

SCIENTIFIC LETTERS

Cervical adenopathy as first symptom of a neuroendocrine ampullary tumor[☆]



Adenopatía cervical como presentación de ampuloma neuroendocrino

Non-pancreatic gastrointestinal neuroendocrine tumors (NETs) include a wide group of diseases mainly located in the ileum and appendix and usually with no clinical signs of hormone hypersecretion. At least 140 cases have been reported in the ampulla of Vater, whose symptoms usually derive from ampullar obstruction and include abdominal pain, pancreatitis, jaundice, or gastrointestinal bleeding.

Locoregional nodal metastatic involvement, unrelated to tumor size and not leading to a poorer prognosis, is found in half of these tumors at diagnosis.

Cervical nodal involvement by occult intra-abdominal neoplasms (Troisier's sign), particularly gastric or pancreatic adenocarcinomas, has been known for longer than a century. We report an ampullar NET in which the first sign was a metastatic cervical adenopathy.

A 59-year-old woman attended the clinic for a palpable mass in the left side of the neck with no other symptoms. A computed tomography (CT) of the neck showed a 4-cm adenopathy in the left side of the neck that compressed the left thyroid lobe (Fig. 1). Biopsy showed a lymph node infiltrated by a well differentiated NET with immunohistochemistry (IHC) positive for chromogranin A (CgA) and synaptophysin and negative for calcitonin. Thyroid ultrasonography showed no changes.

Laboratory tests showed normal serum levels of neuroendocrine tumor markers (CgA, gastrin, PP, somatostatin, glucagon, and calcitonin), and elevated transaminase and alkaline phosphatase levels (AST 75 U/L, NR < 32; ALT 82 U/L, NR < 32; γ GT 1167 U/L, NR < 33; FA 279 U/L, NR < 36) and normal bilirubin. Abdominal CT revealed a dilated bile duct (15 mm) with prominent papilla, with no tumor or luminal occupation and pancreatic duct dilation (Fig. 2). An endoscopic ultrasonography showed a hypoechoic mass in the

duodenal ampulla with periportal adenopathies up to 24 mm in size. Tumor biopsy and adenopathies showed a NET.

A cephalic pancreatoduodenectomy (Whipple operation) with regional lymph node resection showed a neuroendocrine tumor 1.7 × 1.4 cm in size that invaded the duodenal mucosa and pancreas, with peripancreatic, preaortic, and mesenteric lymphatic and nodal involvement (17/23). Microscopically, the condition characterized by proliferation of small rounded cells with a solid pattern and 2 mitoses/10 high power fields. IHC found a low cell proliferation index (Ki67 < 2%) with positive neuroendocrine markers (CgA, synaptophysin); other hormones were not tested by IHC due to technical problems. One month later, a left functional cervical dissection showed 9/41 lymph nodes involved, up to 4.5 cm in size.

A postoperative ¹¹¹-octreotide scan showed nodal uptake at peripancreatic and superior mediastinal level, with bone involvement in the 7th costovertebral joint, confirmed by bone scan.

Patient continues to be symptom-free after two years, with gradual elevation of serum CgA level (NR × 3) in the last year, lesion stabilization in T7 and occurrence of a new lesion in L5, with adenopathy enlargement. No treatment has been started yet.

The Troisier sign refers to left lateral neck adenopathies occurring as the initial sign of an intra-abdominal malignant tumor due to lymphatic dissemination through the thoracic duct. Ampullar NETs are exceptional tumors, with less than 140 cases reported, accounting for less than 2% of malignant tumors in the ampulla and 0.3% of gastrointestinal NETs.^{1–3} We have found no reported case with this presentation.

NET incidence and prevalence rates have increased in recent years, probably because of improved diagnostic procedures.^{1,4} Mean age at diagnosis of ampullar NETs is 58 years, and tumors are more prevalent in males.^{1,4} Twenty-five percent of cases are related to von Recklinghausen syndrome.^{2,4,5}

The most common signs and symptoms of ampullar NETs are jaundice (60%), abdominal pain (40%), and pancreatitis (6%), with weight loss and gastrointestinal bleeding occurring less commonly.^{2,4,6} Carcinoid syndrome is uncommon, except in the presence of liver metastases.²

The 2010 histopathological staging of the World Health Organization is the most adequate classification for prognosis of these tumors,¹ and recent studies suggest an association between greater biological aggressiveness of the

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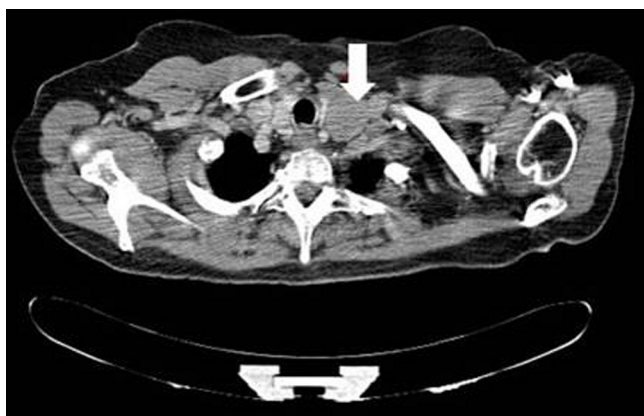


Figure 1 Neck adenopathy.

tumor and possibility of distant metastases with higher Ki-67 index.²

Non-specific neuroendocrine tumor cell markers (chromogranin A, specific neuronal enolase, and synaptophysin) are positive in almost all ampullar NETs studied (92%, 100%, and 100% respectively). As regards specific hormone production markers, not tested in our patient, the most common is somatostatin (58–67%), followed by insulin (25%), serotonin (17%), and CCK (17%).^{1,2,5}

The diagnostic procedure of choice for locating primary tumor is endoscopic retrograde cholangiopancreatography (ERCP). ERCP and endoscopic ultrasonography (EUS) allow for assessing the possibility of infiltration into the bile ducts. EUS has high sensitivity for small tumors or local angioinvasion. CT and MRI have little sensitivity for diagnosis of primary lesion, being useful for showing metastases in the



Figure 2 Common bile duct and Wirsung duct dilation.

liver, mainly in the early arterial phase,⁷ or in the mesentery; depending on clinical signs and course, other imaging tests such as bone scan, octreoscan, PET, or MIBG should be performed.^{1–3}

Standard treatment consists of cephalic pancreatoduodenectomy (Whipple operation). Endoscopic ampullectomy may be a viable option for treating selected cases with highly differentiated carcinomas confined to the mucosa without vascular or lymphatic invasion.^{2,6}

In the reported series, tumor size did not correlate to tumor potential to metastasize to lymph nodes.^{1,2,4–6} Coexistence of locoregional nodal metastases (50% at diagnosis) has shown no impact on disease-free survival or on perineural or venous involvement. Factors correlated to poorer prognosis include local tumor extension (serosa, pancreas, retroperitoneum, and other adjacent tumors), size > 2 cm, and high mitotic grade (G3).^{1,2,4–6}

Five- and 10-year survival rates are 82% and 71% respectively, but lower for high grade tumors (15% at 5 and 10 years). The recurrence rate is 40–50%, and metastases mainly occur in the liver.^{1,2,8}

The reported case is interesting because of a number of unusual characteristics. This was a rare presentation, at an advanced stage, of an uncommon tumor with a silent course until self-detection of the adenopathy. Despite the fact that the tumor was less than 2 cm in size and had a Ki-67 less than 2%, there was widespread nodal and bone metastatic involvement with no evidence of liver involvement, which is most common in dissemination of these tumors.

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Pseudohypoaldosteronism type 1 secondary to vesicoureteral reflux: An endocrinologic emergency[☆]



Pseudohipoaldosteronismo tipo 1 secundario a reflujo vesicoureteral: una urgencia endocrinológica

Hypoaldosteronism is an endocrine disease characterized by hyperkalemia and mild hyperchloremic metabolic acidosis with normal anion gap (type 4 renal tubular acidosis).

Causes of hypoaldosteronism include acquired disorders (hyporeninemic hypoaldosteronism, drug-induced angiotensin II inhibition, heparin therapy and primary adrenal insufficiency) and, less commonly, hereditary disorders. Adrenal aldosterone synthesis or renin release is affected in all these conditions.¹

Aldosterone is a mineralocorticoid mainly acting in the kidney and, secondarily, in other organs (colon, lung, and sweat, lacrimal, and salivary glands). Aldosterone action, which requires a mineralocorticoid receptor and a sodium transporter protein, called sodium epithelial channel (SEC), regulates plasma sodium reabsorption and urinary potassium excretion.² It is essential to differentiate decreased aldosterone production from aldosterone resistance.

The most commonly reported causes of the aldosterone resistance syndrome include treatment with potassium-sparing diuretics and antibiotic therapy with co-trimoxazole and pentamidine. A particularly uncommon condition is pseudohypoaldosteronism type 1 (PHA1).

PHA1 may have a genetic basis and be inherited as a recessive autosomal disorder which affects SEC, impacting on all target organs (multiple form), or a dominant autosomal form, characterized by mutations in the gene encoding for the renal aldosterone receptor (renal form).^{3,4} Among secondary or acquired forms, special mention should be made of those derived from obstructive (organic or functional) and/or infectious uropathy, tubular interstitial disease, and side effects of drugs⁴ (Table 1).

PHA1 is characterized by aldosterone resistance, associated to hyponatremia, hypovolemia, hyperkalemia, and hyperchloremic metabolic acidosis. Plasma renin and aldosterone levels are markedly increased.

Although the syndrome has an insidious course, it may exceptionally lead to water and electrolyte emergencies. We therefore report the clinical case of a patient with severe dehydration, critical hyperkalemia, and urine output excessively high for the degree of dehydration. This was a 19-day-old male infant who was admitted to the pediatric ICU for dehydration and 19% weight loss (birth weight 3090 g [10th–25th percentiles] after vaginal eutocic delivery at 41 weeks of pregnancy). The infant had not had clinical signs or symptoms of infection or fever.

Family history included grade 1 left vesicoureteral reflux (VUR), complicated with pyelonephritis at 15 days of life and requiring hospital admission, in a 6-year-old sister.

Laboratory tests showed leukocytosis (27,100 WBC/mm³), with presence of band cells (9%). Chemistry showed greatly impaired renal and electrolyte profiles (urea, 234.9 mg/dL; creatinine, 1.67 mg/dL; sodium, 122.6 mEq/L; chlorine, 90.4 mEq/L; potassium, 11.25 mEq/L; and calcium, 11.6 mg/dL). Because of this critical potassium level, factitious hyperkalemia or preanalytical error (hemolyzed serum, EDTA-K³ contamination, excess compression or tourniquet time, and a drug-induced effect) were ruled out. Arterial blood gases showed metabolic acidosis (pH, 7.17; pCO₂, 15 mmHg; pO₂, 105 mmHg; HCO₃⁻, 5.5 mmol/L, and SBE, -20.1 mmol/L). Analysis of urine collected by suprapubic puncture showed microscopic hematuria, pyuria, negative nitrites, proteinuria (150 mg/dL), pH 6, specific gravity 1010, sodium 21 mEq/L, and potassium 27.3 mEq/L, with an osmolality of 228 mOsmol/kg. Blood, urine, and rectal swab samples for culture showed urinary tract infection (UTI) by *E. coli* susceptible to aminoglycosides, third-generation cephalosporins, and fosfonates. The patient is a rectal carrier of ESBL-producing *K. pneumoniae*, with negative blood cultures. Lumbar puncture provided no findings of interest, including cultures.

ECG showed characteristic signs of hyperkalemia (spiking T waves and PR in the upper limit of normal).

The etiological study was completed by abdominal ultrasonography, which showed bilateral ureterohydronephrosis, winding ureters, and hyperechogenic contents related to turbid urine. Based on these findings, voiding cystoureterography was performed, which ruled out structural obstruction and showed enlarged bladder, grade IV right and grade V left VUR, and incoordination of urinary detrusor/sphincter muscles consistent with functional obstruction, valve-like syndrome, uncoordinated voiding in the male infant, or Hinman–Allen syndrome.⁵ A renal scan with dimercaptosuccinic acid (DMSA) showed kidney function impairment (60% in the right and 40% in the left).

Adrenal function tests showed aldosterone levels higher than 2000 pg/mL (17–130), plasma renin activity (PRA) of

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