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Ana Alicia Tejera Hernández^{a*}, María Isabel Gutiérrez Giner^a, Juan Carlos Rocca Cárdenas^b, Fructuoso Rodríguez Rodríguez^a, Juan Ramón Hernández Hernández^a

^aServicio de Cirugía General y del Aparato Digestivo, Hospital Universitario Insular de Gran Canaria, Universidad de las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Las Palmas, Spain

^bServicio de Medicina Física y Rehabilitación, Hospital Universitario de Gran Canaria Dr. Negrín, Universidad de las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Las Palmas, Spain

*Corresponding author.

E-mail address: anath15@hotmail.com

(A.A. Tejera Hernández).

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Acute Gastrointestinal Bleeding, Multiple GIST and Intestinal Ganglioneuromatosis in a Patient With Neurofibromatosis[☆]



Hemorragia digestiva aguda en paciente con neurofibromatosis tipo 1 afecto de múltiples GIST y ganglioneuromatosis intestinal

Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary syndrome with an incidence of 1:3000 births; it is caused by alterations in the NF1 gene, which involve the development of different tumors.^{1,2} Its gastrointestinal manifestations can lead to acute gastrointestinal hemorrhages, which endanger the life of the patient.^{3,4} Although this situation is exceptional, diagnostic suspicion is essential to establish appropriate treatment, and decision making should be individualized.

We present the case of a 74-year-old man with COPD and home oxygen therapy. He had been diagnosed with NF1 at the age of 35, but refused follow-up. The clinical symptoms began with syncope, so the patient was admitted for further studies. An abdominal computed tomography scan demonstrated images of cutaneous nodules, a solid retroperitoneal mass (neurofibroma), neuroendocrine tumors in the pancreaticoduodenal groove, and gastrointestinal stromal tumors (GIST) in the jejunum and duodenum. The patient presented an episode of rectal bleeding with hemodynamic instability, requiring transfusion of packed red blood cells and perfusion of noradrenaline.

Colonoscopy and gastroscopy discovered no pathological findings. After another episode of rectal bleeding, we decided to perform urgent surgery. During the operation, multiple fibrous-looking lesions (more than 30) were identified from the angle of Treitz to the ileocecal valve, all of different sizes (up to 3 cm). Suspecting that these lesions were causing the hemorrhage, we removed the 7 largest tumors in the jejunum and intestine. A large, umbilicated and fibrous lesion was observed in the cecum, and ileocectomy and ileocolic anastomosis were performed. The gallbladder was large and the bile duct dilated, although no mass was detected in the head of the pancreas. The postoperative period was uneventful.

The pathological anatomy of the ileocectomy piece reported diffuse intestinal ganglioneuromatosis. The pathology study of the resected jejunal tumors reported multicentric GIST with multiple nodules measuring 0.5-5 cm; the predominant cell type was fusiform, histological grade 1, and resection margins were involved in more than one nodule.

Immunohistochemistry reported abnormal proliferation of fibers and enteric nerve plexuses in the submucosa and

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1. Six or more café-au-lait macules over 5 mm in diameter in prepubertal individuals and over 15mm in diameter in postpubertal individuals
2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. Freckling in the axillary or inguinal regions
4. Optic glioma
5. Two or more Lisch nodules
6. A distinctive osseous lesion (sphenoid dysplasia or thinning of long-bone cortex, with or without pseudoarthrosis)
7. First-degree relative with NF1, according to the above criteria

Fig. 1 – Diagnostic criteria for type 1 neurofibromatosis.

transmural invasion, with the presence of isolated nerve cells and small accumulations.

In the intestinal ganglioneuromatosis, positivity was reported for S-100 protein in the neural fusocellular component, negativity for CD117 (c-KIT), DOG-1, desmin, caldesmon and alpha-actin, and intense positivity of ganglion cells for calretinin.

In the multiple GIST, diffuse positivity was reported for the tumor cells for CD117 (c-KIT), DOG1 and Ki-67<1%. No change in c-KIT or PDGFR-alpha was identified, and the mutational result for exon 13 of the c-kit gene was negative.

After evaluation by the Multidisciplinary Oncology Committee for sarcomas, it was considered a multicenter wild-type GIST (negative C-KIT, negative PDGFR-alpha) with a Performance Status 3, which prevents considering treatment with tyrosine kinase inhibitors (imatinib mesylate). In the outpatient clinic visits, the patient has presented good progress, with no further episodes of rectal bleeding.

In the scientific literature from the last 10 years, there have been 3 reviews published about the gastrointestinal manifestations of NF1, and most of the references come from isolated clinical cases or short case series.

NF1 can present intra-abdominal manifestations (gastrointestinal or retroperitoneal) in 10%–25% of cases, 5% of which are symptomatic and only 2.5% require surgery.^{3,4} They usually appear in middle age, after cutaneous manifestations, as in the case presented (Fig. 1).

Intestinal involvement appears as tumors of neurogenic origin, neuroendocrine tumors, GIST and adenocarcinomas.³

GIST appear in less than 5% of cases of NF1. The majority of GIST associated with NF1 present as small, asymptomatic lesions with low mitotic activity and benign; only 15%–20% are malignant. NF1 typically presents with multicentric GIST in the small intestine, absence of mutations in KIT and PDGFR-alpha and, therefore, lack of response to imatinib mesylate, although overall and disease-free survival is similar to sporadic GIST. Treatment consists of surgical resection.^{5–8}

In patients with NF1, GIST can present concomitantly with periampullary neuroendocrine tumors in a pathognomonic manner^{1,8} (as in the case described).

In NF1, GIST and peripheral nerve sheath tumors can also coexist in the gastrointestinal tract, which can be a sign of undiagnosed NF1. Neurofibromas are the most frequent abdominal manifestation; these are benign peripheral nerve sheath tumors that mainly affect the small intestine and retroperitoneum, although they can occur anywhere from the esophagus to the anus, including mesenteric and peritoneal connective tissue. 10% are encompassed in NF1 and can become malignant in 3%–5% of cases.^{1,9,10}

Neurofibromatosis can also be associated with diffuse intestinal ganglioneuromatosis, which entails hyperplasia of the myenteric plexuses and enteric nerve fibers (located in the outer muscular layer) and leads to an intestinal motility disorder.^{9,10}

In this case, the intestinal involvement with hemorrhage could have been due to intestinal GIST and diffuse intestinal ganglioneuromatosis.

Therefore, early diagnosis of abdominal manifestations is important for proper treatment and to avoid complications. In NF1, the concomitant presence of multiple GIST and peripheral nerve sheath tumors or periampullary neuroendocrine neoplasms is pathognomonic, so these entities should be considered diagnostic markers.

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Noa de la Fuente*, Manuel Rodríguez Blanco, Gemma Cerdán, Vicenç Artigas

Unidad de Cirugía Hepatobiliopancreática y Cirugía Oncológica, Servicio de Cirugía General y del Aparato Digestivo, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

*Corresponding author.

E-mail address: noa_fh@hotmail.com (N. de la Fuente).

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Hepatic Hydatidosis in Human Immunodeficiency Virus-positive Patients[☆]



Hidatidosis hepática en pacientes positivos para el virus de la inmunodeficiencia humana

Echinococcosis is a parasitic disease that can develop as hydatidosis due to *Echinococcus granulosus* (EG) (cystic echinococcosis), cystic alveolar disease due to *E. multilocularis*, or polycystic echinococcosis.¹ Human echinococcosis continues to be endemic, and Spain is one of the countries affected, although there are no official data since 1996. Most cases are detected incidentally; when symptoms appear, these depend on the size and location of the lesions.

In patients with human immunodeficiency virus (HIV) infection, opportunistic infections are common. However, HIV-EG coinfection is rare and can be associated with disseminated echinococcosis.²

Our objective is to present 2 patients with HIV infection and cystic echinococcosis, while reviewing the literature on this rare co-infection.

A 47-year-old woman with stage A3 HIV infection came to the emergency room due to fever over the previous 2 weeks and pain in the right hypochondrium. On examination, she presented 3-finger hepatomegaly, and the lab analysis demonstrated: 12 800 leukocytes/L; alkaline phosphatase 251 IU/L; GGT 178 IU/L; PCR 156 mg/L.

Computed tomography showed a hepatic hydatid cyst measuring 11.5 cm in segments VII–VIII, with biliary communication and compression of the inferior vena cava (IVC) (Fig. 1A). The serology was positive for *Echinococcus* (1/1280). Treatment was started with oral albendazole 400 mg/12 h and piperacillin-tazobactam 4 g/0.5 g/8 h/iv. Percutaneous drainage was performed, and *Streptococcus oralis* was isolated in the sample.

ERCP revealed cystobiliary communication, cystic material in the bile duct and papillary stenosis, and balloon dilation

was performed. Elective surgery was scheduled, during which a hydatid cyst was observed, adhered to the diaphragm and causing partial compression of the IVC. Subtotal cystectomy was performed, leaving a patch over the IVC.

The postoperative period was uneventful, and the patient was discharged on the 4th postoperative day (POD) (Clavien 0), with albendazole treatment for one month.

A 41-year-old man, with a history of partial cystectomy due to hepatic hydatidosis, stage B3 HIV infection and HCV infection with F2 fibrosis, came to the emergency room for fever, jaundice and abdominal pain that had persisted for 4 days. Lab work revealed: 13 200 leukocytes/L; GGT 472 U/L; alkaline phosphatase 144 U/L; total bilirubin 5.3 mg/dL.

Computed tomography revealed recurrence of a 6.4-cm hydatid cyst that almost completely occupied the left liver lobe, with compression of the left bile duct, splenomegaly and signs of portal hypertension (Fig. 1B).

Treatment was started with oral albendazole 400 mg/12 h and piperacillin/tazobactam 4 g/0.5 g/8 h/iv. During elective surgery, a hydatid cyst was observed with left intrahepatic biliary communication and signs of chronic liver disease; and left hepatectomy was carried out with biliary reconstruction over plastic prosthesis. In the postoperative period, the patient presented ascites, which was managed with spironolactone, and a biliary fistula that was resolved by repositioning the prosthesis and percutaneous drainage (Clavien IIIA). The patient received treatment with oral albendazole for one month.

Hydatidosis is a health problem in endemic areas such as Spain. Its most frequent locations are the liver (70%–80%) and lungs, and less frequently the spleen and kidneys.^{1,3}

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