

Pancreatic tumor and Gitelman syndrome

To the Editor,

We report the first case of an association between a pancreatic tumour and the Gitelman syndrome, possibly paraneoplastic.

A male patient, 55 years old, having undergone retrograde cholecystectomy and choledochoduodenal anastomosis performed for distal choledochus stenosis associated with chronic alcoholic pancreatitis 7 months before presentation, followed after 4 months by subtotal distal gastric resection with end-to-side duodeno-jejunal anastomosis on Roux en Y loop, for tight duodenal stenosis and insufficient gastric emptying. The patient presented at the emergency unit with severe edematous syndrome, pancreatic secretion failure, severe hypokaliemia and metabolic alkalosis.

The diagnosis of chronic pancreatitis was established. A pancreatic tumor with liver metastases was suspected, based on a pancreatic mass by US, CT and on the CA 19-9 level 50 times over the normal.

Among the causes of hypokaliemia associated with metabolic alkalosis we excluded one by one: a secreting pancreatic neuro-endocrine tumor (5-hydroxy-indolacetic acid 10.7 mg/24h, chromogranin A 51 ug/l), secondary hyperaldosteronism (serum aldosterone < 50 pmol/l), villous adenoma (colonoscopy), prolonged diuretic treatment (patient history), salt-depleting nephropathy. We then considered a paraneoplastic pathology and Bartter/Gitelman syndrome [1].

Gitelman syndrome is a hereditary, autosomal recessive disease. It is a variation of the Bartter syndrome that occurs in adulthood. A defective co-transport of Na-K-2Cl occurs at the level of the cortical distal tubule (CDT), similar to the effect of a thiazidic diuretic [2]. The bio-humoral alterations described in Gitelman syndrome are: metabolic alkalosis, hyper-reninemia, hyper-aldosteronism, hypokaliemia, Na, K, Cl loss at the kidney level in a patient with normal blood

pressure [3]. The diagnosis is established by evidencing the mutation of gene SLC12A3 on the 16q13 chromosome. Therapy consists of sodium and potassium supplements, long-term potassium savers, NSAIDs, IECA and magnesium supplements [4].

The literature reports one case of Gitelman-like syndrome in a female patient diagnosed with ovarian cancer and treated with Cisplatin after the operation. The question was raised whether the Gitelman syndrome is caused by chemotherapy or it occurs as a paraneoplastic syndrome [5].

Palliative treatment for adenocarcinoma was initiated with Gemcitabin 2000 mg total dose [6]. We tried to discontinue treatment with Spironolactone several times, but edema recurred, which reinforced the suspicion of paraneoplastic Gitelman-like syndrome.

Subsequently, after four chemotherapy sessions, MRI of the upper abdomen was performed, which evidenced the pancreatic head tumor of 4.8 cm that had caused the stenosis of the Wirsung and its retrograde dilation and invaded the upper mesenteric vein > 50%, atrophy of the pancreatic parenchyma at the level of the head, corpus and tail, a pancreatic cyst at the tail of 3.3 cm and liver metastases (Fig 1).

The peculiarity of this case is represented by the differential diagnosis between pseudotumoral chronic pancreatitis and a malignant pancreatic tumor. The case is distinctive due to the association of hypokaliemia with

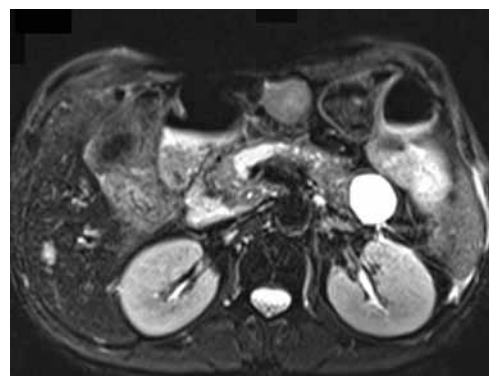


Fig 1. Upper abdomen MRI: tumor at the head of the pancreas.

metabolic alkalosis and renal loss of electrolytes (Gitelman syndrome) in a patient with a pancreatic tumor.

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References

1. Gennari J. Hypokalemia. *N Engl J Med* 1998; 339:451-458.
2. Hansen KW, Mosekilde L. Gitelman syndrome. An overlooked disease with chronic hypomagnesemia and hypokalemia in adults. *Ugeskr Laeger* 2003 Mar; 165:1123-1127.
3. Kurschat C, Heering P, Grabensee B. Gitelman's syndrome: an important differential diagnosis of hypokalemia. *Deutsche Med Wschr* 2003; 128:1225-1228.
4. Pistor K, Heemann K, Olbing H. Asymptomatic hypokalemia and hypomagnesemia with renal cation loss (Gitelman syndrome). *Monatsschr Kinderheilkd* 1987; 135:340-342.
5. Panichpisal K, Angulo-Pernett F, Selhi Sh and Nugent KM. Gitelman-like syndrome after cisplatin therapy: a case report and literature review. *BMC Nephrology* 2006; 7: 10
6. Yeo CJ: Pancreatic cancer: 1998 update. *J Am Coll Surg* 1998; 187: 429-442.

Hepatic arteriovenous malformation with hyperammonemia in Rendu-Osler-Weber syndrome

To the Editor,

A 55-year-old Japanese woman was admitted to our hospital because of frequent epistaxis. Physical examination revealed multiple small telangiectasias of the finger tips (Fig. 1) and tongue (Fig. 2). She had a family history (her mother, two sisters and two daughters) of cutaneous telangiectasia, and had episodes of severe recurrent epistaxis and anemia similar to her family. Hemoglobin, aspartate transaminase, alanine transaminase, gamma-glutamyl transpeptidase, alkaline phosphatase, and ammonia were 7.2 g/dl (range 12-16), 107 IU/l (range, 8-30), 68 IU/l (range, 4-45), 164 IU/l (range, 9-32), 419 IU/l (range, 80-260), and 96 microg/dl (range, <-36), respectively, and the albumin, total bilirubin and prothrombin time were normal. The computed tomography revealed a large hepatic arteriovenous malformation (Fig. 3), which was confirmed by a hepatic arteriography which revealed dilated hepatic arteries with early filling of hepatic veins (Fig. 4). Based on the clinical presentation and the Curacao criteria [1], she was diagnosed with Rendu-Osler-Weber syndrome with hepatic arteriovenous malformations. Laser ablation and septal dermoplasty were performed, and recurrent epistaxis was partially improved. Another operation or embolization for hepatic arteriovenous malformations were not suggested.

Rendu-Osler-Weber syndrome, also known as hereditary hemorrhagic telangiectasia (HHT), is an autosomal dominant disorder of the fibrovascular tissue characterized



Fig 1. Telangiectasias on the tongue.



Fig 2. Multiple small telangiectasias of the finger tips.



Fig 3. Computed tomography: large hepatic arteriovenous malformation.

by hemorrhagic manifestations, cutaneous or mucosal telangiectases and visceral shunting due to arteriovenous malformations [1]. It is caused by mutations in a number of genes involved in the transforming growth factor-beta / bone morphogenetic protein (BMP) signaling cascade, Endoglin and activin receptor-like kinase 1 (ACVRL1) genes have been most commonly identified so far [2]. Molecular analyses were performed in this patient, although known genetic abnormality was not evident. Arteriovenous malformations occur in a variety of organs including the skin, brain, nose, lungs, gastrointestinal tract and liver.



Fig 4. Hepatic arteriography: dilated hepatic arteries with early filling of the hepatic veins.

In most patients, liver lesions remain clinically asymptomatic, but hepatic vascular lesions as diffuse hepatic telangiectasias, a dilated common hepatic artery, and biliary abnormalities with shunts between portal hepatic artery and hepatic vein can present as high-output cardiac failure, portal hypertension, liver fibrosis, and liver failure [3]. Therapeutic options include hepatic artery embolization, hepatic artery ligation and liver transplantation. However, both hepatic artery embolization and hepatic artery ligation have been associated with liver failure and death [4, 5]. Hepatic dysfunction restricts the patient's quality of life and leads to a fatal clinical course. HHT should be considered in the differential diagnosis of hyperammonemia or multiple arteriovenous malformation with mucosal telangiectasias.

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References

1. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet* 2000;91:66-67.
2. Plauchu H, Dupuis-Girod S. Hereditary hemorrhagic telangiectasia. *Rev Prat* 2009;59:899-903.
3. Sharathkumar AA, Shapiro A. Hereditary haemorrhagic telangiectasia. *Haemophilia* 2008;14:1269-1280.
4. Sabba C, Pompili M. Review article: the hepatic manifestations of hereditary haemorrhagic telangiectasia. *Aliment Pharmacol Ther* 2008;28:523-533.
5. Alexander BG, Khoo EW, Arstall MA, Roberts-Thomson IC. Education and imaging. Hepatobiliary and pancreatic: hepatic arteriovenous malformations in hereditary hemorrhagic telangiectasia. *J Gastroenterol Hepatol* 2007;22:1549.

Unexplained jaundice after squirrel bite

It's not what you look at that matters, it's what you see (H. D. Thoreau)

To the Editor,

A 25-year-old male presented to our department with malaise, dry cough, sore throat and severe pruritus since three weeks. Two days before he had developed a scleral icterus and severe pruritus leading to considerable itching wounds. The patient denied any other abnormalities. Apart from several abdominal scars the physical examination was unremarkable.

The patient reported a bite of a wild squirrel. Furthermore, he mentioned a car accident causing multiple traumata. A similar episode of jaundice and pruritus was present 18 months ago. At that time, leptospirosis was suspected. A secondary sclerosing cholangitis after the accident was excluded by ERCP at that time.

Laboratory tests showed elevated alanine aminotransferase (88 U/l, normal range <45 U/l), aspartate aminotransferase (71 U/l, normal range <35 U/l), serum bilirubin (32 $\mu\text{mol/l}$, normal range <17 $\mu\text{mol/l}$) and bile acid levels (184 $\mu\text{mol/l}$, normal range <10 $\mu\text{mol/l}$). Alkaline phosphatase was moderately elevated (AP, 171 U/l, normal range 40-129 U/l), but gamma-glutamyl transpeptidase (GGT) was in normal range.

Because of the squirrel bite in the patients' history we assumed a zoonotic disease. A recurrence of leptospirosis was excluded by negative IgM and IgG antibodies and diverse serological tests including viral, microbiological, and parasitic pathogens. We treated the patient with ursodeoxycholic acid (UDCA) and cholestyramin without any clinical benefit.

Total bilirubin level increased (211 $\mu\text{mol/l}$, conjugated 116 $\mu\text{mol/l}$) and the general condition of the patient severely worsened, so we performed a liver biopsy. Histology showed canalicular cholestasis with otherwise largely normal hepatocytes and no inflammatory or fibrotic changes (Fig. 1).

Considering the elevated serum AP and bile acids, normal GGT, histology and recurrent character of the cholestasis into account we hypothesized a hereditary cholestatic disorder.

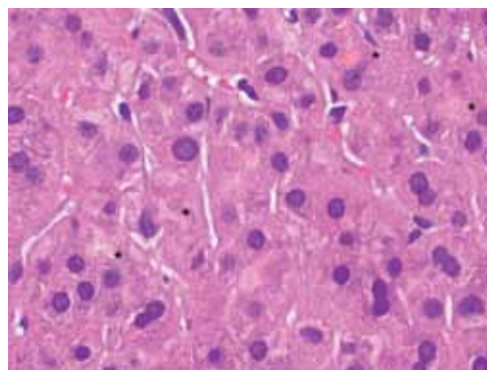


Fig 1. Liver histology (H&E x 400). Canalicular cholestasis (*) "bland", e.g. without necro-inflammatory lesions.

Genetic sequencing analysis revealed mutations compatible with a benign recurrent intrahepatic cholestasis (BRIC) type 2. Consequently, we started the patient on rifampicin and the pruritus improved after 12 hours dramatically. All laboratory tests normalized during the following weeks and rifampicin was discontinued.

Familial cholestasis is a rare and heterogeneous group of autosomal recessive liver disorders which can be divided into three main groups: PFIC, BRIC and intrahepatic cholestasis of pregnancy (ICP) (1). Due to mutations in the hepatocanalicular transporters the process of bile formation is altered resulting in benign or progressive cholestatic liver disease. Alterations in ATP8B1, ABCB11 can result in a less severe phenotype called BRIC type 1 and 2, respectively [1, 2]. Laboratory findings include elevated aminotransferases, serum bile acids and bilirubin. Characteristically, GGT is not elevated in ATP8B1 and ABCB11 deficiency, but in ABCB4 deficiency.

Cholestyramine can be helpful in patients with intermittent cholestasis but seldom in patients with PFIC [3]. UDCA is the main therapeutic agent in ABCB4 deficiency but has inconsistent results in ATP8B1 and ABCB11 deficiency [1]. Especially for patients with BRIC, rifampicin accelerates the hepatic detoxification process via enzyme induction and is capable of completely aborting cholestatic episodes [4]. Biliary diversion and liver transplantation as invasive treatment options are available.

To conclude, though there are frequent and also rare diagnoses it is very important not to overlook the latter as it may lead to unnecessary (in this case 46 examinations of GGT one after the other), potentially harmful and expensive processes. Also, the normality of some laboratory

results is sometimes, as in this case, not fully appreciated. Retrospectively, pruritus with elevated serum bile acids in the presence of normal GGT in a young adult should have prompted us to perform a genetical analysis of the ATP8B1 and ABCB11 gene. Nevertheless, a liver biopsy can yield valuable information for the diagnostic process in unclear cases.

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References

1. van der Woerd WL, van Mil SW, Stapelbroek JM, et al. Familial cholestasis: progressive familial intrahepatic cholestasis, benign recurrent intrahepatic cholestasis and intrahepatic cholestasis of pregnancy. *Best Pract Res Clin Gastroenterol* 2010;24:541-553.
2. Stapelbroek JM, van Erpecum KJ, Klomp LW, et al. Liver disease associated with canalicular transport defects: current and future therapies. *J Hepatol* 2010;52:258-271.
3. van Ooteghem NA, Klomp LW, van Berge-Henegouwen GP, et al. Benign recurrent intrahepatic cholestasis progressing to progressive familial intrahepatic cholestasis: low GGT cholestasis is a clinical continuum. *J Hepatol* 2002;36:439-443.
4. Cancado EL, Leitao RM, Carrilho FJ, et al. Unexpected clinical remission of cholestasis after rifampicin therapy in patients with normal or slightly increased levels of gamma-glutamyl transpeptidase. *Am J Gastroenterol* 1998;93:1510-1517.