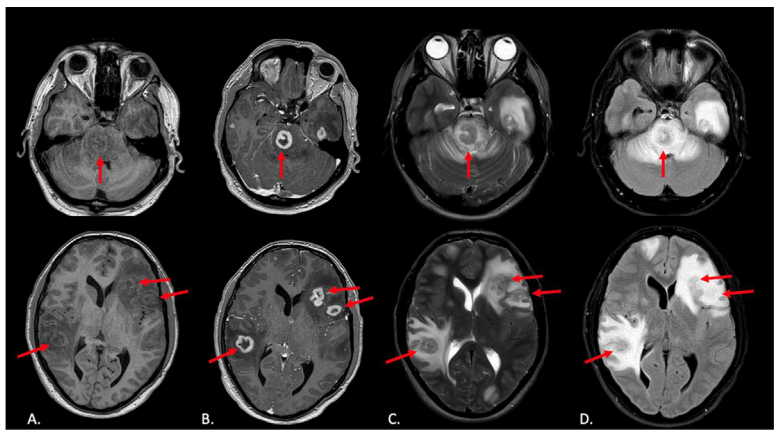

Fig. 2 – Axial sections of an MRI with and without intravenous contrast demonstrates numerous enhancing supratentorial and brainstem lesions, with significant surrounding edema and mass effect (red arrows). Column A. is a T1 weighted image. Column B is a T1 weighted, post-gadolinium image. Column C is a T2 weighted image. Column D is a T2 FLAIR image.

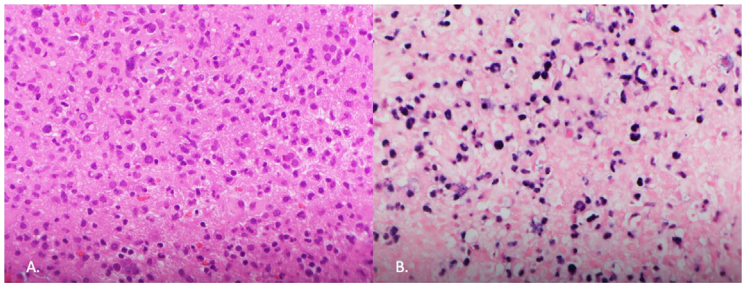

Fig. 3 – Immunohistologic slides from a right frontal lesion biopsy, revealing EBV-positive diffuse large B-cell monomorphic post-transplant lymphoproliferative disorder. On the left, image A shows a hematoxylin and eosin (H&E) stain of the intracranial lesion at 40x magnification. On the right, image B shows an EBV-encoded RNA (EBER) stain of the intracranial lesion at 40x magnification.

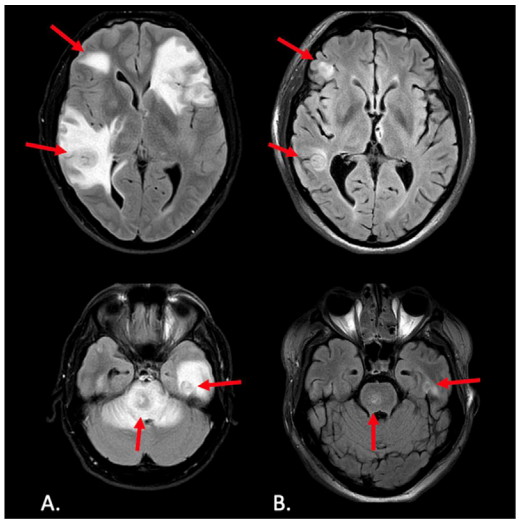

Fig. 4 – Axial sections of pre- and post-treatment T2 FLAIR MRI demonstrating a decrease in size of the intracranial lesions (red arrows), as well as a significant decrease in the surrounding edema. Column A is the pre-treatment MRI, and column B is the post-treatment MRI.

tiated on a two-week induction protocol of weekly intravenous antiviral therapy (zidovudine and ganciclovir), intravenous dexamethasone, intravenous rituximab, and intrathecal rituximab. He continued outpatient treatment with weekly IV rituximab, oral valganciclovir, oral zidovudine, and oral dexamethasone.

The patient returned to clinic 4 weeks after initiating therapy and reported complete resolution of his headache and dizziness. Physical exam demonstrated no neurologic deficits. Repeat MRI was ordered without intravenous contrast because of the patient's poor renal function, and showed a marked decrease in size and number of the intracranial lesions (Fig. 4). Post-treatment FDG PET-CT of the head demonstrated a decrease in size and number of the PTLD lesions, with no increased FDG uptake within the intracranial lesions (Fig. 5).

Materials and methods

PRISMA systematic review

PRISMA guidelines were followed to conduct our systematic review. We conducted a systematic review using PubMed, Scopus, and MEDLINE databases and all articles reporting PCNS-PTLD were screened. The search terms were ("post-transplant* lymphoproliferative disorder" OR "posttransplant* lymphoproliferative disorder" OR "post-transplant* lymphoproliferative disease" OR "posttransplant* lymphoproliferative disease") AND ("central nervous system" OR "CNS" OR "neuro*" OR "brain*" OR "spinal cord" OR "cauda equina"). Two reviewers conducted the search independently for articles published until May 22, 2023. Search results were initially screened by title and abstract using the *Rayyan* software and potentially eligible articles were reviewed in full detail using the reference management *Mendeley* software. In addition, the bibliographies of the articles that received full-text review were manually cross-checked for additional relevant publications.

Inclusion criteria were case studies with PCNS-PTLD with sufficient CT/MRI data and without extra-CNS PTLD. Studies that discussed both PCNS-PTLD and secondary PTLD were included, but only the cases of PCNS-PTLD were included for analysis. Exclusion criteria were articles describing only extra-CNS PTLD, articles without CT/MRI data, and articles not written in English.

The type of transplant and latency period from transplant to development of PCNS-PTLD were recorded. The articles were reviewed for imaging findings, and the following data was recorded if available: hypoattenuating or hyperattenuating on CT, hypointense or hyperintense on MRI T1 sequences, hypointense, isointense, or hyperintense on MRI T2 sequences, presence or absence of intralesional hemorrhage, multifocal or unifocal intracranial involvement, enhancement pattern (for the purposes of this review, rim enhancement, heterogenous enhancement, solid/homogenous enhancement, or no enhancement were the enhancement patterns included), presence or absence of intratumoral susceptibility signal, presence or absence of intralesional radio-

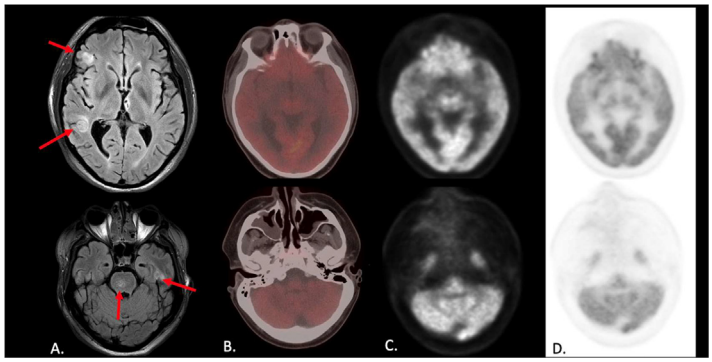

Fig. 5 – Column A. shows axial sections of a T2 FLAIR MRI sequence, with a few T2 hyperintense intracranial lesions (red arrows). Columns B, C, and D show axial sections of a post-treatment FDG PET-CT, which does not show FDG avidity corresponding to the lesions seen on MRI. .

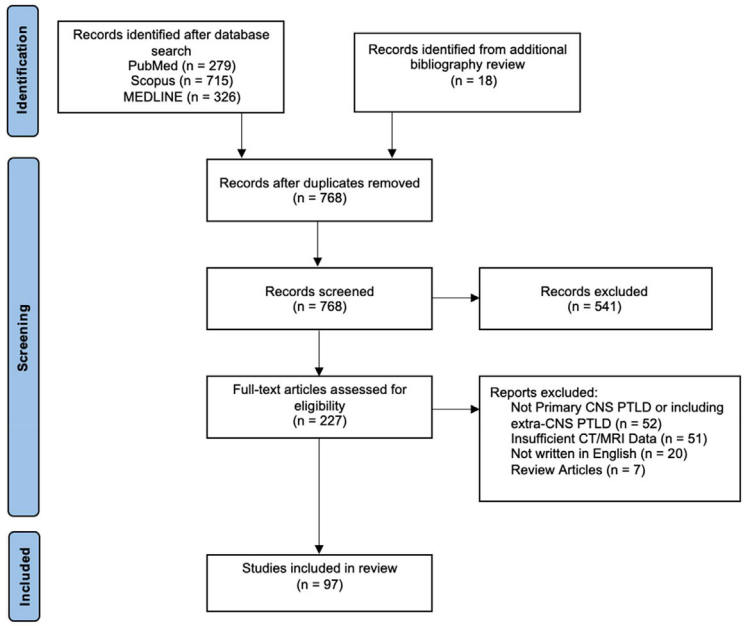

Fig. 6 – A PRISMA flowchart of our screening and review process. [2,3,6–13,16–24,26–36,38,40–49,51–54,57,61–111].

tracer avidity on FDG PET-CT, and presence or absence of restricted diffusion on DWI.

Our review yielded 1320 articles. We found 18 additional studies during our bibliography review that were not found in the database search. 768 articles remained after duplicates were removed. The initial search yielded 541 articles that mentioned PTLD without further description. These 541 articles were excluded, and 227 articles were reviewed in full text. Cases of secondary CNS PTLD and extra-CNS PTLD were excluded. Articles without data on imaging findings pertaining the PCNS-PTLD, articles not written in English, and review articles were excluded. After these exclusions, 97 primary sources remained. A PRISMA flowchart of our screening and review process is illustrated in Figure 6 [7].

Quality assessment

The risk of study bias was addressed by establishing inclusion and exclusion criteria prior to data analysis. Two independent reviewers conducted the literature search within the guidelines of the above criteria, and discrepancies in the included articles were addressed by each researcher independently re-evaluating the article in question. The articles were reviewed to ensure that their included cases and article design were appropriate for our research question. The imaging descriptions discussed in each article were compared with their provided images to ensure accuracy and minimize errors in data extraction.

Table 1 – Table 1 shows the type of transplants identified in our review, with each corresponding number of patients and mean latency period from transplant to the development of PCNS-PTLD in months.

Type of transplant	Number of patients	Mean latency (months)
Renal	53	112.89
HSCT	34	5.57
Liver	12	51.60
Heart	6	110.00
Renal-pancreas	3	37.33
Immunosuppression only	3	92.00
Lung	2	55.00
Lower limb	1	15.00

There was no financial support provided for our review. The reviewing authors have no competing interests. The review was not registered. All included articles and their contributing data may be accessed online through PubMed, Scopus, or Medline.

Table 2 – Summary of the CT and MRI imaging findings recorded from our review.

	number of patients	Percentage (%)
CT characteristics		
Hypoattenuating	25	69.4
Hyperattenuating	11	30.6
MRI characteristics		
Hypointense on T2/FLAIR	13	23.2
Isointense on T2/FLAIR	8	14.3
Hyperintense on T2/FLAIR	35	62.5
Hypointense on T1	25	86.2
Isointense on T1	4	13.8
Ring enhancement	96	59.3
Heterogenous enhancement	34	21.0
Solid/homogenous enhancement	30	18.5
No enhancement	2	1.2
Intratumoral susceptibility signal present	3	100.0
Intratumoral susceptibility signal absent	0	0.0
Focal radiotracer avidity on FDG PET-CT	5	100.0
No focal radiotracer avidity on FDG PET-CT	0	0.0
Diffusion restricting	9	81.8
Facilitated diffusion	2	18.2

Results

From our 97 sources, 212 cases of PCNS-PTLD were recorded. Renal transplants were most reported prior to the development of PCNS-PTLD, as summarized in Table 1. The latency period was reported for 115 patients. The mean latency from transplant to the development of PTLD was recorded in months, summarized in Table 1, with renal transplants having the longest mean latency period of 112.89 months and stem cell transplants having the shortest mean latency period of 5.57 months.

Table 2 summarizes the imaging characteristics obtained from our systematic review. CT descriptions were reported for 36 patients. About 25 patients had hypoattenuating PTLD lesions on CT, while 11 patients had hyperattenuating PTLD lesions on CT. The MRI T2 sequence signal was reported for 56 patients; 35 patients had lesions that were hyperintense on T2 sequences, 8 patients had lesions that were isointense on T2 sequences, and 13 patients had lesions that were hypointense on T2 sequences. The MRI T1 sequence signal was reported for 29 patients; 25 patients had lesions that were hypointense on T1, and 4 patients demonstrated lesions that were isointense on T1. 124 patients presented with multifocal PCNS-PTLD lesions, while 63 patients presented with unifocal PCNS-PTLD. The MRI enhancement patterns were reported for 162 patients. About 96 patients had lesions that demonstrated ring enhancement, 34 patients had lesions that demonstrated heterogenous enhancement, 30 patients had lesions that demonstrated solid or homogenous enhancement, and 2 patients had lesions that did not demonstrate enhancement. Only 10 articles mentioned tumor hemorrhage, and of these all 10 patients had hemorrhagic PTLD lesions. 3 articles recorded data on intratumoral susceptibility signal and reported 3 patients with susceptibility signal within the lesions. FDG PET-CT characteristics were reported for 5 patients, of which all 5 demonstrated radiotracer avidity within the PCNS-PTLD lesions. Diffusion weighted imaging characteristics were reported for 11 patients; 9 patients had lesions that demonstrated restricted diffusion, and 2 patients had lesions that did not restrict diffusion.

Discussion

Clinical features

The clinical presentation of PCNS-PTLD is variable, and patients most commonly present with headache, confusion, fatigue, dizziness, nausea, and seizures [1]. Neurologic deficits have been reported in many cases, and include gait ataxia, dysarthria, and hemiparesis [2,6,8–10]. Facial nerve palsy has been reported in a few isolated cases [11–13]. PCNS-PTLD is most frequently diagnosed in patients with a history of SOT or HSCT, with renal transplants being the most predominant. In our review, 46% of the recorded patients had received renal transplants, followed by HSCT (27%), liver (11%), and heart (5%). Cavaliere et al reports that 25 out of 34 (74%) cases received renal transplants with 6 patients receiving dual renal-pancreas transplants, followed by liver (6%), kidney-heart (3%), and heart (3%) transplants [2]. Although the latency between transplantation and diagnosis ranges from months to years, most authors report the risk of PCNS-PTLD to be greatest during the first year after transplant [14,15]. In a review of 84 cases, Evens et al reports the average time from transplant to diagnosis to be approximately 54 months. Most authors note the latency period following HSCT to be the shortest [16–18].

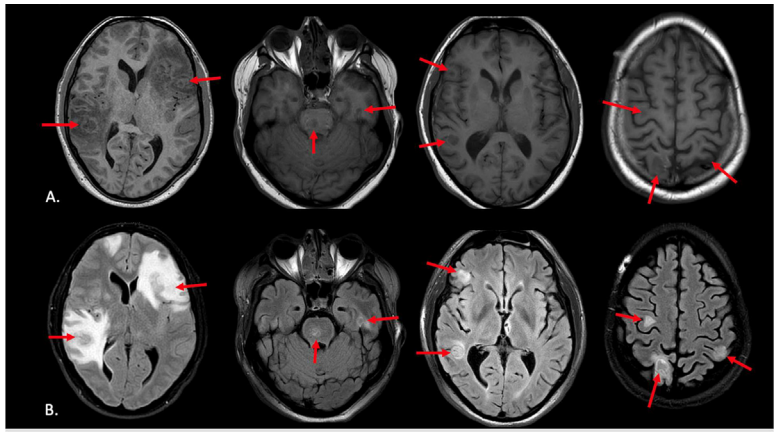

Fig. 7 – Row A. shows axial sections of T1 weighted MRI, which reveals hypointense to isointense PCNS-PTLD lesions (red arrows). Row B. shows axial sections of a T2 FLAIR weighted MRI, which reveals the corresponding lesions primarily as T2 hyperintense (red arrows).

Pathologic features

In healthy individuals, cytotoxic T cells regulate the body's response to EBV, a function that is lost with immunosuppression. Primary EBV infection or EBV reactivation in transplant recipients can lead to the uninhibited growth of EBV-infected B cells, ultimately leading to PTLD lesions [5]. Polymorphic, EBV negative, and T-cell types of PCNS-PTLD have also been reported [4,19].

Polymerase chain reaction to detect EBV DNA in the peripheral blood and CSF has been unreliable. Many case reports describe negative EBV in peripheral blood and CSF samples despite biopsied lesions resulting positive for EBV [20–22]. Occasionally, EBV will be detected in peripheral samples, as Kesari et al reported a case of CNS-PTLD where EBV was detected in both CSF and peripheral blood [17,23]. Many reports have described cases of PCNS-PTLD initially misdiagnosed as another entity, often attributed to peripheral blood and CSF samples resulting negative for EBV. For example, Reis et al reported a case of PCNS-PTLD that was initially diagnosed as toxoplasmosis [24]. On the contrary, Kweh et al reported a case where presumed PCNS-PTLD was ultimately diagnosed as EBV encephalitis after a biopsy revealed no abnormal B cells [25]. Because of these discrepancies, many clinicians rely on tissue biopsy for final diagnosis [26].

Treatment

Standard treatment protocols for PCNS-PTLD are still being established. The most frequently employed treatment regimen includes reducing immunosuppression and initiating high dose steroids, intravenous, or intrathecal chemotherapy or monoclonal antibody therapy (such as methotrexate and rituximab), and whole-brain radiation [10,17,27–35]. Surgical resection has shown limited efficacy, and medical therapy is considered by many to be the most promising approach. Valavoor et al. reports a case of PCNS-PTLD in which the patient was unable to tolerate chemotherapy or radiation therapy but achieved complete remission with the reduction of immunosuppression alone [36]. Several new EBV-specific cytotoxic T-lymphocyte therapies have also been used with promising results, although additional research into the efficacy is required [37]. The mean survival for CNS-PTLD patients is variable [38], with Phan et al reporting a median survival of 13 weeks following diagnosis (attributed in part to high perioperative mortality), with other case series reporting median survivals of 26 and 47 months [2,6]. Median survival is thought to be dependent on patient age, other post-transplant complications, type of immunosuppression regimen, as well as the type of therapy employed after diagnosis [9].

Imaging features

The imaging modalities most used to evaluate PCNS-PTLD are CT and MRI.

On noncontrast CT imaging, PCNS-PTLD lesions can range from hypoattenuating to hyperattenuating relative to white matter, although most authors describe hypoattenuation (Fig. 1) [6]. PCNS-PTLD may be hemorrhagic; White et al reported 7.8% of lesions demonstrated hemorrhage, and other retrospective reviews have reported hemorrhage in up to 56% of lesions (Fig. 8) [39,9].

On MRI, signal intensity on both T1 and T2 sequences are variable [1,13,40,41] (Fig. 7). T1 hypointense signal is most frequently observed, as seen in 86.7% of PTNC-PTLD patients in our review. Snanoudji et al and Phan et al, in a case series of 25 patients and 8 patients respectively, observed that most lesions were hypointense on T1-weighted sequences [3,6]. A few cases of T1-hyperintense PCNS-PTLD lesions have been reported, likely secondary to intratumoral hemorrhage [6,9] (Fig. 8). PCNS-PTLD T2-weighted signal was hyperintense in 63.2% of patients in our review, and hypointense in 22.8% of patients. T2 weighted images demonstrate perilesional edema with hyperintense signal [1]. The variations between hypointense and hyperintense signal within the PTLD lesion on T2-weighted sequences is related to the degree of hypercellularity and tumor necrosis, respectively [1].

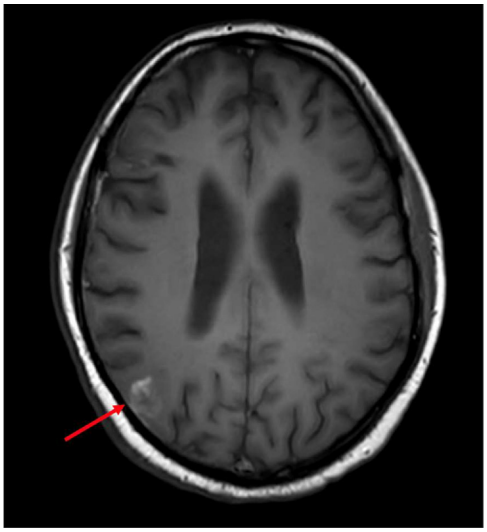

Fig. 8 – An axial section of a T1 weighted MRI of the brain reveals a T1 hyperintense lesion in the right parietal lobe (red arrow).

In our review, 66% of patients had multifocal intracranial disease. PCNS-PTLD is reported by other authors as multifocal in 61% to 88% of cases [1]. Lesions are most commonly supratentorial, with a predilection for lobar, basal ganglia, and periventricular regions [2,6]. One study of 37 patients reported 40.5% of lesions in lobar regions, 29.7% in periventricular regions, and 8% in the basal ganglia [9]. Imafuku et al and Nelson et al reported a case of PCNS-PTLD with lesions in the cerebellopontine and pontomedullary angle, respectively [11,12]. Nishiyama et al reported a rare case of cauda equina CNS-PTLD [42]. Lesions contacting the meningeal and ependymal surfaces have also been reported [2,3,43]. Moscato et al reported a rare case of leptomeningeal predominant PCNS-PTLD lesions [13].

On postgadolinium T1 weighted imaging, variable enhancement patterns of PCNS-PTLD lesions have been reported. Most commonly, lesions demonstrate ring enhancement, thought to be related to central necrosis or hemorrhage [1,6,10–12,24,31,38,44–48]. Our review revealed 59.5% of PCNS-PTLD patients had lesions with ring enhancement. In a series of 25 cases by Snanoudj et al., 87% of lesions demonstrated ring enhancement [6] (Fig. 9). Other reported enhancement patterns include heterogenous and solid/homogenous enhancement [9,39,49]. The enhancement pattern has also been linked to lesion size. Brennan et al reported ring enhancement was observed more frequently in larger PCNS-PTLD lesions, and homogenous enhancement in smaller lesions [43] (Fig. 10). Some case reports have described nonenhancing lesions, and in a review by White et al., 7.8% of PCNS PTLD lesions did not enhance [1,39,44]. Our review recorded 1.2% of patients had PCNS-PTLD lesions without enhancement. Leptomeningeal enhancement in cases of PCNS-PTLD has been reported rarely, often in cases with concomitant lesions contacting the ependymal surface [3,43].

Susceptibility weighted imaging may be useful in the evaluation of PCNS-PTLD lesions, and a peripheral pattern of punctate intratumoral susceptibility signal (ITSS) has been described [1,50] (Fig. 13). Evidence of hemorrhage or hemosiderin staining has been reported in PCNS-PTLD. Lake et al. reported hemorrhage in 56% of lesions [9]. However, in a review of 51 PCNS-PTLD lesions, White et al found only four hemorrhagic lesions [39]. Further, in a retrospective review of six CNS-PTLD patients, Ginat et al reports that all lesions contained foci of ITSS [50]. ITSS within intracranial lesions is thought to be the result of tumoral microhemorrhage, necrosis, and angiogenesis. A few cases of significant hemorrhage causing acute neurological symptoms, attributed to PCNS-PTLD, have been reported [20,51]. Hemorrhage and necrosis are known to increase following treatment, and increased ITSS is expected (Fig. 12). Intracerebral hemorrhage after biopsy is a known occurrence [3].

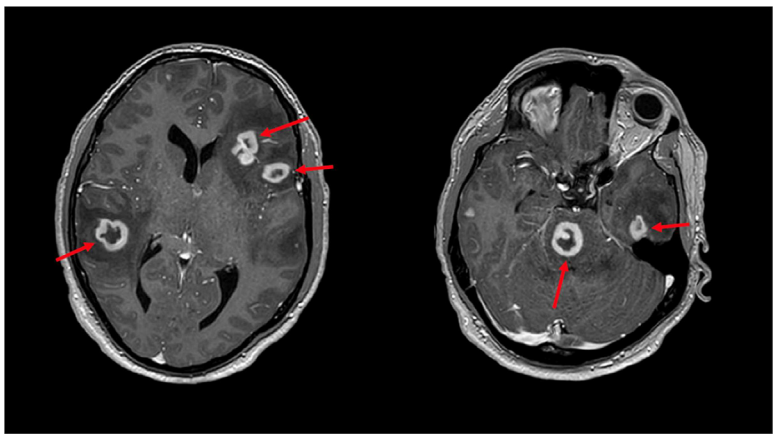

Fig. 9 – Axial sections of a T1 weighted post-gadolinium MRI of the brain reveal numerous intracranial lesions, demonstrating ring enhancement (red arrows).

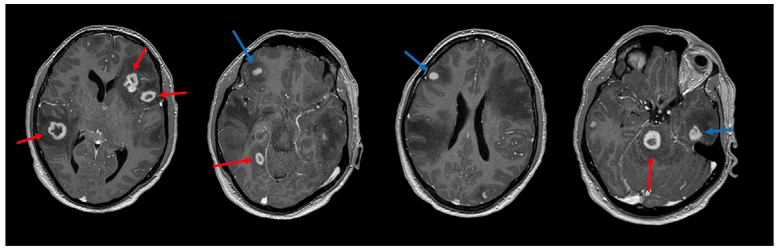

Fig. 10 – Axial sections of a T1 weighted post-gadolinium MRI of the brain reveal numerous enhancing lesions; the larger lesions demonstrate ring enhancement (red arrows), while the smaller lesions demonstrate more homogenous enhancement (blue arrows).

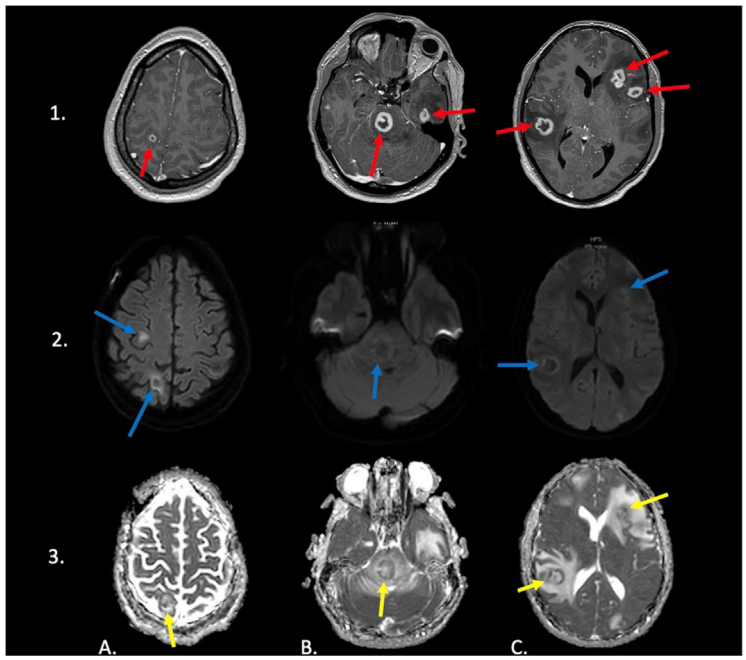

Fig. 11 – Up to 37% of PCNS-PTLD lesions demonstrate restricted diffusion within the solid components of the lesion [1]. Figure 11 shows axial sections of an IV contrast enhanced brain MRI. Row 1 shows axial sections of a T1 weighted post-gadolinium sequence, with enhancing lesions (red arrows). Row 2 shows axial sections of a DWI b1000 image, with high signal corresponding to some of the solid, enhancing components of the lesions shown in column 1 (blue arrows). Row 3 shows the corresponding ADC sequences, with low signal corresponding to some of the enhancing components, referring to lesions demonstrating true restricted diffusion (yellow arrows).

Advanced imaging

The diffusion characteristics of CNS-PTLD lesions can vary [13,20,38,40]. Solid components restrict diffusion likely due to hypercellularity, and necrotic lesions often restrict diffusion within solid areas at the periphery of the tumor [1]. A study by White et al found 37% of all PCNS-PTLD lesions to be diffusion restricting, with a relative mean apparent diffusion coefficient (rADC) of 0.87 +/- 0.32 (standard deviation) [39] (Fig. 11). Similarly, Ginat et al reports a mean ADC value of 0.89 +/- 0.082 (standard deviation) in CNS-PTLD lesions [50]. In our systematic review, the DWI characteristics were reported for 11 patients; of these, 9 patients had lesions demonstrating restricted diffusion.

The use of magnetic resonance spectroscopy to characterize CNS-PTLD is a relatively recent development. Most authors report elevated lactate, lipid, and choline peaks, and decreased N-acetylaspartate [1,24,40,52]. An increased Choline/Creatine ratio and decreased *N*-acetylaspartate/choline ratio has also been reported [1].

There is limited data on the use of perfusion MR, or Dynamic Contrast Enhancement (DCE), in the evaluation of CNS-PTLD. In a review of 23 PCNS-PTLD cases, none of the lesions demonstrated elevated relative cerebral blood flow (rCBF) on perfusion imaging [39]. Reis et al. reports one case of PCNS-PTLD with elevated rCBF within the tumor [24]. Perfusion imaging is useful in identifying disease progression or disease recurrence for intracranial processes such as glial tumors or

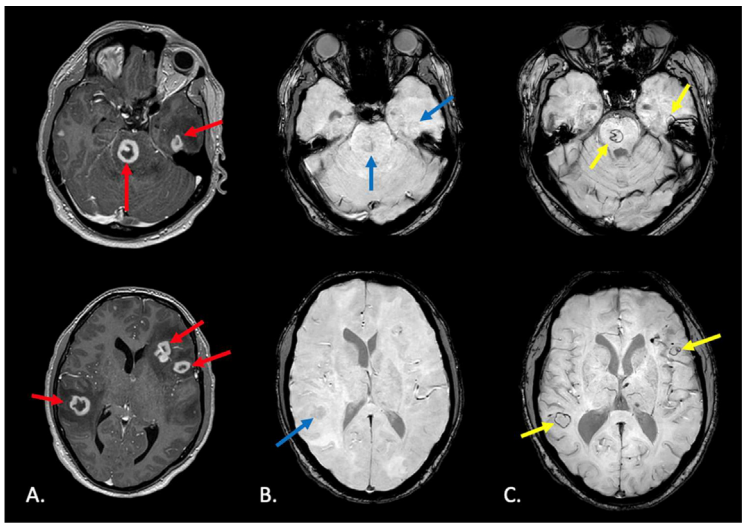

Fig. 12 – Column A. shows axial sections of a T1 weighted post-gadolinium MRI of the brain, revealing numerous enhancing PCNS-PTLD lesions, pre-treatment (red arrows). Column B. shows corresponding axial sections of a gradient echo MRI of the brain, revealing minimal punctate intratumoral susceptibility signal (ITSS) predominately within the brainstem lesion, pre-treatment (blue arrows). Column C. shows corresponding axial sections of a gradient echo MRI of the brain, revealing a peripheral pattern of intratumoral susceptibility signal (ITSS), post-treatment (yellow arrows).

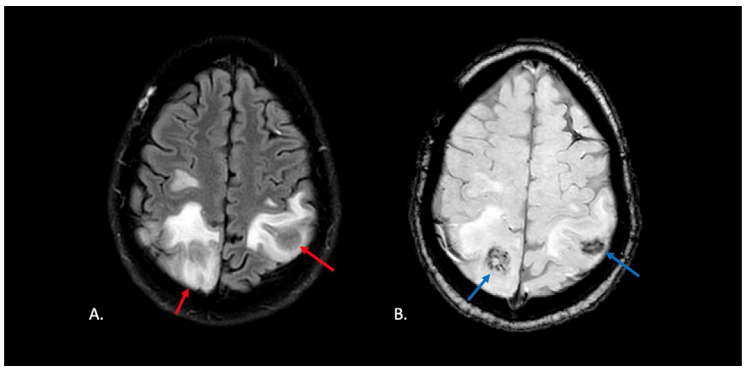

Fig. 13 – Column A. shows an axial section of a T2 FLAIR sequence Brain MRI, demonstrating intracranial PCNS-PTLD lesions (red arrows). Column B. shows a corresponding axial sections of a gradient echo sequence of a brain MRI; the blue arrows depict the peripheral pattern of punctate intratumoral susceptibility signal.

intracranial metastases, and may be applicable to PCNS-PTLD pending further studies [1,39].

Fluorodeoxyglucose (FDG) PET-CT has been used in the evaluation of CNS-PTLD. The high physiologic uptake of FDG in the brain can make detecting intracranial PTLD lesions challenging, and some consider FDG PET-CT more useful in the evaluation of extracranial disease [1]. Despite this limitation, authors have reported intracranial CNS-PTLD lesions that demonstrate elevated FDG uptake relative to surrounding brain parenchyma (Fig. 14) [48,53]. We gathered FDG PET-CT data from 5 patients in our review, and all 5 patients had PCNS-PTLD lesions with focal radiotracer avidity. Additionally, an elevated SUV within an intracranial lesion on PET-CT can help differentiate between residual tumor and necrosis [39]. Patients that are at risk for developing CNS-PTLD are also at risk for intracranial infection, such as cerebral toxoplasmosis [54]. FDG PET-CT will demonstrate FDG avid lesions with infectious/inflammatory etiologies, which is an important consideration when evaluating for CNS-PTLD [1].

From our review, functional MRI (fMRI) techniques and diffusion tensor imaging (DTI) have not been documented in PCNS-PTLD patients. fMRI has been studied in glial tumors, and has been particularly useful in preoperative surgical planning in cases involving eloquent areas [55]. DTI generates useful white matter tractography images, also of particular use in surgical planning [55]. These techniques would be valuable when examining CNS-PTLD lesions and planning biopsies and treatment.

Differential considerations

Primary differential considerations when evaluating for PCNS-PTLD include metastases, PCNS lymphoma, glial tumors, and intracranial abscesses [1].

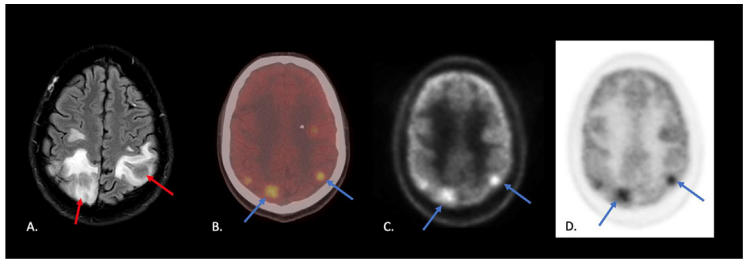

Fig. 14 – Column A is an axial section of a T2 FLAIR MRI of the brain, showing PCNS-PTLD lesions in the bilateral parietal lobes (red arrows) with significant surrounding edema. Columns B, C, and D show the corresponding FDG PET-CT axial sections, demonstrating focal FDG avidity within the intracranial lesions (Blue arrows).

Metastatic disease

Metastatic disease is hypoattenuating to isoattenuating on non-IV contrast enhanced CT, and usually demonstrates nodular or ring enhancement on contrast enhanced exams [39]. Hemorrhagic metastases and metastatic melanoma are hyperattenuating on CT. MR usually shows iso- or hypointense T1 signal and hyperintense T2 signal. Hemorrhagic metastases and metastatic melanoma demonstrate T1 hyperintense signal and ITSS. Metastases tend to be multifocal [39]. Involvement of the gray-white matter junction is seen in up to 49% of metastatic lesions, and vascular border zones are another common location [39]. DWI usually demonstrates facilitated diffusion, with elevated ADC values [39]. Metastases usually demonstrate high rCBV on perfusion imaging [1,39]. MR spectroscopy shows decreased N-acetylaspartate, an elevated choline/creatine ratio, and elevated lipid and lactate peaks [1].

One retrospective review of 10 patients with PCNS-PTLD and 25 patients with intracranial metastases found that deep gray matter and periventricular lesions are more frequently found in PCNS-PTLD [39]. Hemorrhage is more common in metastatic disease, as White et al reported 56% of metastases demonstrated hemorrhage, greater than expected for CNS-PTLD lesions [39]. PCNS-PTLD is more likely to restrict diffusion when compared with metastases.

Primary CNS lymphoma

Primary CNS lymphoma (PCNS Lymphoma) is commonly hyperdense on CT and demonstrates homogenous enhancement [1]. On MR, most PCNS lymphoma is T1 hypointense and T2 isointense to hyperintense, and typically demonstrates homogenous enhancement with well-defined margins [1]. Eichler et al described a linear enhancement pattern at the margins of a lesion, tracking along the Virchow-Robin perivascular spaces, which is highly specific for PCNS Lymphoma [56]. PCNS Lymphoma is unifocal in up to 70% of immunocompetent patients, whereas patients with pre-existing immunocompromise commonly have multifocal disease. PCNS Lymphoma involves the corpus callosum in up to 12% of cases [1,56]. Like CNS-PTLD, periventricular and the deep gray nuclei involvement is common [1]. Leptomeningeal involvement of intracranial disease is common [56]. In immunocompromised patients, PCNS lymphoma may be more heterogeneous and centrally necrotic [1,50,57]. Spectroscopy can show high lipid and/or lactate peaks, increased choline/creatine ratio, and decreased N-acetylaspartate [1]. On perfusion imaging, rCBV values significantly lower than high-grade gliomas, and the signal recovery of the perfusion curve is significantly higher than high-grade gliomas [1].

A few imaging characteristics may help differentiate PCNS Lymphoma from CNS-PTLD. Hemorrhage and calcification are rare in PCNS Lymphoma prior to treatment, and the lack of ITSS signal changes may help to differentiate PCNS Lymphoma from PCNS-PTLD [1,50]. PCNS Lymphoma most commonly demonstrates more marked restricted diffusion, and the ADC values are typically lower and more homogenous than in PCNS-PTLD [1,50].

Glial tumors

Glial tumors share several imaging features with CNS-PTLD. The 2021 World Health Organization (WHO) classification of brain tumors established new terminology categorizing glial tumors. Adult-type diffuse gliomas are IDH-mutant astrocytoma, IDH-mutant oligodendroglioma and IDH-wildtype astrocytoma or glioblastoma [58]. IDH-mutant diffuse astrocytomas are described as CNS WHO grades 2-4 neoplasms, and the terms IDH-mutant "anaplastic astrocytoma" and "glioblastoma" are no longer used [58]. The typical CNS WHO grade 2 IDH-mutant diffuse astrocytoma is a homogenous, T2 hyperintense, circumscribed supratentorial mass, often in the frontal or temporal lobes without calcification or enhancement [58]. The T2-FLAIR mismatch sign, characterized by T2 homogenous hyperintense signal with corresponding hypointense signal throughout most of the lesion on FLAIR (except for a peripheral rim of hyperintense signal), is highly specific for IDH-mutant diffuse astrocytoma [58]. Imaging features of CNS WHO grade 3 IDH-mutant astrocytomas may be indistinguishable from CNS WHO grade 2, although grade 3 astrocytomas are more likely to have T2 heterogeneity and enhancement, and an elevated maximum rCBV [58].

If an IDH-mutant diffuse astrocytoma exhibits CDKN2A/B homozygous deletion, it is a CNS WHO grade 4 neoplasm [58]. CNS WHO grade 4 IDH-wildtype diffuse astrocytoma is categorized as a glioblastoma (previously known as glioblastoma

multiforme) if the tumor exhibits microvascular proliferation or necrosis, TERT promotor mutation, EGFR gene amplification, or +7/-10 chromosome copy number changes [58]. CT demonstrates an iso- to hyperattenuating mass with irregular margins, with occasional central necrosis. IDH-wildtype glioblastoma is typically T1 hypo-to isointense and T2 hyperintense. Enhancement is usually peripheral with irregular nodular components surrounding areas of necrosis [1]. Hypercellular components of the tumor demonstrate restricted diffusion, with low ADC values [59]. IDH-wildtype glioblastoma is typically supratentorial and frequently involves the corpus callosum [1]. ITSS hypointense signal is often observed and may represent microhemorrhages or calcification, and massive hemorrhage has been reported [1]. MR spectroscopy usually demonstrates elevated lipids and/or lactate peaks, and low N-acetylaspartate/choline ratios [1]. Solid components of the tumor demonstrate elevated rCBV [1].

PCNS-PTLD is more likely to be multifocal than glial tumors. Glial tumors usually present as a solitary lesion but can be multifocal up to 33% of cases [1]. To illustrate the overlap in imaging appearance between diffuse astrocytoma wild type and CNS-PTLD, Tanaka et al reported a case of CNS-PTLD that presented as a single, enhancing lesion in the corpus callosum and was initially misdiagnosed as grade IV astrocytoma [49].

Intracranial abscesses

Intracranial abscesses are usually hypoattenuating on CT, hypointense on T1 weighted images and hyperintense on T2 weighted images, with well-defined, thin ring enhancement [1]. A T2 hypointense rim has been described, and susceptibility weighted imaging frequently shows a thin rim of peripheral hypointensity (dual-rim sign) in pyogenic abscesses [39]. Luthra et al reported smooth borders in 60.4% of cases and lobulated borders in 39.6% of cases [60]. Intracranial abscesses are most frequently pyogenic, tubercular, or fungal. Pyogenic abscesses of hematogenous origin are usually solitary and located at the gray-white matter junction, though daughter abscesses often arise along the medial wall of the parent abscess [60].The most common bacterial etiology is streptococcus, and less common etiologies include toxoplasmosis, aspergillus, nocardia, listeria, tuberculosis, and cryptococcus [1,13]. Abscesses tend to restrict diffusion centrally [1]. MR spectroscopy demonstrates elevated amino acids, a useful identifier [1]. Toxoplasmosis shows increased lactate and lipids and reduced choline, creatine, and N-acetylaspartate [1]. On perfusion weighted imaging, abscesses typically have mildly elevated rCBV.

Intracranial abscesses are more commonly unifocal when compared with CNS-PTLD, and CNS-PTLD typically exhibits thicker and more irregular rim enhancement [1]. Although both entities restrict diffusion centrally, the central cavity of an abscess has significantly lower ADC values compared to CNS-PTLD [1]. The necrotic cavities of tumors usually demonstrate high ADC values [1]. ITSS changes in abscesses often produce a peripheral rim of hypointensity or central hypointensity, as opposed to the punctate hypointensities more frequently seen in pretreatment PCNS-PTLD [1].

Conclusion

PCNS-PTLD is a rare diagnosis, occurring primarily in patients following either SOTs or HSCTs. Biopsied lesions tend to be monomorphic DLBCL, and the pathogenesis is commonly associated with EBV infection [3]. PCNS-PTLD remains a diagnostic challenge due to its rare incidence. Many intracranial pathologies can resemble the imaging appearance of PCNS-PTLD, including primary CNS lymphoma, glial tumors, metastatic disease, and intracranial abscesses. From our 97 sources, PCNS-PTLD lesions are typically multifocal, ring-enhancing and diffusion-restricting. PCNS-PTLD lesions typically demonstrate focal FDG avidity. Despite advancement in medical imaging, PCNS-PTLD remains a diagnostic challenge due to its rare incidence. Limited data is available on advanced imaging techniques that may help further differentiate PCNS-PTLD, and further research is needed on perfusion imaging, functional MRI, and diffusion tensor imaging to completely characterize PCNS-PTLD. With the nonspecific clinical presentation and potentially devastated neurologic effects, the radiologist should remember to consider PCNS-PTLD in the appropriate patient population to expedite time to treatment.

Patient consent

The patient has provided consent for clinical information relating to their case, including diagnostic imaging, to be reported in a neuroradiology journal, such as *Radiology Case Reports*.

The patient understands that their identity will be concealed, so that their name, initials, identifying features, or any protected health information such as identification number, billing information, address, etc. will not be published. In giving this consent, the patient understands that that de-identified medical diagnostic radiology imaging will be included in the published material.

The patient has read this statement, and has provided a signed agreement.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.radcr.2024.02.030.

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