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Review Article

Paraneoplastic Limbic Encephalitis Preceding the Diagnosis of Small Cell Lung Carcinoma: A Review of Published Cases

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Abstract

Background: Paraneoplastic limbic encephalitis (PLE) is an immune-mediated syndrome of subacute memory loss, seizures and psychiatric change that often precedes recognition of its underlying malignancy, most commonly small cell lung carcinoma (SCLC).

Objective: To review published cohorts, series and case reports of PLE preceding SCLC diagnosis, summarising epidemiology, pathophysiology, presentation, diagnosis, management and outcome.

Methods: Narrative review of case reports, series, cohorts and diagnostic-criteria literature.

Findings: Neurological onset preceded cancer diagnosis in 60% of PLE patients (median 3.5 months) in one landmark series, and in 71% of anti-Hu encephalomyelitis patients in another. Published cases show intervals from days to months, antibody status spanning anti-Hu, anti-GABA-B receptor, anti-amphiphysin and seronegative disease, and FDG-PET detecting the tumour in 70-90% of cases when conventional imaging is negative. Neurological improvement, seen in under half of patients overall, is strongly linked to complete tumour response.

Conclusions: PLE should prompt urgent SCLC screening even with normal imaging, since oncological treatment remains the dominant modifiable outcome determinant.

Keywords: Paraneoplastic limbic encephalitis; Small cell lung carcinoma; Anti-Hu antibody; Autoimmune encephalitis; Paraneoplastic neurological syndrome

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Introduction

Paraneoplastic limbic encephalitis is a subacute, immune-mediated disorder of the medial temporal lobes producing memory impairment, seizures, and behavioural or psychiatric change, classically associated with onconeural antibodies directed against intracellular antigens such as Hu and Ta/Ma2 [1]. Its defining clinical challenge is that the neurological syndrome frequently appears before the causative cancer is detectable: in the largest published series of 50 patients, neurological symptoms preceded cancer diagnosis in 60%, at a median

interval of 3.5 months [1], and in a cohort of 200 patients with anti-Hu-associated paraneoplastic encephalomyelitis the neurological syndrome preceded tumour diagnosis in 71% [2]. Small cell lung carcinoma is the tumour most strongly linked to limbic encephalitis, reflecting shared expression of onconeural antigens by tumour and neuronal tissue [3,4]. International criteria have formalised the diagnostic framework, from the original 2004 "definite/possible" classification built around classical syndromes and well-characterised onconeural antibodies [5], through criteria for autoimmune encephalitis broadly [6], to the 2021 update incorporating a wider antibody repertoire and a PNS-Care probability score [7]. This narrative review surveys published cohorts, case series and individual case reports describing PLE preceding SCLC diagnosis, synthesising what the literature supports about epidemiology, pathophysiology, presentation, diagnosis, management and prognosis.

Epidemiology

Population-based data are sparse, but a Friuli-Venezia Giulia registry study identified 89 definite paraneoplastic neurological syndromes over the study period, an incidence of 0.89 per 100,000 person-years and prevalence of 4.37 per 100,000; limbic encephalitis accounted for 31% of these, anti-Hu for 26% of antibody-positive cases, and lung cancer for 17% of associated tumours, with paraneoplastic syndromes complicating roughly 1 in every 334 cancers [8]. In prospective screening of 264 consecutive SCLC patients at diagnosis, a paraneoplastic neurological disorder was found in 9.4%, with limbic encephalitis specifically in 1.5% [9]. Among unselected series of anti-Hu-associated disease, 78% of tumours were SCLC and limbic encephalopathy occurred in roughly one-fifth of patients [4], while a dedicated cohort of lung-cancer-associated PLE found a median interval from neurological onset to cancer diagnosis of only 66 days (range 18-234) [10]. After tumour treatment, roughly

one-third of anti-Hu patients remained neurologically stable in the longer term [11], underscoring that most affected patients present neurologically first and are diagnosed with SCLC only during the ensuing work-up. Because interval and detection depend heavily on how aggressively occult malignancy is pursued, published individual case intervals vary widely, from around five days [12] and seven weeks [13] to roughly three months [14,15], with two reported cases giving no interval at all [16], and one case in which encephalitis instead appeared at cancer recurrence, several months after the original SCLC diagnosis [17] — a reminder that PLE is not exclusively an antecedent phenomenon.

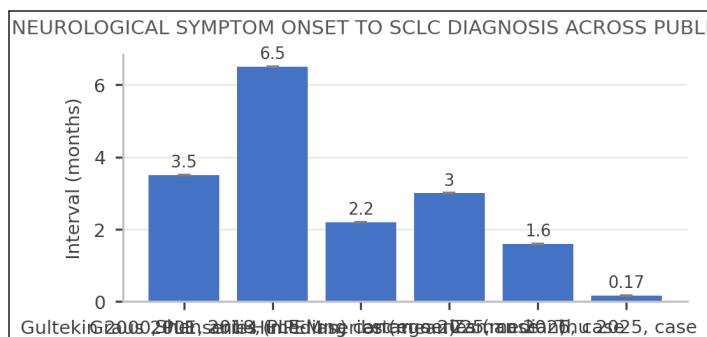


Figure 1: Interval from neurological symptom onset to small cell lung carcinoma diagnosis: 3.5 months median in a 50-patient limbic encephalitis series [1]; 6.5 months mean in a 200-patient anti-Hu series [2]; 2.2 months (66 days) median in a 16-patient lung-cancer series [10]; individual published cases ranging from about 5 days to 3 months [12,13,14].

Pathophysiology

PLE is thought to arise from cross-reactive immunity against onconeural antigens co-expressed by tumour and limbic neurons. Histopathological study of encephalitis brain tissue shows that syndromes associated with intracellular antigens (Hu, Ma2, GAD) are characterised by a high CD8/CD3 T-cell ratio, granzyme-B-positive cytotoxic T cells apposed to neurons, and neuronal loss, consistent with a cytotoxic T-cell-mediated mechanism, in contrast to antibody-mediated surface-antigen syndromes such as NMDA receptor encephalitis, which show minimal neuronal pathology [18]. This mechanistic distinction underlies the sharply different treatment

responsiveness of intracellular- versus surface-antigen disease: in a cohort of 39 limbic encephalitis patients, those with an identifiable cell-membrane antibody were significantly more likely to respond to immunotherapy than those with intracellular antigens ($p=0.003$) [19]. CRMP-5/CV2 antibodies, found in association with SCLC and thymoma, mark a related but distinct intracellular-antigen syndrome with frequent CSF inflammation [20], while anti-Ma2 encephalitis, more often linked to testicular germ-cell tumours than SCLC, produces limbic, diencephalic or brainstem dysfunction in the great majority of patients with MRI abnormality in about three-quarters [21]. Anti-GABA-B receptor encephalitis, a surface-antigen syndrome strongly associated with SCLC, illustrates the more favourable end of this spectrum [22]. Comparative cohort data additionally show that survival differs by antibody class even when tumour type and syndrome frequency are similar, with CV2/CRMP5-antibody patients surviving significantly longer than Hu-antibody patients [23].

Clinical Presentation

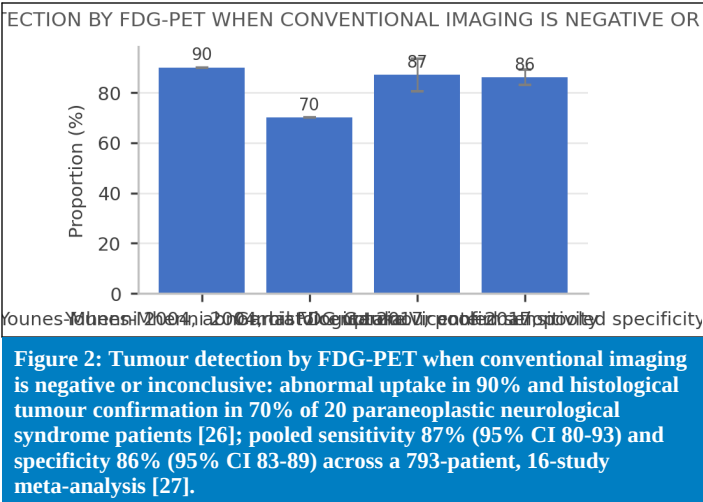
Published cases illustrate marked heterogeneity in antibody status, tempo and severity. Antibody-positive presentations include a 69-year-old man with anti-Hu antibodies who developed disorientation, seizures and severe hyponatraemia with bitemporal atrophy [16], a 78-year-old man with strongly positive anti-Hu who progressed from sensory neuronopathy to hallucinations and seizures over roughly two to three months before SCLC was confirmed [15], and a patient in his mid-50s with anti-GABA-B receptor antibodies whose personality change and seizures preceded cancer diagnosis by only about five days [12]. Amphiphysin antibodies have also been reported, including an 83-year-old man with progressive memory loss and hyponatraemia [16] and a 74-year-old woman in whom encephalitis instead followed SCLC diagnosis, at cancer recurrence, by roughly four months, co-occurring with anti-GAD antibodies [17].

Seronegative presentations occur despite full onconeural and surface-antigen panels: a 57-year-old woman with behavioural change and seizures had a normal MRI and negative antibody panel, with SCLC diagnosed seven weeks later [13], and a 53-year-old woman with hallucinations and cognitive decline remained antibody-negative throughout a fatal course [14]. Refractory status epilepticus was the presenting feature in a 68-year-old woman found to have anti-Hu antibodies and SCLC on the same admission [24]. Across the largest series, MRI limbic-system signal abnormality was present in 57% of patients [1], and in antibody-negative PLE with SCLC, outcomes after cancer treatment were more favourable than in antibody-positive disease [3].

Table 1: Published cases and case series of paraneoplastic limbic encephalitis preceding small cell lung carcinoma diagnosis reviewed here [16,24,12,13,14,15,17,1,3]; N = 10 rows (8 individual cases, 2 series).				
Report	Age/sex	Antibody	Interval to SCLC diagnosis	Outcome
Xu 2015, case 1	69/M	Anti-Hu	Not stated	Died
Xu 2015, case 2	83/M	Anti-amphiphysin	Not stated	Died
Abu-Hashyeh 2020	68/F	Anti-Hu 1:512	Same admission	Palliative, seizures controlled
Thu 2025	Mid-50s/M	Anti-GABA-B receptor	~5 days	Full recovery by 8 months
Zaman 2026	57/F	Seronegative	7 weeks	Near-complete remission at 3 months
Letargo 2025	53/F	Seronegative	~3 months	Died
Goorkiz 2025	78/M	Anti-Hu	~2-3 months	Partial improvement; died at 3 months
Sadamatsu 2019	74/F	Anti-GAD, anti-amphiphysin	Encephalitis at recurrence, +4 months	Died at 4 months
Gultekin 2000, n=50	Group data	Hu, Ta/Ma2, negative	Median 3.5 months	44% improved at median 8 months

Diagnostic Approach

Table 2: Paraclinical yield of investigations in paraneoplastic limbic encephalitis associated with lung cancer [1,25,10,22,21,20].			
Investigation	Result	N	Source
MRI limbic/temporal signal abnormality	25/44 (57%)	44	gultekin2000
MRI T2 temporal hyperintensity	15/18 (83%)	18	lawn2003
MRI bilateral mesial temporal FLAIR change	4/16 (25%)	16	shen2018
MRI hippocampal/amygdala change (GABA-B)	9/20 (45%)	20	hoftberger2013
MRI abnormal (anti-Ma2, all patients)	74%	38	dalmau2004
Abnormal CSF (any)	18/23 (78%)	23	lawn2003
CSF lymphocytic pleocytosis, median 37 WBC	11/16 (69%)	16	hoftberger2013
CSF inflammatory (CRMP-5/CV2 cohort)	86%	116	yu2001
EEG abnormal	22/22 (100%)	22	lawn2003
Neuronal autoantibody detected	14/22 (64%)	22	lawn2003



Evaluation for suspected PLE combines MRI, cerebrospinal fluid (CSF) analysis, electroencephalography (EEG) and antibody testing. In a cohort of 24 patients with suspected paraneoplastic limbic encephalitis (13 with SCLC), MRI showed T2 temporal-lobe hyperintensity in 83%, CSF was abnormal in 78%, EEG was abnormal in all patients tested, and a neuronal autoantibody was detected in 64% [25]. When conventional cross-sectional imaging fails to localise a

tumour, FDG-PET substantially increases yield: in 20 patients with negative or inconclusive imaging, FDG-PET was abnormal in 90% and led to histological tumour confirmation in 70%, with SCLC the most common tumour identified [26], a finding corroborated by a meta-analysis of 793 patients across 16 studies reporting pooled sensitivity of 87% and specificity of 86% for malignancy detection [27]. Because tumours can remain occult at first screening, an EFNS Task Force recommends CT of the thorax followed by FDG-PET, with repeat screening every six months for up to four years if initial screening is negative [28]. The 2021 updated diagnostic criteria formalise this staged approach, incorporating antibody type, syndrome specificity and a structured probability score to guide the intensity of tumour search [7]. Antibody testing itself remains imperfect: several published cases with typical limbic MRI or CSF findings tested negative on full onconeural and surface-antigen panels, and diagnosis rested instead on the temporal association between neurological onset and subsequent SCLC detection [13,14], underscoring that a negative antibody panel does not exclude a paraneoplastic aetiology and should not defer tumour screening.

Management

Two therapeutic pillars recur throughout the literature: treatment of the underlying tumour and immunotherapy directed at the neurological syndrome, with tumour treatment consistently the stronger driver of neurological outcome. In a cohort of 200 anti-Hu paraneoplastic encephalomyelitis patients, tumour treatment was associated with an odds ratio of 4.56 for neurological improvement or stabilisation [2], and in a related cohort of 51 patients, complete tumour response was the sole significant predictor of neurological stability, while immunotherapy did not alter the course [11]. This contrasts with surface-antigen disease: in a series of 20 anti-GABA-B receptor encephalitis patients, all 15 who received treatment showed some neurological

improvement with immunotherapy [22], consistent with the greater immunotherapy-responsiveness of cell-membrane-antibody syndromes generally [19]. Published individual cases mirror this pattern of combined treatment: plasma exchange, corticosteroids and prompt carboplatin-etoposide chemotherapy with radiotherapy produced complete recovery in a patient with anti-GABA-B receptor encephalitis [12] and near-complete remission in a seronegative patient [13], whereas oncological treatment was declined or delayed in fatal cases [24,17]. Immunotherapy regimens across the published cases were similarly heterogeneous, ranging from single-agent corticosteroids to combined plasma exchange, intravenous immunoglobulin and corticosteroids layered onto standard platinum-etoposide chemotherapy [13,12], with no published case-level comparison establishing an optimal immunotherapy sequence — a gap that mirrors the cohort-level finding that immunotherapy itself did not alter neurological outcome once tumour-response status was accounted for [11].

Outcomes and Prognosis

Neurological improvement in PLE is inconsistent and antibody-dependent. In the largest cohort, only 44% of patients with follow-up improved at a median of eight months, with improvement in 38% of anti-Hu, 30% of anti-Ta/Ma2 and 64% of antibody-negative patients [1]. In anti-Ma2 encephalitis, roughly a third improved after tumour treatment while nearly half deteriorated [21]. Case-level outcomes reflect this divide: patients with rapid diagnosis and combined oncological/immunological treatment achieved full recovery [12] or near-complete remission [13], while several antibody-positive and seronegative cases progressed to death despite treatment [16,15,14,17]. In a cohort restricted to PLE preceding predominantly limited-stage SCLC, cancer response rate reached 75% and two-year overall survival was 74.7% [10], appreciably better than historical anti-Hu cohorts, likely

reflecting earlier detection and limited-stage disease at diagnosis. These figures collectively support tumour-response status as the dominant modifiable prognostic factor, with antibody class shaping both immunotherapy-responsiveness and baseline trajectory.

Conclusion

Published evidence consistently shows that limbic encephalitis often precedes, rather than follows, the diagnosis of small cell lung carcinoma, sometimes by only days and sometimes by many months. Recognising this syndrome — using structured diagnostic criteria [6,7], MRI, CSF, EEG and antibody testing, escalating to FDG-PET when conventional imaging is unrevealing — and pursuing early tumour detection and treatment offers the best chance of neurological recovery, particularly in antibody-negative and surface-antigen disease [8,10]. Clinicians evaluating unexplained subacute amnesic or psychiatric syndromes, especially in smokers, should maintain a low threshold for repeated occult-malignancy screening even when initial imaging is normal. The evidence base remains dominated by cohorts assembled decades ago and by scattered, heterogeneously reported case reports; prospective, antibody-stratified registries linking neurological onset, tumour stage at detection and standardised immunotherapy regimens to long-term outcome would do more than any single new case report to clarify which patients benefit most from early, aggressive combined treatment.

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