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LETTER TO THE EDITOR

New onset refractory status epilepticus and neuroendocrine tumour: a case report and review of the literature

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Dear Editor,

We would like to report the case of a 57-year-old man, mail carrier, who was admitted to the emergency department due to agitation and acute confusion that lasted for two days. He had signs of gastrointestinal tract infection for a few days, headaches for 15 days, without fever. He had no specific history other than substituted hypothyroidism. The patient was restless, and all communications were impossible. This required light sedation with midazolam, sufentanyl, and propofol to allow for further investigations. Blood parameters were within the norm except for increased potassium levels (5.9 mmol/L), decreased phosphates (0.64 mmol/L) and minor elevation of hepatic enzymes (TGO 40 UI/L, LDH 472 UI/L). A lumbar puncture showed increased white blood cells (95/mm^3) 95% of which were lymphocytes, and an increased protein levels at 1.23 g/L. Brain MRI showed a non-specific cystic formation (11 mm long axis) on the internal part of the right temporal lobe without contrast enhancement, and was otherwise normal. Empirical treatment of infectious encephalitis was started (IV acyclovir, ampicillin, and ceftriaxone), until the infectious panel returned negative. On the same day, the patient suffered from an inaugural bilateral tonic–clonic seizure, treated by intravenous (IV) levetiracetam. The patient later suffered from several recurrences, despite deepening the already on-going sedation, then developed a generalized tonic–clonic status epilepticus. IV phenobarbital and IV valproate were added to the treatment, and he was transferred to our centre for further management.

On admission, continuous EEG monitoring was set up, showing both generalized convulsive and non-convulsive seizures (Fig. 1). Anti-seizure medications were progressively adapted to control refractory status epilepticus (levetiracetam 4500 mg/24 h, valproate 3000 mg/24 h, lacosamide 400 mg/24 h), and midazolam sedation was increased up to 0.65 mg/kg/h (i.e. 50 mg/h). Several lumbar punctures revealed persistent inflammatory signs with increased lymphocytes counts and protein levels. All the infectious and autoimmune tests performed were negative: a complete list can be found in Supplementary Material A. The exception was antineuronal antibodies that were slightly positive but not characterized. A whole body CT-scan demonstrated a highly vascularized duodenal (D2) nodular lesion with multiple mesenteric adenopathies, and several liver metastases. These lesions showed increased metabolism according to ^{18}F-FDG PET and increased fixation on ^{68}Ga-DOTA-NOC PET (Fig. 2). Target biopsy revealed a well-differentiated non-secreting grade II neuroendocrine tumour (NET). IV methylprednisolone of 1 g/day for 5 days was started upon the hypothesis of a paraneoplastic super refractory status epilepticus, and lead to new improvement. Seizure stopped after 14 days of intensive care. Midazolam could be gradually stopped after 17 days. The patient was weaned off the ventilator after 22 days of ICU stay. After a brief period of confusion, he regained normal consciousness. Lanreotide 120 mg every 4 weeks was started with additional cycles of leucovorine, 5-fluorouracil, and oxaliplatine chemotherapy.

At the last follow-up (6 months later), a radical cephalic duodenopancreatectomy was performed due to incomplete response and partial progression after the combined

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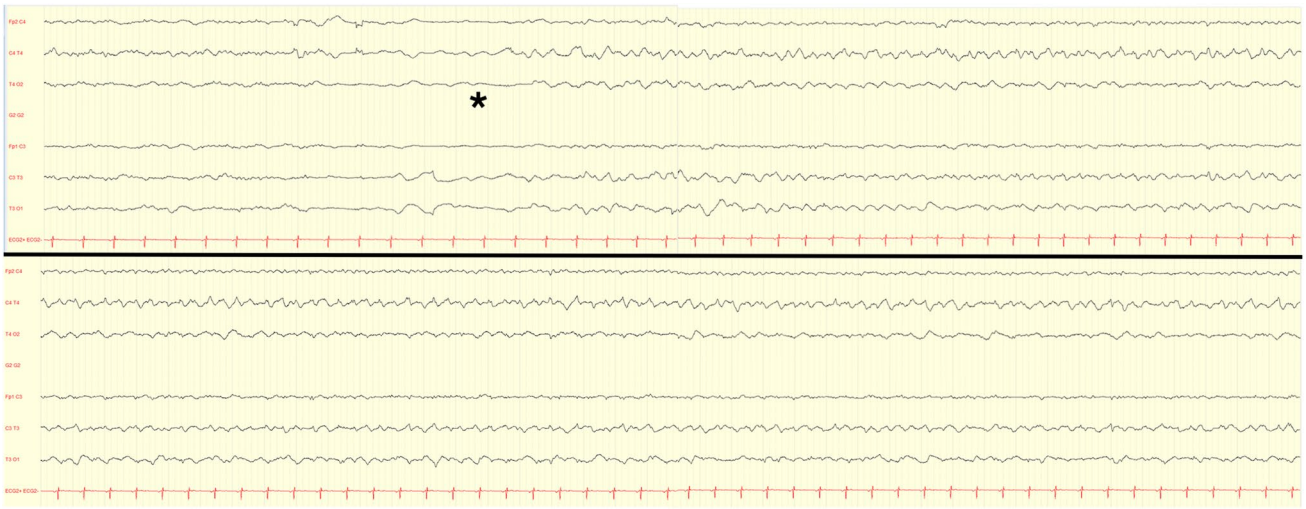

Fig. 1 Example of one of the seizures recorded on continuous EEG monitoring. EEG traces showing an epileptic seizure (starting at *) as a delta rhythmic discharge with triphasic components, lasting several minutes (end not shown). It was accompanied by bilateral clonic movements

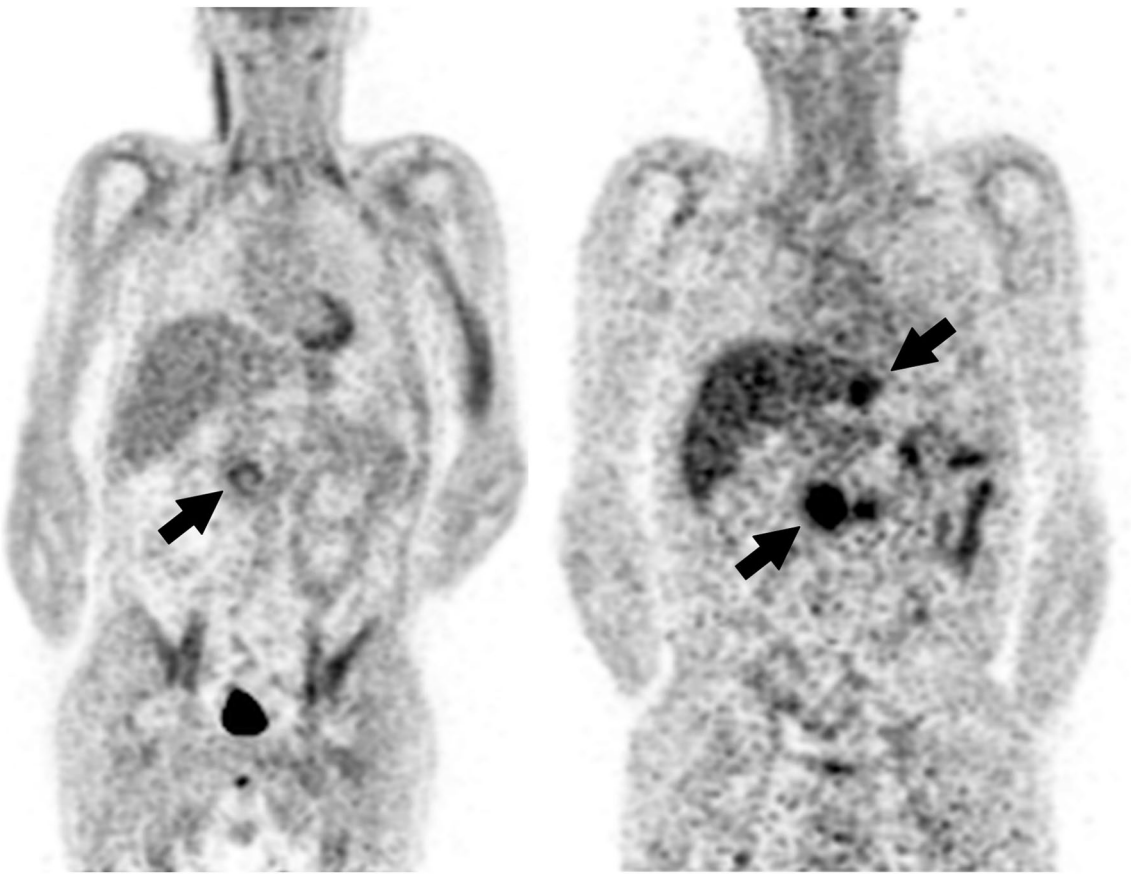

Fig. 2 Representative extract of both ^{18}F-FDG and ^{68}Ga-DOTA-NOC PET-CT in sagittal slices. On the left, ^{18}F-FDG PET-CT showing an hypermetabolic, partially necrotic duodenal lesion. On the right, ^{68}Ga-DOTA-NOC PET-CT showing an hypermetabolic duodenal tumour (lower arrow) with locoregional lymphadenopathy and hepatic metastasis (upper arrow)

chemotherapy. Pathological analyses confirmed the presence of duodenal and hepatic well-differentiated non-secreting grade II neuroendocrine tumour. TNM grade was pT3N1Mx. The patient remained seizure-free while treated by levetiracetam and lacosamide. Neurological examination revealed persistent mild cognitive impairment (including slight non-fluent aphasia, dysexecutive syndrome, impulsivity, impairment of memory recall, Montreal Cognitive Assessment 23/30), and proprioceptive ataxia. Swallowing also improved and the patient could be gradually weaned off the gastrostomy.

Our patient presented with a new-onset refractory status epilepticus (NORSE) that led to the discovery of a locally advanced and metastatic duodenal neuroendocrine tumour (NET). NORSE is by definition challenging, often occurring in patients without pre-existing epilepsy in whom an evident cause cannot be readily identified. In 50–60% of the cases, no aetiology can be found despite an extensive assessment. Most of the identified causes are immune-mediated, of which 19% autoimmune and 18% paraneoplastic [1]. The management of NORSE involves the use of antiepileptic drugs and general anaesthesia to control seizures. Despite best medical care, the outcome is poor, with up to 20% of death and 62% of poor functional outcome (modified Rankin scale of 4 or more) in the series of Gaspard et al. [1].

Paraneoplastic encephalitis is often characterized by new onset of epilepsy, which is frequently immediately very active, by subacute onset of altered mental status, and by CSF pleocytosis, among other criteria. MRI findings and specific antibodies greatly contribute to the diagnosis, but both may be absent [2]. In our patient's case, antineuronal antibodies were positive, but at a low dilution, and were not characterized despite extensive testing, and MRI were repeatedly normal. The management relies mainly on finding and treating the underlying tumour. Immunomodulatory drugs such as corticosteroids, intravenous immunoglobulin infusions, and plasma exchanges can be used with some success in neuronal cell-surface antibodies [2].

Neuroendocrine tumours (NET) are a rare heterogeneous group of tumours, most commonly arising in the gastro-entero-pancreatic tract and in the lungs. They may be benign or malignant tumours, and be either "secreting" a biologically active substance characteristic of the original tissue, or "secreting" an unrelated substance, or being "not secreting". They can be rarely associated with paraneoplastic syndrome [3], affecting the peripheral nervous system (neuropathy, plexopathy, or Lambert–Eaton myasthenic syndrome [3]), or the central nervous system. In the latter, there are reports of cerebellar degeneration, myelitis, brainstem, limbic, or global encephalitis [3]. In most cases, these paraneoplastic syndromes appeared in locally advanced tumour or in metastatic diseases, as was the case in our patient.

In our literature search, we found only one case of anti-$GABA_BR$ limbic encephalitis secondary to a metastatic pulmonary neuroendocrine tumour, which has led to new-onset seizures [4]. We found no description of status epilepticus or of NORSE associated with NET. As brain MRI remained normal even at distance from onset, and since antineuronal antibodies were not characterized, we cannot say with certainty that NORSE was caused by an NET in our patient. However, these conditions are rare, making the accidental discovery of both of them in the same patient quite unlikely. An extensive work-up did not reveal any other potential aetiology of refractory status epilepticus. Finally, the fact that our patient condition improved after corticosteroids administration is an additional argument for an autoimmune/paraneoplastic origin.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13760-022-01886-4.

Declarations

Conflict of interest The authors did not receive support from any organization for the submitted work and have no conflict of interest to declare.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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