



Polymorphous Low-Grade Neuroepithelial Tumor of the Young (PLNTY): Scoping Review of Case Reports and Case Series

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Abstract

Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) is considered one of the low-grade neuroepithelial tumors, as per the World Health Organization 2021 classification of brain tumors. First described in 2016, these morphologically variable tumors are characterized by oligodendroglioma-like cellular components, infiltrative growth patterns, and cluster of differentiation 34 immunopositivity. A literature search of the PubMed/MEDLINE, SCOPUS, ScienceDirect, and COCHRANE databases (from inception to 20th June 2022) was carried out to identify relevant studies. To identify additional studies, we performed a recursive search of the bibliographies of the selected articles and published systematic reviews on this topic. The search yielded a total of 64 results. After removing duplicates, 26 articles were eligible for the review. The diagnostic criteria for these glioneuronal variants, representing a broad neuropathological spectrum, are not distinct and hence impede proper diagnosis and prognosis. Frequent genetic abnormalities involving mitogen-activated protein kinase pathway constituents, such as B-Raf proto-oncogene or fibroblast growth receptor 2/3, are harbored by PLNTYs. Recent advances in molecular diagnostics have resulted in more accurate tumor classification systems, based on gene expression profiles and DNA methylation patterns. Gross total resection seems curative, with a low recurrence rate. Malignant transformation is rare; however, adjuvant radiation therapy and chemotherapy may be beneficial in selected cases.

Keywords

- ▶ polymorphous low-grade neuroepithelial tumor of the young (PLNTY)
- ▶ scoping review
- ▶ low-grade neuroepithelial tumor
- ▶ calcification
- ▶ pseudorosetting

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Introduction

Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) was introduced in the World Health Organization (WHO) 2021 classification of central nervous system tumors as a diffuse low-grade glioma variety. Huse et al first described this novel entity in 10 patients who fulfilled the criteria for PLNTY.¹ Approximately 55 such cases have since then been reported.² Since Huse et al's pioneering work, every additional case has contributed valuable information to understanding this rare disease entity. These morphologically variable tumors are characterized by oligodendroglioma-like cellular components, infiltrative growth pattern, and a cluster of differentiation 34 (CD34) immunopositivity.¹ Because the topic of PLNTY has not been adequately reviewed and is complex and heterogeneous with a variable presentation, we conducted a scoping review to summarize the literature.^{3,4} This scoping review of case reports and case series was conducted to search all relevant cases of PLNTY in the literature from the selected electronic databases, and to understand the demographics, clinical presentations, imaging findings, management offered, and the overall outcome of this newly recognized entity. This review aimed to map the existing literature regarding patient characteristics, disease characteristics, and newer understanding. The review also aims to identify the literature gaps to guide future research.

Methods

The study design was a scoping review of case reports and series. We conducted the scoping review following the Arksey O Mailley guidance and definition of scoping reviews comprising six iterative stages and the Joanna Briggs Institute manual for scoping reviews.^{3,5} Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA ScR) guidelines were adhered to in synthesizing and reporting this scoping review.⁶

Stage I: Identifying the Research Question—Purpose

Relevant research questions for this review were: What are the clinical and radiological characteristics of the PLNTY? What are the histopathological characteristics of PLNTY? What are the immunopathological, molecular and genetic alterations in PLNTY? What is the outcome of PLNTY patients?

Stage II: Identifying Relevant Data Sources and Searches

The literature search included PubMed/MEDLINE, SCOPUS, Science Direct, and COCHRANE databases (till 20th June 2022). To identify additional studies, we performed a

recursive search of the bibliographies of the selected articles and published systematic reviews on this topic. Details of the search strategy and keywords are listed in ►Table 1. For this review, case reports, case series, and letter to editors were considered as relevant studies. The case should include the patients' demographics, clinical presentation, radiology, management details, histopathology, and outcome.

Stage III: Study Selection

We included studies that reported histopathologically confirmed PLNTY cases. Reviews and commentaries were excluded. The abstracts presented in conferences were searched in different search engines to identify if they were published as article. If the conference presentations were not published or did not have sufficient details, the same were excluded from the review. There were no restrictions applied on the language and year of publication.

Stage IV: Data Extraction

Two reviewers (VPM and AA) screened the titles and abstracts of all articles, the full text of the selected articles was reviewed, and any discrepancies between the two reviewers were evaluated and sorted by a third independent reviewer (RM). Detailed data were collected in a predesigned proforma. The details included study authors, year, type of publication, country of the corresponding author, number of cases, demographic details (gender and age), clinical presentation, imaging findings, offered management, histopathological details, and overall outcome of the patient (including follow-up clinical and imaging characteristics or any malignant transformation)

Stage V: Summarizing, Reporting and Collating the Results

We summarized and characterized the patient demographics, clinic-radiological characteristics, histopathology, immunopathology, and outcome in patients with PLNTY.

Results

The search yielded a total of 64 results. After removing duplicates, 27 articles were found to be eligible for inclusion in the review.^{1,2,7-30} One article was excluded as there was a publication available in English by the same authors with similar reported findings.³¹ The details of the study selection process in the form of a flowchart are shown in ►Fig. 1. This review consists of a total of 80 reported PLNTY patients. The mean age of the patients was 18.2 years (range: 4–57 years). There were 34 males and 46 females. The most common

Table 1 Details of search terms and strategy

| | |
|---------------|---|
| ScienceDirect | Title, abstract, keywords: polymorphous low-grade neuroepithelial tumor of the young |
| SCOPUS | Title, abstract, keywords: polymorphous low-grade neuroepithelial tumor of the young |
| PubMed | "Polymorphous" [All Fields] AND "Low"[All Fields] AND "grade"[All Fields] AND "Neuroepithelial"[All Fields] AND "tumor"[All Fields] AND "young"[All Fields] |
| COCHRANE | Title, abstract, keywords: polymorphous low-grade neuroepithelial tumor of the young |

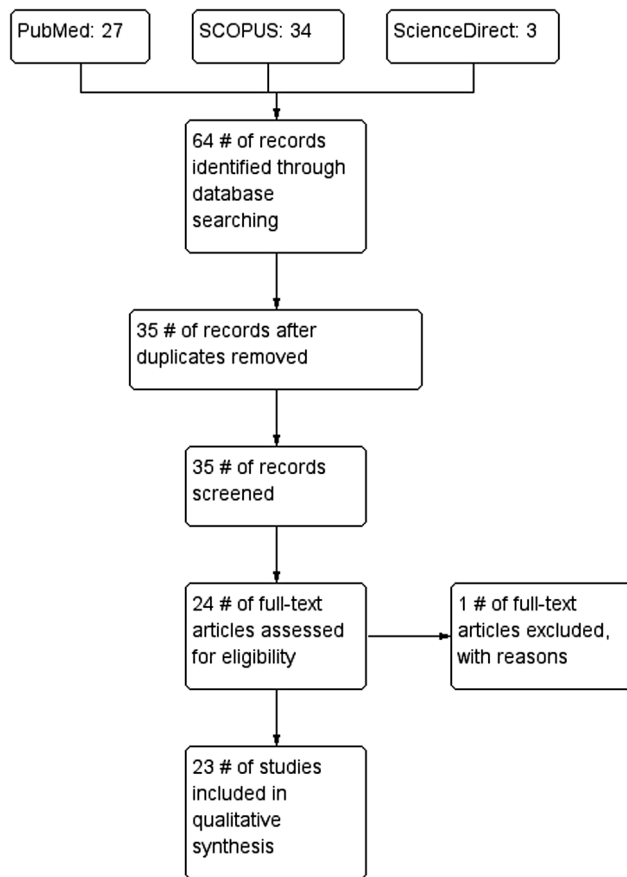


Fig. 1 Study flow diagram.

presenting symptom was seizures (in 59/80 patients) and nonseizure symptoms (in 27/80 patients). Presenting symptom of seizure was not reported in four patients. The non-seizure symptoms consist of headache, depression/manic depressive psychosis (esp., suicidal ideations), and visual disturbance. The lesion was located in temporal lobe in 65% of cases (52/28), followed by parietal lobe 12.5% (10/80), frontal 8.7% (7/80), and occipital 5% (4/80) lobes. There were two reports of intraventricular lesion, one in caudate nucleus, one in insula, one in temporoparietal, one in temporooccipital location, and not reported in one patient. The characteristics of the included studies is listed in ►Table 2. Excluded studies with reason for exclusion is mentioned in ►Table 3.

Discussion

Low-grade neuroepithelial tumors (LGNTs) are a diverse group of epileptogenic lesions that are encountered in children and young adults.³² LGNT exhibits a varying spectrum of histological features and glial or glioneuronal differentiation. The LGNT subtypes include diffuse astrocytomas, pilocytic astrocytomas, gangliogliomas, pleomorphic xanthoastrocytomas (PXA), dysembryoplastic neuroepithelial tumors, angiocentric gliomas, and oligodendrogliomas.²⁴ The diagnostic criteria for these LGNTs (especially glioneuronal variants), which represent a broad neuropathological spectrum, are not distinct, and hence impede proper diagnosis and prognosis. In contrast,

recent advances in molecular diagnostics have resulted in more accurate tumor classification systems based on gene expression profiles and DNA methylation patterns.

Patients' Characteristics

PLNTY is the recently described distinct type of LGNT and as the name suggest, it is seen in children and young adults. As per the literature, the median age described for PLNTY is 16 years. In this review of cases, the mean age of PLNTY patients was 18.2 years. PLNTY is reported more in females. In this review, we found 42.5% (34/80) males and 57.5% (46/80) females. About 73.7% patients presented with seizures followed by headache.

As consistent with most of the case series, the most common location was temporal in 65% of patients. However, there were reports of tumor in intraventricular location, caudate nucleus, and insula.

Clinicoradiological Characteristics

PLNTYs are derived from the cortex layer and appear as a solid or solid cystic mass with an unclear boundary with normal brain tissue. It is most commonly located in the temporal lobe, followed by occipital and frontal lobes. Tumors in most of the cases was well-circumscribed, cortical or subcortical, had calcifications and peripheral cystic components with minimal mass effect. Radiologically, PLNTYs are T1 iso-or-hyperintense and T2 hyperintense with slight or no contrast enhancement.^{11,33} Though the age predilection for PLNTYs has been reported to be 2 to 57 years, most cases are under 30 years of age.^{1,2,7-27} It has an equal sex preponderance. Among the 49 cases accounted for in ►Table 1, only five cases (including the index case) had nonepileptic clinical presentations, such as headache, imbalance, and behavioral abnormalities.^{1,9,24} These nonepileptic presentations are predominantly associated with extratemporal lesions, which account for about one-third of the cases.^{1,24} Kurokawa et al described the radiological features of PLNTY.²¹ They found PLNTY to be exclusively supratentorial tumors, with characteristic radiological features, such as cortical or subcortical masses (95.8%) in the temporal lobe (66.7%), calcification (83.3%), circumscribed margins (72.7%), solid cystic components (66.6%), and T2-weighted imaging hyperintensity (50.0%). The “trans-mantle-like” T2 /FLAIR (fluid-attenuated inversion recover) hyperintense signal was observed in 47.1% of the patients and was reported to be associated with a longer seizure duration (24 vs. 5 months) and cortical dysplasia.

Histopathology

Majority of the long-term epilepsy-associated brain tumors (LEAT) are low grade (WHO grade I or WHO grade II) with many morphological variants.¹¹ The pathological features of PLNTY include a polymorphous appearance, presence of cellular components, infiltrative growth pattern, and intense CD34 positivity. The addition of new term PLNTY in 2016 WHO update of brain tumor classification represents a molecularly unique category of LGNT representing a significant portion of oligodendroglioma like tumor noted in

Table 2 Characteristics of included studies

| Author | Year | Country | Patients, n | Age in years | Gender, n | Symptoms, n | Tumour location | Radiological characteristics | Outcome at last follow-up (surgical outcome) | Reported mutations |
|----------------------------------|------|--------------|-------------|--------------------------|----------------------|---------------------------------|---|---|--|---|
| Huse et al ¹ | 2017 | USA | 10 | 17.5 (4–32) ^a | Male: 4 Female: 6 | Epileptic: 8 Nonepileptic: 2 | Temporal: 7 Frontal: 1 Occipital: 2 | Calcified, cystic, enhancing lesions | Stable: 8 (GTR 7, STR: 1) Recurrence: 1 ^c (GTR) NR: 1 | BRAF V600E: 3 FGFR2: 3 ^c FGFR3: 1 NR: 3 (Temporal 2, occipital 1) |
| Bitar et al ⁹ | 2018 | USA | 1 | 31 | Male | Epileptic | Temporal | NR | Stable (GTR) | BRAF V600E |
| Riva et al ²⁴ | 2018 | Italy | 1 | 57 | Male | Nonepileptic | Frontal | Cystic lesion | Stable (NR) | FGFR3 |
| Zhang and Sassooun ²⁸ | 2018 | China | 2 | 12 | Female | Epileptic | Temporal | Heavily calcified, solid, cystic | Stable (GTR) | GFAP +, CD34 +, IDH-, BRAF 600VE-, P53-ATRX retained, 1p-19Q codeletion absent, FGFR2 mutation + |
| Gupta et al ¹⁵ | 2019 | USA | 1 | 12 | Female | Epileptic | Parietal | Heavy calcifications | Stable (GTR) | GFAP +, CD34 +, IDH-, BRAF 600VE-, P53-ATRX retained, 1p-19Q codeletion absent, FGFR2 mutation absent |
| Johnson et al ¹⁸ | 2019 | USA | 9 | 16 (5–34) ^a | Male: 2 Female: 7 | NR | Temporal: 6 Parietal: 2 3 rd ventricular: 1 | Circumscribed lesion | Stable (GTR) | BRAF V600E |
| Kamalboor et al ¹⁹ | 2019 | Saudi Arabia | 1 | 23 | Female | Epileptic | Temporal | NR | NR | BRAF V600E: 4 BRAF Fusion: 1 FGFR2: 3 None.: 1 |
| Sumdani et al ²⁵ | 2019 | USA | 1 | 19 | Male | Epileptic | Parietal | Calcified, cystic, circumscribed, enhancing lesions | NR | NR |
| Surrey et al ²⁶ | 2019 | USA | 6 | 12 (7–16) ^a | Male: 4 Female: 2 | Epileptic: 6 | Temporal: 3 Parietal: 1 Temporo-parietal: 1 Temporo-occipital: 1 | Calcified, circumscribed lesion | Stable (NR) | BRAF V600E |
| Kamalboor et al ¹⁹ | 2019 | Saudi Arabia | 1 | 23 | Female | Epileptic | Temporal | NR | GTR | NR |
| Benson et al ⁸ | 2020 | USA | 1 | 44 | Female | Nonepileptic | Temporal | Calcified lesion | Stable (GTR) | BRAF V600E |

(Continued)

Table 2 (Continued)

| Author | Year | Country | Patients, n | Age in years | Gender, n | Symptoms, n | Tumour location | Radiological characteristics | Outcome at last follow-up (surgical outcome) | Reported mutations |
|------------------------------|------|---------|-------------|---------------------------|----------------------|--------------|-----------------------------|--|---|---|
| Chen et al ¹¹ | 2020 | China | 3 | 15 (14–16) ^a | Male: 2 Female: 1 | Epileptic: 3 | Temporal: 2 Frontal: 1 | Calcified, circumscribed lesions cystic lesion (frontal lesion) | Stable: 3 (GTR 3) | BRAF V600E: 1 FGFR3: 1 NR: 1 (Frontal) |
| Lelotte et al ²² | 2020 | Belgium | 1 | 33 | Female | Epileptic | Temporal | Cystic, circumscribed, cortical lesion | NR | BRAF V600E |
| Tateishi et al ²⁷ | 2020 | Japan | 1 | 14 | Male | Epileptic | Temporal | Circumscribed, calcified, cystic lesion | Stable (GTR) | BRAF V600E |
| Gilani et al ²⁹ | 2020 | USA | 2 | 6 | Female | NA | Insula | Ill-defined solid cystic mass lesion | Stable (GTR), no residual lesion at 13 months follow-up | FGFR2:K1AA1598 |
| | | | | 11 | Female | NA | Temporal | Heterogenous mass with numerous small cystic components | No recurrence at 9 months follow-up | FGFR3:TACC3 |
| Bale et al ⁷ | 2021 | USA | 1 | 15 | Female | Epileptic | Temporal | Circumscribed, calcified, cystic, enhancing lesion | Recurrence (GTR); additional NTR + adjuvant radiation & chemotherapy given. | FGFR3 |
| Broggi et al ¹⁰ | 2021 | Italy | 1 | 50 | Female | Epileptic | Temporal | Calcified lesion | NR (GTR) | BRAF V600E: absent FGFR2/3: NR |
| Danyeli et al ¹² | 2021 | Turkey | 1 | 33 | Female | Epileptic | Parietal | Circumscribed, noncystic, focal enhancing | Stable (GTR) | BRAF and FGFR: absent EGFR mutation (probably not driver mutation) |
| Ge et al ¹³ | 2021 | China | 2 | 19.5 (14–25) ^a | Female: 2 | Epileptic: 2 | Temporal: 1 Occipital: 1 | Mixed-signal cortical lesions | Stable: 2 (GTR 2) | BRAF V600E: 1 NR: 1 |
| Gupta et al ¹⁴ | 2021 | USA | 5 | 17.4 (11–38) ^a | Male: 3 Female: 2 | Epileptic: 5 | Temporal: 4 Frontal: 1 | NR | Stable: 5 (GTR 5) | BRAF V600E: NR FGFR2: 5 |

Table 2 (Continued)

| Author | Year | Country | Patients, n | Age in years | Gender, n | Symptoms, n | Tumour location | Radiological characteristics | Outcome at last follow-up (surgical outcome) | Reported mutations |
|-------------------------------|------|----------------|-------------|-------------------------|-----------------------|--|---|---|--|---|
| Hendrych et al ¹⁶ | 2021 | Czech Republic | 1 | 27 | Male | Epileptic | Parietal | Noncircumscribed, nonenhancing, calcified | Stable (GTR) | BRAF V600E |
| Ida et al ¹⁷ | 2021 | USA | 13 | 16 (5–52) ^b | Male: 3 Female: 10 | Epileptic: 9 Nonepileptic: 3 NR: 1 | Temporal: 9 Parietal: 3 NR: 1 | Calcification: 10 (out of 11 available radiologies) | Stable: 7 (GTR 6) Outcome data available in 7 cases | BRAF V600E: 6 FGFR2: 5 QKI-NTRK2: 1 KIAA1549-BRAF: 1 |
| Kikuchi et al ²⁰ | 2021 | Japan | 1 | 18 | Male | Epileptic | Temporal | NR | Stable (NR) | NR |
| Fei et al ² | 2022 | Italy | 8 | 8.5 (2–50) ^a | Male: 7 Female: 1 | Epileptic: 8 | Temporal: 4 Frontal: 3 Occipital: 1 | Circumscribed, calcified, cystic lesions | Stable: 8 (GTR 8) | BRAF V600E: 4 NR: 4 |
| Palejwala et al ²³ | 2022 | USA | 1 | 31 | Female | Epileptic | Temporal | Circumscribed, cystic, calcified lesion | Stable (NR) | BRAF V600E |
| Zhao et al ³⁰ | 2022 | China | 5 | 25 (10–39) | Male: 2 Female: 3 | Epileptic: 3 Nonepileptic: 2 | Temporal: 3 Lateral ventricle: 1 Caudate nucleus: 1 | NR | Stable (NR) | BRAF V600E: 2 PAK5-Q337R missense mutation: 1 FGFR2-CTNNA: 1 FGFR2-INA & FGFR2-PPRC1 fusion: 1 |

^aMean (range).

^bMedian (range).

^cRecurrence in FGFR2 tumor; FGFR, fibroblast growth factor receptor; GTR, gross total resection; NR, not reported; NTR, near total resection; STR, subtotal resection.

Table 3 List of excluded articles with reasons

| Sl. no. | Study authors | Year of publication | Title | Journal | Country | Reason for exclusion |
|---------|----------------------------------|---------------------|--|--|---------|---|
| 1. | Ge et al ¹³ | 2020 | Clinicopathological features of polymorphous low-grade neuroepithelial tumor of the young | Chinese Journal of Pathology | China | A similar article in the English language in another journal present |
| 2. | Métais et al ³⁴ | 2022 | Low-grade epilepsy-associated neuroepithelial tumours with a prominent oligodendrogloma-like component: the diagnostic challenges | Neuropathology and Applied Neurobiology | France | PLNTY was not reported separately and did not include the information required for the review |
| 3. | Slocum et al ³⁵ | 2022 | Cerebellar tumor with FGFR2-KIAA1598 fusion and features of polymorphous low-grade neuroepithelial tumor of the young | Journal of Neuropathology and Experimental Neurology | USA | It was a meeting abstract. The abstract did not have the details required for the review, and the full-length abstract could not be retrieved |
| 4. | Cases-Cunillera ³⁶ | 2022 | Heterogeneity and excitability of BRAF(V600E)-induced tumors is determined by Akt/mTOR-signaling state and Trp53-loss | Neuro-oncology | Germany | Animal study |
| 5. | Kurokawa et al ²¹ | 2022 | Neuroradiological features of the polymorphous low-grade neuroepithelial tumor of the young: five new cases with a systematic review of the literature | Pediatric Neuroradiology | USA | Systematic review and details of fresh cases was not provided separately |
| 6. | Golub et al ³⁷ | 2022 | Polymorphous low-grade neuroepithelial tumor of the young with FGFR3-TACC3 fusion mimicking high-grade glioma: case report and series of high-grade correlates | Neuro-oncology | USA | It was a meeting abstract. The abstract did not have the details required for the review, and the full-length abstract could not be retrieved |
| 7. | Vandenhoevel et al ³⁸ | 2022 | A case of polymorphous low-grade neuroepithelial tumor of the young with polysomy of chromosome 1 and 19 lacking BRAF mutation | Pediatric Blood and Cancer | USA | It was a meeting abstract. The abstract did not have the details required for the review, and the full-length abstract could not be retrieved |
| 8. | Majeed et al ³⁹ | 2021 | Polymorphous low-grade neuroepithelial tumor of the young in a 47-year-old man presenting with headache and visual deficits | Journal of Neuropathology and Experimental Neurology | USA | It was a meeting abstract. The abstract did not have the details required for the review, and the full-length abstract could not be retrieved |
| 9. | Sharma et al ⁴⁰ | 2018 | Polymorphous low-grade neuroepithelial tumor of the young: a case report with genomic findings | Journal of Neuropathology and Experimental Neurology | USA | It was a meeting abstract. The abstract did not have the details required for the review, and the full-length abstract could not be retrieved |

Abbreviations: FGFR, fibroblast growth factor receptor; PLNTY, polymorphous low-grade neuroepithelial tumor of the young.

pediatric age group. These tumors behave indolently and gross total resection leads to surgical cure of the patient. The molecular alterations of PLNTY in the form of MAP Kinase pathway activation are potential target for small molecular inhibitors. These lead to options for targeted therapy in patients of PLNTY with supposedly better outcome in the days to come.¹

Calcification and fibrous astrocyte formation were also observed. Tumor mitosis, necrosis, and microvascular proliferation are rare.² This neoplasm is associated with a history of epilepsy in young people, diffuse growth patterns, the frequent presence of components similar to oligodendroglioma, calcification, CD34 immunoreactivity, and genetic abnormalities that activate the mitogen-activated protein kinase (MAPK) pathway.³²

According to Vornetti et al, the expression of CD34 in considerable number of patients with PLNTY harboring B-raf (BRAF) mutation and BRAF wild-type represents a subset of LEATs. Presence of these immunomodulations and mutations lead to appearance of a variety of seizures as well as persistence of seizure for long time.⁴¹ The surgical management in DRE needs attention with regard to the localization of exact seizure discharging foci. Special attention is warranted with regard to DRE cases in contrast to resections for oncological cases because of the modulation in neuronal network and fresh recruitment of neuronal population acts as source of seizures. Hence, electrophysiological identification of seizure foci is mandatory beside clinicoradiological localization during surgical resection of such cases.¹ Although morphologically variable, they are found to have oligodendroglioma-like cellular components, infiltrative growth patterns, and intense CD34 immunopositivity. The DNA methylation signature of PLNTY closely resembled that of gangliogliomas. The cases described in the pilot study demonstrated a predominance in the temporal region, were right-sided, and had cystic components. Histopathological examination showed an infiltrative pattern, intra- and inter-tumor heterogeneity, variation in nuclei, perinuclear halo, and pseudorosetting. Calcification was defined as discrete calcospherules and confluent calcified masses. Imaging studies revealed unifocal regions of FLAIR hyperintensity with increased or mixed signal intensities on T2-weighted images.¹ The 2021 WHO central nervous system-5 (CNS-5) classification incorporated molecular advancements and recognized six new tumor types in LGNTs alone.³² Frequent genetic abnormalities in PLNTY involve components of the MAPK pathway, such as the B-raf proto-oncogene (BRAF) or fibroblast growth receptor 2/3 (FGFR 2/3). Radiologically, these are well-circumscribed lesions with calcified and cystic components that primarily affect the temporal lobe. Clinically, they present with seizures/epilepsy in young adults (aged <30 years).¹

Immunopathological Characteristics

PLNTY's low-grade nature of PLNTY, the presence of infiltrating oligodendrocyte-like cells, and their common association with cortical dysplasia are well established.²³ The exclusive immunopositivity of the PLNTYs solves the diagnostic dilemma of

differentiating these tumors from oligodendroglioma.¹ CD34, a transmembrane phosphoglycoprotein of early neurulation, is not expressed in mature brain cells. The presence of CD34 has been shown to correspond to drug-resistant epilepsy. Markers of glial differentiation (GFAP and Olig2) may be positive in both tumors. Notably, PLNTYs also lack immunopositivity for markers of neuronal differentiation, such as NeuN, which plays a pivotal role in differentiating them from other LGNTs.³⁴ In every case, the final diagnosis should be made only after considering the molecular profile and not on a pure histology basis. Despite their oligodendrogliomatous appearance, they did not show labelling for IDH1 R132H or chromosome 1p / 19q.¹ Consistent expression of CD 34, as seen in the PLNTY, is not found in the adult CNS and is generally foreign to infiltrating the lower grade and neoplasms of the oligodendroglioma group.¹ It has been hypothesized that CD34 expression originates from dysplastic and/or differentiating differently.¹⁰ Extravascular CD 34 positivity is commonly found in large neural or ramifying neuroepithelial cells.¹⁰

Genetic Alterations in PLNTY

DNA methylation signature for PLNTYs, along with frequent genetic abnormalities involving either B-Raf proto-oncogene (BRAF) or FGFR2, FGFR3, has been reported.¹ Identification of FGFR mutations in low-grade histological entities generated enthusiasm for the therapeutic potential and describing histological hallmarks. However, the FGFR genetic alterations are heterogenous concerning age (adult vs. pediatric) and grade of the tumor (low-grade and high-grade). Because of the heterogenous nature of FGFR alterations and its impact on the natural history of LGNTs, it has not yet been incorporated for classification of CNS tumors. Further, the challenge is that many cases reporting LGNTs or PLNTY do not report the genetic alterations present. Genetic changes in PLNTY involve MAP kinase pathways such as BRAF-V600E mutations or FGFR3 transforming acidic coiled coil containing protein 3 (TACC3), FGFR2- KIAA 1598, and FGFR- CTNNA3 fusion.¹⁰ Notably, FGFR fusions are mutually exclusive with BRAF V600E mutations.¹ Ki- 67 labelling index is typically less than 5%.²³

PLNTYs are known to harbor MAPK pathway alterations in the form of demonstrable BRAF or FGFR2/FGFR3 mutations.¹⁷ On the contrary, their typical mimic, oligodendrogliomas, have IDH mutations and 1p/ 19q co-deletions. Consistent with their low-grade classification, PLNTYs have a Ki-67 labelling index typically less than 5%. BRAF V600E mutations are not unique to PLNTYs alone. They also have associations with other LGNTs (like gangliogliomas, and PXAs).¹⁷ Alterations in FGFR2/3, belonging to the transmembrane tyrosine kinase receptor family, have been described with several different fusion partners (such as FGFR3TACC3, FGFR2-KIAA198, FGFR2-CTNNA3). The result of these fusions is an alteration of downstream effectors enhancing activation of the MAPK pathway.¹⁷ Although thought to be benign, one case of malignant transformation has been documented to date by Bale et al.⁷ The case presented by Bale et al demonstrated that a pediatric patient diagnosed with PLNTY with FGFR3- TACC3 fusion had a recurrence within less than

18 months. The recurrent lesion did not express CD 34 and had a high-grade focus similar to WHO grade IV. Associated with an indolent course, seizure control in PLNTY can be achieved with gross-total resection.²³ FGFR3-TACC3 (also described in a few glioblastomas) has been reported from the only PLNTY with malignant transformation.⁷ FGFR-TACC fusion has most of the features of PLNTY; however, the difference is that the FGFR-TACC fusion tends to occur more in elderly and has more invasive nature. Till date, there has been no case reported of PLNTY with FGFR2-CTNNA3 fusion suggesting a high-grade or aggressive tumor. Though FGFR2-CTNNA3 fusion is the signature genetic alteration found in PLNTY, other mutations like BRAF and FGFR3 are also seen in PLNTY cases and therefore, it should not be interpreted that these alternative mutations also suggest indolent and benign nature of these tumors and portend a favorable prognosis.⁴² In Huse et al's original series, three out of seven patients had BRAF 600VE mutation; however, no BRAF fusion was detected. More studies on genetic alterations in PLNTY will enhance the understanding the natural history of these rare tumors. The available literature on PLNTY strongly supports the association of focal cortical dysplasia, especially Focal cortical dysplasia (FCD) type IIIb. This association with FCD is a surrogate marker for increased frequency of seizure disorder in this subset of PLNTY. This is due to the fact that FCD is noticed in the developing brain and may infiltrate in the adjacent neocortex as tumor deposits which acts as source of increased epileptogenicity.^{43,44}

Outcome and Follow-Up

Gross total resection appears to be curative. Only three cases with radiological recurrence have been reported during follow-up periods.^{1,7,26} Adjuvant radiation therapy and chemotherapy were predominantly used in cases of malignant transformation.⁷ Data on seizures in PLNTYs need further elaboration. Fei et al observed that the epileptic zone identification is critical for every case of PLNTY, and an enlarged surgical resection (vs. recommended gross total resection) may provide better postoperative seizure controls.² At present there are very limited literature available regarding suicidal ideations having implications on other general neurological symptoms such as depression and personality changes. Commenting on these symptoms would be too early and we should wait for more convincing data soon.

Strengths and Limitations

The whole process of this scoping evaluation was conducted using exacting and open standards. A research group with knowledge synthesis and scoping review experience conducted the study. The search approach utilized two online search engines, the reference lists of several publications, four electronic bibliographic databases, the websites of pertinent organizations, and the snowball method to ensure a thorough literature search. The main strength is the comprehensive inclusion of articles from different study designs. Articles presenting relevant information even if they were meeting abstracts were included as per the criteria laid in the methodology. All reviewers reviewed and agreed

to the screening and data characterization forms, which were adjusted as necessary before being used. Two impartial reviewers looked at each reference and piece and got together regularly to work out any issues.

Even though we conducted the scoping review with iterative steps and an extensive search of the literature, there remains the possibility of missing an article in grey literature. We included several keywords in our search algorithm, but as PLNTYs is a relatively newer entity, some other words may also exist that have escaped the search strategy. Our search was conducted using only English terms, which introduces publication bias. It is also possible that we might not have captured all the case reports published in other languages, which is one of the limitations of the present review. Furthermore, we did not contact any researchers or experts for additional cases we may have missed.

Arksey and O'Malley's³ definition for scoping reviews was generally valuable for guiding study selection. However, we encountered challenges as many articles did not use the word PLNTY in the title or the abstract. Though PLNTY was present in the title and abstract in most of the included studies, some studies have used the term low-grade dysembryoplastic to indicate PLNTY. Two authors performed unbiased inclusion, screening, and interpretation of the literature in this review. Still, the reviewer bias could not be entirely removed as the individual judgment of the authors on screening, inclusion, characterization, and interpretation could be subjective.

Conclusion

LGNTs are an array of epileptogenic lesions encountered that originate from the cortex layer appearing as a solid or solid cystic mass with an ill-defined boundary with normal brain tissue. PLNTY has emerged as a substantial differential for low-grade glioma and should be considered during the diagnosis. The diagnostic criteria for these glioneuronal variants, representing a broad neuropathological spectrum, are not distinct and hence impede proper diagnosis and prognosis. Recent advances in molecular diagnostics have resulted in more accurate tumor classification systems based on gene expression profiles and DNA methylation patterns. Gross total resection seems curative, with a low recurrence rate (only three cases have been reported). Malignant transformation is rare; however, adjuvant radiation therapy and chemotherapy may need to be treated. All in all, introducing PLNTY as a variant of LGNTs has not changed its overall incidence, but has helped better manage and prognostic this patient cohort.

Note

PLNTY has emerged as one of the differential diagnoses for low-grade glioma. The diagnostic criteria and optimum management are not well defined in view of rarity of the condition. Well-circumscribed tumors situated in temporal lobe, with variegated appearance, central calcifications, and peripherally located cysts with minimal mass effects are characteristic radiological features. Gross total resection seems curative, with a low recurrence rate.

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Conflict of Interest

None declared.

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