Case Report

Unusual paraneoplastic syndromes in pancreatic cancer: a case report of Lambert-Eaton myasthenic syndrome (LEMS) associated with intraductal papillary mucinous cancer of the pancreas

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Background: Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disorder of the neuromuscular junction. It can occur as a paraneoplastic disorder associated with various types of carcinomas, usually small cell lung cancer or as an autoimmune disease. LEMS can be misdiagnosed as myasthenia gravis or as an oncological sequela, causing delays in diagnosis. We present a rare case of a male adult with confirmed LEMS occurring with pancreatic carcinoma.

Case Description: A 66-year-old man presented with a newly diagnosed pancreatic tumor. He had been experiencing weakness and fatigue in his lower extremities since the summer of 2020. Over time, the weakness progressed to include his proximal upper extremity muscles. Dysphonia, dysarthria, decreased appetite and significant weight loss were also observed. A computed tomography (CT) scan revealed a 3 cm locally resectable cystic tumor in the pancreatic head. Blood tests showed elevated carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) levels. A Whipple procedure was performed, which revealed a poorly differentiated pancreatic adenocarcinoma inside an intraductal pancreatic mucinous neoplasm. Postoperatively, the patient was admitted to the intensive care unit (ICU) because he had no spontaneous breathing and manifested areflexia signs. A train of four (TOF) monitoring of peripheral nerve stimulation was performed and pyridostigmine therapy was initiated, leading to an improvement in symptoms allowing the extubation and transfer to the peripheral ward. Further diagnostic tests revealed a LEMS and an intravenous therapy with cumulative 100 g immunoglobulin (Ig) G was initiated. Upon discharge, 10 days after starting LEMS treatment, the patient showed subjective and objective improvement in strength.

Conclusions: Paraneoplastic syndromes are more common than expected, but rare in pancreatic adenocarcinoma. They can appear before abdominal symptoms, facilitating early diagnosis. Successful treatment of cancer may eliminate paraneoplastic symptoms. LEMS may reveal pancreatic cancer. Early recognition of paraneoplastic syndromes is important for pancreatic cancer management. Further investigation is needed to evaluate the diagnostic approach for LEMS in all patients with pancreatic cancer.

Keywords: Pancreatic cancer; Lambert-Eaton syndrome; paraneoplastic syndromes (PNS); case report

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Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disorder of the presynaptic neuromuscular junction that is related to the loss of functional P/Q-type voltage-gated calcium channels (VGCCs) on presynaptic nerve terminals (1). It may occur as a paraneoplastic disorder, most commonly (between 40% and 62%) in association with small cell lung cancer [cancer-associated (CA) LEMS] (2), or as an autoimmune disease in the absence of cancer [non-tumor (NT)-LEMS] (3-5). Symptoms include gradual onset of fatigue, skeletal muscle weakness, weight loss, and symptoms of the autonomic nervous system such as dry mouth, male impotence, and constipation (1). Both CA- and NT-LEMS demonstrate circulating immunoglobulin (Ig) G antibodies against presynaptic P/Q-type VGCCs; these antibodies modulate expression of functional VGCC and thereby inhibit neurotransmission (2). Because LEMS is a rare disease with fluctuating symptoms, it can be misdiagnosed as myasthenia gravis or as an oncological sequela. In these cases, a diagnosis can be significantly delayed. Only timely and correct diagnosis allows for proper treatment of the neurological disease and any underlying tumor. We describe a rare case of LEMS associated with an intraductal papillary mucinous carcinoma of pancreas. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-22-108/rc).

Highlight box

Key findings

- This report is the first description of an adenocarcinoma of the pancreas associated with paraneoplastic LEMS.

What is known and what is new?

- We reported the rare case of confirmed LEMS as a PNS in a patient with poorly differentiated pancreatic adenocarcinoma with positive P/Q-type calcium channel antibodies. The onset of the neurological symptoms was 1 year before the diagnosis of pancreatic cancer, but did not lead to diagnosis of LEMS. There are no published reports regarding such neurological disorder associated with pancreatic adenocarcinoma in the current literature. What is the implication, and what should change now?

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- Considering that this is the first evidence of the relationship between LEMS and pancreatic adenocarcinomas, we hypothesize a role of pancreatic cancer in revealing LEMS symptoms. If this association is confirmed in other reports, the opportunity for a more exhaustive diagnostic approach to pancreatic cancer and not only to lung cancer in all patients with LEMS might be evaluated.

Case presentation

A 66-year-old Caucasian male presented in October 2021 to our outpatient clinic with a newly diagnosed pancreatic tumor. Since summer 2020 he had noticed weakness and fatigue in his lower extremities with an increasing difficulty to climb stairs and walk long distances. In the following months the weakness progressed to include his proximal upper extremity muscles along with dysphonia and dysarthria. Review of systems was also positive for decreased appetite and a 30-kg weight loss over 1 year. His past medical history was otherwise uneventful except for implantation of a cardiac pacemaker due to arrythmia. Computed tomography (CT) scan revealed a 3-cm measuring locally resectable cystic tumor in pancreatic head (*Figure 1*). Blood test demonstrated elevated carbohydrate antigen 19-9 (CA19-9) of 341 U/mL (norm <27 U/mL) and carcinoembryonic antigen (CEA) of 6.5 ng/mL (norm <5 U/mL). Given the presence of multiple worrisome-features/high-risk stigmata we advised pancreatic resection. On admission the patient had developed a wheelchair dependent adynamia. CT scan and magnetic resonance cholangiopancreatography (MRCP) on admission showed progressive but still resectable disease without metastasis. CA19-9 and CEA levels remained elevated. Neuron-specific enolase (NSE) was also slightly elevated at 18.6 µg/L (range, <16.3 µg/L). In October 2021, the patient underwent Whipple's procedure (pancreaticoduodenectomy with resection of distal stomach) without any major intraoperative complications. Due to a small bile duct a T-tube was placed to support the biliodigestive anastomosis. The histopathological report showed a poorly differentiated pancreatic adenocarcinoma inside an intraductal pancreatic mucinous neoplasm (IPMN). Histopathological staging was pT3 pN2 (7/29), M0, L1, V1, Pn1, Grade 3 (high grade),

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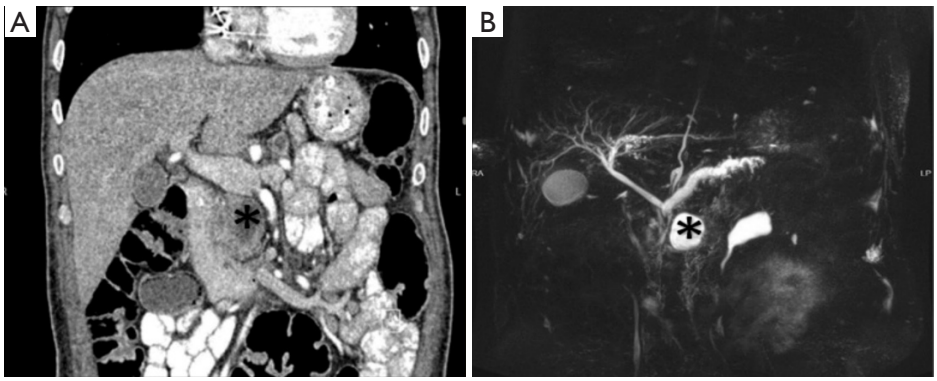

Figure 1 Computer tomographic imaging and MRCP. (A) A partially cystic hypodense tumor (asterisk) in the pancreatic head. (B) A cystic tumor in the pancreatic head (asterisk) with consecutive dilatation of main pancreatic duct. MRCP, magnetic resonance cholangiopancreatography.

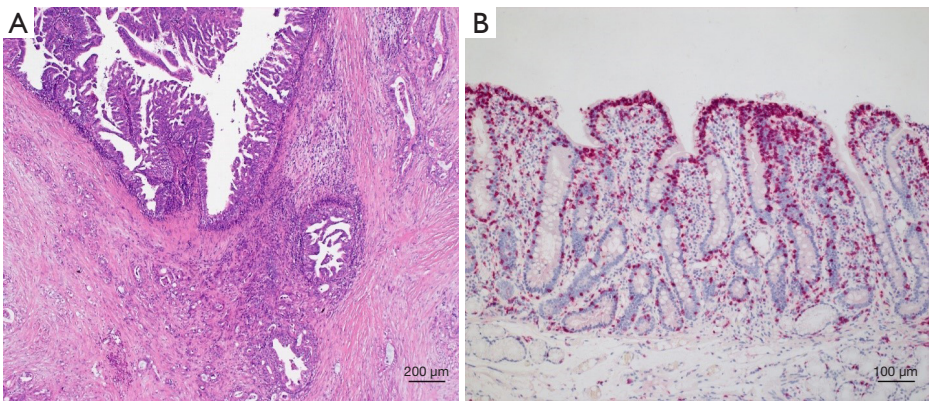

Figure 2 Microscopic features of the resected tissues. (A) Hematoxylin and eosin stain shows the histopathological finding of the intraductal papillary mucinous neoplasm with high-grade dysplasia (at the top) with associated invasive carcinoma of the pancreas (at the bottom). (B) Hematoxylin and eosin stain shows celiac disease with total atrophy with increased intraepithelial T-lymphocytes indicated with CD3, hyperplastic crypts and total atrophy of the villi according Marsh 3C.

R0 close, circumferential resection margin (CRM) positive, Union for International Cancer Control (UICC)-Stadium IIIa. An incidental finding in the histopathological report included a duodenitis with total villous atrophy and crypt hyperplasia, as well as an increase in intraepithelial CD3-positive lymphocytes, consistent with a gluten-sensitive enteropathy (*Figure 2*).

Postoperatively the patient was admitted to the Intensive Care Unit because he had no spontaneous breathing, and manifested areflexia signs. Extubation was performed some days later but he showed signs of respiratory deterioration with saturation drop and was re intubated. In addition, a train of four (TOF) monitoring of peripheral nerve stimulation was performed. More specifically, the ulnar nerve was stimulated with TOF ultra-maximal stimuli of contraction with a stimulation rate of 2 Hertz every 2 seconds and a train frequency of 0.1 Hertz every 10 seconds. As a result, a fading and 60% response of the output potential was manifested by the fourth contraction with a TOF ratio of 0.6. The differential diagnosis was that of myasthenia gravis or LEMS. Following a neurological consultation, we initiated a therapy with pyridostigmine 90 mg daily which led to an improvement of symptoms allowing for extubation and transfer to the peripheral ward. There he manifested a diplopia and dysarthria, and areflexia and paraparesis of the lower extremities. Another neurological consultation was performed. The patient's strength examination revealed [Medical Research Council

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(MRC) scale]: 4/5 deltoids/biceps/triceps, 5/5 wrist flexion/extension, 3/5 hip flexion, 4/5 knee flexion/extension, and 4/5 plantar and dorsiflexion. No fasciculations were noted. His spinal reflexes of the upper and lower extremities were diffusely absent. There was no associated sensory impairment but further neurological examination showed a dysarthria. An electromyogram could not be performed because of the cardiac pacemaker. Creatin kinase (CK) levels were normal. Acetylcholine receptor binding and ganglionic neuronal antibodies were undetected. Serum paraneoplastic work-up was positive for P/Q-type calcium channel antibodies (381.1 pmol/L; range, <40 pmol/L).

Further workup by cranial CT (CCT) and magnetic resonance tomography (MRT) of cerebral vessels didn't show any pathological findings. A subsequent workup with immunological laboratory tests of anti-SOX-1, titin, anti-LRP4 IgG immunofluorescence test (IFT), anti-acetylcholine receptors IgG and anti-MuSK IgG antibodies did not manifest any abnormalities. Based on the above-named clinical findings from the neurological council and primarily the positive values for P/Q-type calcium channel antibodies, the diagnosis of LEMS was made and a therapy with pyridostigmine 60 mg and 4-aminopyridine 10 mg daily was initiated. After determination of the levels of IgA (383 kU/L; range, 70–400 kU/L), IgG (758 kU/L; range: 700–1,600 kU/L), IgM (32 mg/dL; range, 40–230 mg/dL), IgE (21,5 kU/L) in blood and viral antibody testing [hepatitis B &C-negative, human immunodeficiency virus (HIV)-negative], we began an intravenous therapy with cumulative 100 g IgG with subsequent subjective and objective improvement of strength. A further diagnosis with CT scan of thorax excluded a lung tumor. Upon discharge, 10 days after starting LEMS therapy, the patient had intact strength throughout his upper extremities. Lower extremities showed mild impairment for bilateral hip flexion (4/5 on MRC scale). Dysarthria resolved completely under treatment. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

In most cases, pancreatic tumors produce clinical symptoms as a result of local expansion, with obliteration of normal tissues, as the malignant cells proliferate within the confines of the involved organ. Subsequently, the tumor compresses and infiltrates surrounding tissues such as blood vessels, lymphatics, and nerve fibers as well as the adjacent organs. Thus, the principal clinical presentation of pancreatic ductal adenocarcinoma includes abdominal pain and jaundice. Benign cystic tumors and hormone inactive neuroendocrine tumors (NET) are often only detected by imaging studies for other complaints. Hormone active NET may show typical signs and symptoms as a consequence of the overproduction of specific hormones.

Paraneoplastic syndromes (PNS) are rare clinical syndromes due to the systemic effects of tumors; they are unrelated to tumor size, invasiveness or metastases. PNS can occur concurrently with tumor diagnosis, before a tumor is diagnosed and even after tumors have been resected. Also, some primarily considered autoimmune diseases may be found to be PNS when initially occult tumors are identified. Another confounding factor is that many PNS clinically resemble non-neoplastic diseases. PNS are largely due to two main causes: those due to tumor secretions of hormones, functionally active peptides, enzymes cytokines or due to tumors operating through auto-immune/immunological mechanisms with cross-reacting antibodies between neoplastic and normal tissues. Remission of symptoms often follows resection of humoral secretory tumors but symptoms also may last through immunological mechanisms. Clinical symptoms cover a broad spectrum and include systemic and organ-specific manifestations. The former mimicking frequent symptoms of pancreatic cancer patients, such as fever and cachexia. Organ-specific symptoms may present as cutaneous, neurological, hematological, or endocrine symptoms.

We reported the rare case of confirmed LEMS as a PNS in a patient with poorly differentiated pancreatic adenocarcinoma with positive P/Q-type calcium channel antibodies. The onset of the neurological symptoms was 1 year before the diagnosis of pancreatic cancer, but did not lead to diagnosis of LEMS. There are no published reports regarding such neurological disorder associated with pancreatic adenocarcinomas in the current literature. Available literature reports pancreatic cancer in association with a general PNS (deep vein thrombosis, coagulation disorders, hypercalcemia, acromegaly, and Cushing syndrome) (6) and a pancreatic NET inducing neurological PNS (7-11) such as optic neuropathy (positive anti-optic nerve antibodies (8,9,12), encephalitis (positive GAD7 and

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anti-LG1 antibodies) (6,7), myasthenia-like presentation (antibody testing not performed) (13,14). This report is the first description of an adenocarcinoma of the pancreas, that was associated with paraneoplastic LEMs.

Conclusions

Even though the incidence of PNS is more frequent than generally suspected, PNS is still rare in pancreatic adenocarcinoma (6). Nevertheless, symptoms of PNS may precede abdominal complaints and allow for early diagnosis if interpreted correctly. After the successful treatment of the underlying malignant disease, paraneoplastic symptoms may resolve completely. If recurrence of PNS is a robust indicator of tumor recurrence remains unknown. Considering that this is the first evidence of the relationship between LEMS and pancreatic adenocarcinomas, we hypothesize a role of pancreatic cancer in revealing LEMS symptoms. If this association is confirmed in other reports, the opportunity for a more exhaustive diagnostic approach to pancreatic cancer and not only to lung cancer in all patients with LEMS will have to be evaluated. Thus, an early recognition of PNS is very important in the management of patients with pancreatic cancer.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-22-108/rc

Peer Review File: Available at https://acr.amegroups.com/article/view/10.21037/acr-22-108/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-22-108/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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