Added diagnostic utility of PET in a patient with subacute encephalopathy and small-cell lung cancer

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Diagnosis of paraneoplastic neurologic disorder (PND) synthesizes the clinical picture (including the temporal relationship to the cancer diagnosis), detection of onconeural antibodies and exclusion of alternative causes. The mainstay of brain imaging of PNDs is MRI. There is also an increasingly recognized role of PET using radiotracer ¹⁸F-Fluorodeoxyglucose (FDG) in the evaluation of the brain. We describe a 67-year-old female with a 50-year smoking history and small-cell lung cancer developing subacute encephalopathy with MRI and PET abnormalities identifying paraneoplastic encephalitis. PET may complement conventional tools in diagnosing a subset of patients with PND.

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Practice points

- Small-cell lung cancer can present with a range of immune-mediated (paraneoplastic) neurologic symptoms including cognitive changes.
- Not all MRI abnormalities in patients with small-cell lung cancer represent brain metastases.
- PET may capture clinically relevant changes undetected by MRI.
- PET may prove to be an appropriate means to monitor response to therapy in some paraneoplastic syndromes.
- Some onconeural antibodies may not be included in our paraneoplastic panels and a more extensive evaluation should be considered when initial workup is negative.
- Antibody-negative paraneoplastic encephalitis should be considered if history and presentation are suggestive.

Paraneoplastic neurologic disorders (PNDs) were named after their close association with cancer. According to the currently prevailing hypothesis PNDs are caused by misdirected immune attack against the nervous system driven by an underlying neoplasm [1]. It is estimated that 0.5–1% of patients with cancer will develop a clinically disabling PND [2]. If a PND develops, it tends to be the very first symptom of a neoplasm. The primary tumor is detected within a year of PND symptom onset in 90% of the cases [3]. Its incidence is up to 20% in thymoma, 10% in B-cell/plasma-cell neoplasms and about 4% with small-cell lung cancer (SCLC) rendering

KEYWORDS

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these the most commonly implicated malignancies in PNDs [1,4,5]. The common denominators between these tumors are neural tissue content, neuroendocrine activity exposing a wide array of epitopes found in the nervous system or immunomodulatory activity enabling autoimmune responses. The end result is a protean group of diseases often associated with the detection of onconeural antibodies against intra- or extra-cellular antigens, which are currently recognized in 60–70% of cases [6]. The immune-mediated etiology and often overlapping antibodies (e.g., against N-methyl-D-aspartate receptor, or NMDA receptor) blur the line between paraneoplastic and primary autoimmune encephalopathies, however, prognosis and treatment approaches differ between the two groups [2,3,7]. Definite PND can be established in three scenarios: classical syndrome (constellation of symptoms strongly associated with cancer-related autoimmunity) and detection of a neoplasm; a classical syndrome with onconeural antibodies but no neoplasm detected yet (detection may be delayed up to 5 years); nonclassical syndrome with neoplasm identified and either detection of onconeural antibodies or response to cancer therapy [7]. Limbic encephalitis is one of the classical syndromes, which is characterized by seizures, memory loss, confusion and neuropsychiatric changes suggesting involvement of the limbic system. However, clinical and imaging findings often extend beyond the limbic system, rendering the terms ‘limbic encephalitis plus’, or simply immune-mediated encephalitis more accurate to describe such cases [8,9]. Association with cancer is not universal in these, if a malignancy is implicated (i.e., in paraneoplastic cases), SCLC is among the commonly present [2].

The clinical presentation in paraneoplastic encephalitis is typically subacute in onset and consists of a combination of short-term memory loss, confusion and mood-behavioral changes including hallucinations, irritability and/or seizures. The diagnosis relies on the clinical picture (including the temporal relationship to the cancer diagnosis), detection of onconeural antibodies and exclusion of alternative causes such as infections, toxic or metabolic disorders. The tests utilized for the evaluation include cerebrospinal fluid (CSF) and serum inflammatory and autoimmune marker analysis, electroencephalography (EEG), to detect encephalopathy or seizures and finally, imaging with an ever-expanding

role [2]. MRI is the mainstay of brain imaging. There is also an increasingly recognized role of PET using radiotracer ^{18}F -Fluorodeoxyglucose (FDG) in the evaluation of the brain as well as in the search for a primary neoplasm whole-body FDG-PET [10–12]. FDG-PET can be particularly useful in scenarios where MRI is equivocal and serum autoantibodies are undetected [13]. Hence, integration of information provided by multimodality imaging including PET may alter clinical decision making and aid disease surveillance as described in the below case.

• Case presentation

Our patient was a 67-year-old female with a 50-year smoking history developing progressive dementia. She had no personal or family history of early dementia or significant neurologic disorder. Her first symptom was memory impairment for which her initial neurologic evaluation was otherwise unremarkable including normal physical examination. Her mini-mental status examination score was reportedly 28, details of which were unavailable to us. Prior to her presentation, she was given the initial diagnosis of pseudodementia. She was started on escitalopram without improvement. Subsequently, she developed hallucinations with paranoid ideation and violent outbursts. She was hospitalized for respiratory distress at a nonaffiliated hospital, where her encephalopathy workup revealed impaired memory and attention, but without a well localizable neurologic deficit. Her serum paraneoplastic antibody titers were negative, her CSF showed mild pleocytosis with lymphocytic predominance and no malignant cells. There was no electrographic evidence of seizures. MRI of brain revealed approximately 14 nodular cortical T2/FLAIR hyperintense cortical lesions with variable extension into the white matter affecting the temporal poles, the right insular and frontal cortex (**Figures 1A & 2A**). None of these lesions exhibited contrast enhancement or restricted diffusion. A total of 3 weeks later, about 6 months after initial symptom onset, she was referred to our institution for further assessment. On our evaluation, her examination was remarkable for disorientation in space and time, severely impaired attention and short-term memory, intermittent hallucinations, brisk reflexes throughout, bilateral Babinski signs with sustained ankle clonus and unstable wide-based gait. During the admission, the patient developed episodes of spontaneous

Figure 1. MRI T1 with contrast, FLAIR, and PET/FLAIR fusion at level of temporal lobes completed at initial presentation, 3 weeks, 2 months, and 8 months.

myoclonic limb jerks without facial involvement or EEG correlate, which resolved spontaneously after a few days. Her lab workup (summarized in [Table 1](#)) was only remarkable for an elevated antinuclear antibody (ANA) and redemonstrated lymphocytic CSF pleocytosis. Her MRI at our institution revealed new left insular T2/FLAIR involvement with nine new lesions and resolution of three of the initial lesions. No new enhancement or diffusion restriction was present ([Figures 1A & 2B](#)). Brain FDG-PET showed generalized cortical hypometabolism with hyper- and hypometabolic areas variably corresponding to T2/FLAIR lesions. In correlation to the MRI, four out of the nine new T2/FLAIR lesions were purely hypermetabolic and four were hypometabolic with a hypermetabolic edge. Whole-body PET revealed a hypermetabolic lung mass proven to be SCLC on subsequent biopsy.

Given the diagnosis of SCLC and the interim deterioration of her respiratory status, a brain biopsy was not pursued. Metastatic disease was considered given the pattern seen on brain MRI,

but was refuted based on the following findings: lack of contrast enhancement on two consecutive MRIs, cortical rather than gray–white junction or watershed zone involvement, disappearance of many lesions in a matter of 3 weeks (see [Figure 2A vs 2B](#)) without enlargement of any of the initial lesions, as well global brain hypometabolism on PET without evidence of seizures or prior irradiation. Hence, the diagnosis of possible paraneoplastic encephalitis was favored and brain irradiation was postponed to evaluate response to systemic treatment. After two cycles of etoposide combined with carboplatin, associated with improvement at her primary site ([Figure 3](#)), her cognitive decline halted. Her myoclonus and hallucinations resolved, however, her memory impairment persisted. On 6-week post-treatment follow-up, she only showed modest improvement of memory and remained highly dependent for her activities of daily living. On her repeat MRI, half of the previous T2/FLAIR lesions disappeared with near-complete resolution of insular involvement without any signs

Figure 2. MRI FLAIR and PET/FLAIR fusion at level of fronto-parietal and temporal lobes completed at initial presentation, 3 weeks, and 2 months.

of necrosis (Figures 1C & 2C). Marked generalized brain volume loss was visible most prominently in the temporal lobes. Repeat FDG-PET from the same time revealed improved generalized cortical metabolism, and a few new highly FDG-avid foci – all without T2/FLAIR correlate. Of T2/FLAIR lesions that emerged 3 weeks after the initial MRI (i.e., prechemotherapy), all became hypometabolic on the postchemotherapy PET. As her functional status did not return to her baseline, the patient underwent a 5-day course of empiric intravenous immunoglobulin. On follow-up 6 months later, her functional status remained unchanged. Although her MRI from this time showed near-complete resolution of T2/FLAIR abnormalities, it also revealed further progression of generalized brain atrophy suggesting irreversible changes (Figure 1D). The patient was referred to hospice and her family decided to withdraw her oncology care. According to a telephone follow-up, the patient was still alive 1 year later (18 months after initial symptom onset) and remained under hospice care.

Discussion

In the above case, constellation of subacute onset memory and mental status changes with

dynamically changing MRI abnormalities involving cortical and subcortical areas raised the suspicion for an immune-mediated encephalitis [2,10,14]. The discovery of SCLC and negative evaluation for alternative etiologies lead to the diagnosis of definite paraneoplastic encephalitis. This was based on symptom development with concurrent cancer and response to antitumor therapy following the Graus criteria [7]. In our case, history, imaging and CSF analyses were not consistent with alternative etiologies such as primary neurodegenerative dementia, viral encephalitis syndromes or prion disorders [14]. The clinical picture was consistent with limbic encephalitis; however, no routinely tested onconeural antibody was detected in spite of the highly elevated ANA titers that have been described in autoimmune dementias and certain paraneoplastic syndromes [14,15]. Anti-LGI1-related faciobrachial dystonic seizures progressing into limbic encephalitis was a potential differential diagnosis in this case. However, absence of facial symptoms, negative EEG and absence of antibodies against the voltage-gated potassium channel highly suggested against this syndrome. Of note voltage-gated potassium channel negative LGI1-positive cases are

Table 1. Serum and CSF markers evaluated.	
Serum RPR screen	Nonreactive
Serum HIV antibody screen	Nonreactive
Serum antinuclear IFA	2560 (nl: 0–80)
Serum anti-dsDNA	<10
Serum thyroid peroxidase Ab	Negative
Serum thyroglobulin Ab	Negative
Serum anti-SSA/B	Negative
Serum angiotensin convertase enzyme	Negative
Serum anti-RNP	Negative
Serum anti-Smith	Negative
Serum rheumatoid factor	Negative
Serum antichromatin	Negative
Serum Anna-1 [†]	Negative
Serum Anna-2 [†]	Negative
Serum Anna-3 [†]	Negative
Serum PCA 1 [†]	Negative
Serum PCA 2 [†]	Negative
Serum PCA Tr [†]	Negative
Serum amphiphysin [†]	Negative
Serum CRMP 5 IgG [†]	Negative
Serum striational Ab [†]	Negative
Serum Ca channel Ab P/Q type [†]	Negative
Serum Ca channel Ab N type [†]	Negative
Serum AChR binding Ab (receptor) [†]	Negative
Serum AChR ganglionic neuronal Ab [†]	Negative
Serum antiglial nuclear Ab type 1 [†]	Negative
Serum voltage gated K Chan Ab [†]	Negative
CSF anti-NMDA receptor Ab	Negative
CSF 14–3–3 protein	Negative
CSF HSV 1 and 2 DNA	None detected
CSF VZV DNA	None detected
CSF VDRL	Negative
CSF cytology	Negative

[†]Designates antibodies that are routinely tested in the Mayo Paraneoplastic Autoantibody Evaluation panel (PAVAL).
CRMP: Collapsin response-mediator protein; CSF: Cerebrospinal fluid; HSV: Herpes simplex virus; NMDA: N-methyl-D-aspartate receptor; PCA: Purkinje cell cytoplasmic antibody; RNP: Ribonucleoprotein; RPR: Rapid plasma regain; VDRL: Venereal disease research laboratory; VZV: Varicella Zoster virus.

possible, but extremely rare according to the current literature [16]. MRI and PET abnormalities were not favoring the mesiotemporal cortex, which limbic encephalitis typically does. Instead, the lesions were scattered throughout the cerebrum – a pattern concerning for metastatic disease. SCLC, which can frequently metastasize to the brain, detected by whole-body PET, has a common association with PNDs. Brain imaging findings were carefully analyzed to distinguish potential etiologies and were used to drive therapeutic decision making.

Contrast enhancement is the typical MRI finding seen with metastatic lesions. It develops due to local blood–brain barrier breakdown

during tumor invasion to the parenchyma and is almost universally seen in the absence of confounders, such as antiangiogenic chemotherapy [17,18]. Micrometastases may not be detected on MRI due to their size; however, they typically enlarge on follow-up imaging rising above the threshold of detection. In comparison, MRI findings in paraneoplastic encephalitis are highly variable and may even be normal depending on the associated syndrome and antibody type [10–12]. The most typical findings in immune-mediated encephalitis are T2/FLAIR hyperintensities with or without engorgement of the affected area, most commonly in the mesiotemporal cortex and subcortical white matter. Nevertheless, these

Figure 3. CT chest with contrast and native CT Chest/PET fusion at initial presentation. CT chest with contrast at 2 months.
CT: Computed tomography.

may localize anywhere in the brain. Contrast enhancement is less common as it is thought to be a transient phenomenon in the acute inflammatory phase. Diffusion restriction may also be seen in association with the T2/FLAIR hyperintensities [10,19]. The role of magnetic resonance (MR) spectroscopy is unclear; however, changes such as decrease in N-acetyl-aspartate peak have been described in association with dyskinesia in anti-NMDA encephalitis [20]. The longitudinal MRI findings are also variable. The cortical swelling typically subsides in the chronic phase, while T2/FLAIR hyperintensities may or may not persist. Depending on the clinical course, focal or less commonly generalized brain atrophy may occur, which is associated with antibodies against the neural surface (e.g., NMDA receptor, LGI1, GABA-A receptor, etc.) seen in primary autoimmune encephalitis but may be paraneoplastic as well [10,21]. The atrophy is typically permanent, although marked improvement had been described after several years in certain cases [22].

FDG-PET is believed to be more sensitive than MRI to detect changes associated with paraneoplastic encephalitis and is often discordant with MRI [2,10,12,23]. PET changes are usually seen in the temporal lobes, although

other lobes, the basal ganglia and cerebellum may also be affected. The most typical PET finding is focal or diffuse hypermetabolism with or without associated T2/FLAIR hyperintensities. These areas are thought to represent acute inflammation or epileptic activity that may progress into focal hypometabolism as the inflammation resolves. Focal hypometabolism is less commonly associated with corresponding MRI findings, while generalized hypometabolism may visualize as atrophy on MRI. In a recent study of limbic encephalitis, FDG-PET findings seemed to differentiate paraneoplastic encephalitis based on their antibody characteristics better than MRI. PET was abnormal in all five patients without onconeural antibodies detected, whereas MRI was abnormal only in three of four cases [23]. Overall, PET seems to have a better correlation with the clinical picture and hence may be more appropriate to monitor response to therapy [10–12].

In our case, multiple new T2/FLAIR lesions developed in a matter of weeks with variable focal hypo- and hypermetabolism associated on PET. After initial treatment, all newly developed T2/FLAIR lesions became hypometabolic, whereas new hypermetabolic PET lesions had no MRI correlate. This suggests

that PET may be more appropriate to capture clinically relevant changes than MRI. It also seems consistent with the notion that these PET abnormalities represent differing stages of inflammation with hypermetabolism on PET acutely followed by hypometabolism chronically [10,12,24]. All this information leads to our decision of targeting the primary malignancy and the partial clinical response to systemic chemotherapy with etoposide and carboplatin confirmed the appropriateness of this choice. Of note, both agents have poor CSF penetration through an intact blood–brain barrier that is evidenced by absence of contrast enhancement [25,26]. Hence, we speculate that the clinical improvement is less likely attributable to a direct effect on the brain and more so to the reduction of antigenic stimuli from the primary cancer. On postchemotherapy scans, this manifested as normalization of glucose uptake from the previous generalized cortical hypometabolism. Further confirmation was provided with the complete radiographic response seen after intravenous immunoglobulin (IVIG) administration. Of note, some of the associated neurologic damage was irreversible; hence the clinical response remained partial, but sufficient to confirm the diagnosis of definite paraneoplastic encephalitis [7]. The development of marked atrophy on MRI may be a marker of such irreversible damage and may develop in a matter of few weeks and is detected earlier on PET.

We found no onconeural antibodies in this case, which may reflect our failure to detect those involved. We did evaluate a limited set of antibodies against the neural surface, however, not testing a wider array of these such as anti-GABA-A or anti-LGI1 is a major limitation. Alternatively, the process may have occurred in the absence of such antibodies. In experimental models, cerebellar degeneration could be elicited in the absence of onconeural antibodies, and it may be

a possibility in the clinical setting as well [27]. In general, T-regulatory cell function has been associated with more aggressive antitumor responses at the cost of increasing risk for therapy-resistant PNDs [28]. Last, FDG-PET may provide more clinically relevant information for diagnosis and response monitoring than MRI.

Conclusion

SCLC can present with a range of immune-mediated (paraneoplastic) neurologic symptoms including cognitive changes. Not all MRI abnormalities in patients with SCLC represent brain metastases. Clinically relevant changes that are not detected by MRI can be detected by PET. PET may prove to be an appropriate means to monitor response to therapy in some paraneoplastic syndromes. Furthermore, it is important to note that some onconeural antibodies may not be included in our paraneoplastic panels. When initial workup is negative, a more extensive evaluation should be considered. If history and presentation are suggestive, antibody-negative paraneoplastic encephalitis should be considered.

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Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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