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Limbic Encephalitis due to Pancreatic Cancer

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Dear Sir,

Paraneoplastic limbic encephalitis (PLE) is a classical paraneoplastic neurological syndrome characterized by the subacute onset of short-term memory loss, seizures, and confusion. Anti-Hu antibodies (HuAbs) are so-called well-characterized antibodies and are frequently found in small-cell lung cancer (SCLC) or prostate cancer [1], but rarely in gastrointestinal tumors [2–6]. Here, we report an unusual and unpublished combination of PLE and small-cell pancreatic cancer.

Case Report

An 83-year-old man was admitted to our emergency department after a generalized-convulsive status epilepticus (GCSE). Recent complaints included weight loss, night sweats, and a progressive amnestic syndrome for 3 months without prior dementia or other relevant diseases. At the time of neurological examination, he was agitated and disorientated without palsies or Babinski's sign. There were no signs of jaundice, fever, or abdominal pain. C-reactive protein (CRP) was normal; serum sodium was slightly reduced (130 mmol/l). The patient developed complex-partial status epilepticus and respiratory failure necessitating mechanical ventilation. Cerebral computerized tomography (CCT) showed no relevant structural brain abnormalities. Lumbar puncture on the day of admission revealed pleocytosis (96 white cells/μl), elevated protein (80 mg/dl; normal < 45 mg/dl), and signs of disrupted blood-brain barrier. Cerebrospinal fluid (CSF) cytology showed lymphocytosis without malignant cells. Under the presumption of an infectious meningoencephalitis, aciclovir and ceftriaxone were administered. Electroencephalography (EEG) revealed focal slowing and continuous rhythmic epileptiform activity over the right temporal region. Accordingly cerebral magnetic resonance imaging (cMRI) on day 3 demonstrated high T2 and fluid-attenuated inversion recovery (FLAIR) signals of the right temporal region without hemorrhagic lesions, contrast enhancement, or diffusion restriction (fig. 1A). Herpes simplex virus (HSV) type 1/2 as well as varicella zoster virus (VZV) polymerase chain reaction (PCR) of the CSF were both negative. Blood and CSF cultures were sterile; human immunodeficiency virus (HIV) and syphilis serology were negative. HuAbs could be detected by enzyme-linked immunosorbent assay and Western blot in serum and CSF (titers 1:1000 in serum and CSF; normal < 1:100). Chest computed tomography (CT) did not demonstrate a suspected lung cancer, but was suggestive of a tumor mass in the pancreas, which was then confirmed by abdominal CT. Pancreas biopsy revealed a small-cell neuroendocrine carcinoma (fig. 1B, C). Bone scintigraphy did not detect metastases; electroneurography showed no signs of neuropathy. cMRI follow-up (on day 20) revealed no changes compared to the initial findings. No further seizures occurred under anticonvulsive treatment with phenytoin. The patient could be discharged with a Karnowsky index of 80%. 4 months later, the amnestic syndrome improved after 6 cycles of etoposide and carboplatin. Neuron-specific enolase (NSE) as a tumor marker declined from 18.6 μg/l (before therapy) to 9.6 μg/l (normal < 13 μg/l). Chest CT and abdominal CT were performed for restaging and demonstrated partial remission, while the serum HuAb titers remained high (1:1000).

Discussion

Among the known paraneoplastic diseases associated with pancreatic cancer and HuAbs are disorders of the eye movement [6], cerebellar ataxia [5], and subacute sensory neuropathy [2, 4]. As neurological symptoms often precede the diagnosis of cancer [7], it is of utmost importance to recognize the clinical signs of paraneoplastic diseases. Although PLE is a relatively rare disease, prompt diagnosis of cancer is crucial for the affected subject in order to establish an early tumor-specific therapy. A tumor search tailored to the antibody type improves the diagnostic yield [8], whereas pancreatic cancer is best shown by triphasic pancreatic-protocol CT and endoscopic ultrasound [9]. HuAbs have a high positive predictive value for cancer [1], whereas small-cell-type tumors are generally supposed to trigger the production of HuAbs [10]. Nevertheless empirical chemotherapy in patients without obvious malignancy seems not to be feasible [11].

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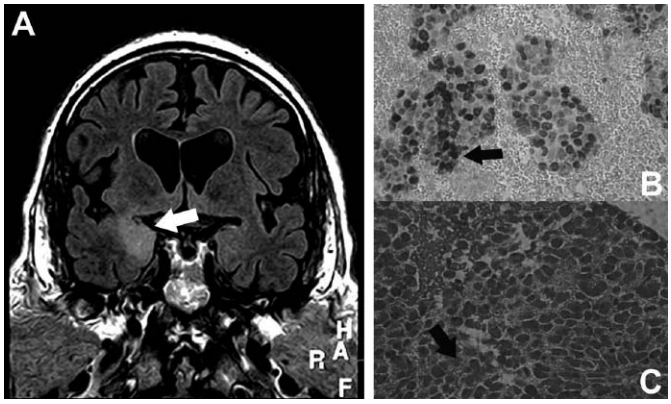

Fig. 1. (**A**) High intense signal (white arrow) of the right temporal region in the FLAIR sequence. (**B**) Neuroendocrine cancer cells (black arrow) of the pancreas head in immunostaining (× 400; anti-human thyroid transcription factor 1 (TTF-1) clone 8G7G3/1, mouse IgG1 kappa; Zytomed Systems®, Berlin, Germany). (**C**) Tumor cells (black arrow) with typical small-cell morphology in hematoxylin-eosin staining (× 600).

The most important differential diagnosis in this case was HSV encephalitis (HSE), which usually presents with an acute onset of confusion, memory impairment, and seizures. The PCR assay has a high sensitivity and specificity (> 95%) for detecting HSV DNA in CSF. Furthermore, findings on MRI, in contrast to limbic encephalitis, often reveal hemorrhagic lesions [12]. High intense T2 and FLAIR signals of one or both temporal lobes are typical of PLE. EEG findings are nonspecific and may indicate focal or generalized slowing over the temporal region, with epileptic activity in 50–60% [13]. CSF findings in PLE usually show lymphocytotic pleocytosis with oligoclonal immunoglobulin G (IgG) bands [14, 15]. HuAbs can be detected in serum or CSF and only fulfill the criteria of so-called well-characterized antibodies when tested by immunohistochemistry and immunoblotting on recombinant proteins [1]. In patients with HuAbs, tumor treatment appears to be more effective on paraneoplastic symptoms than the use of immune modulation [7]. Accordingly, our patient showed improvement of cognitive functions and seizure freedom after chemotherapy.

This case indicates that limbic encephalitis could be the first clinical presentation of small-cell pancreatic cancer. Although PLE and HuAbs are frequently associated with SCLC, other possible malignancies – particularly other small-cell-type cancers – should be included in staging and long-term follow-up.

Disclosure Statement

The authors declare that they have no competing interests.

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