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CLINICAL NOTE

Peutz-Jeghers syndrome and duodeno-jejunal adenocarcinoma – therapeutic implications

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ABSTRACT

The Peutz-Jeghers syndrome (PJS) is an autosomal dominant hamartomatous poliposis described in 1921. Hemminki in 1997 described the presence of LKB-1 mutation tumor-suppressor gen.

The patients with PJS develop a higher cumulative incidence of gastrointestinal, pancreas and extraintestinal tumors, being occasion of a renew interest on hamartomatous polyposis syndromes regarding the clinical care, cancer surveillance treatment and long term follow-up.

We report the case of a 38 years old male, diagnosed of PJS who developed a multiple adenocarcinoma in duodenum and yeyunum. Surgically treated and with a long-term free disease survival of 11 years represents the sixth case reported in the spanish literature of PJS associated with a gastrointestinal tumor.

A critical review, molecular alterations and the established criteria of tumor screening and surveillance are reviewed.

Key words: Peutz-Jeghers syndrome. Hamartomatous. Carcinogenesis. Intestinal polyposis. Hereditary cancer.

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INTRODUCTION

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disease characterized by the presence of multiple hamartomatous polyps throughout the entire gastrointestinal tract and mucocutaneous melanin pigmentation (1-6).

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Hemminki, in 1997, described a deletion in the short arm of chromosome 19, a mutation in the LKB-1 gene (also known as STK11) (7-10). In this syndrome a high cumulative incidence of tumors in the gastrointestinal tract and other locations (breast, lung, gynecologic) has been reported. A renewed interest in its molecular pathogenesis and in the surveillance and screening strategy has been observed (1,4-6).

CASE REPORT

A 38-year-old male with a previous diagnosis of PJS was hospitalized in another center for nausea, vomiting, and abdominal pain. Upper endoscopy revealed a complete obstruction of the duodenal lumen by an extrinsic mass, which prompted referral to our center.

An abdominal computed tomography (CT) scan (Fig. 1) revealed a solid mass with hypodense areas and infiltrating appearance compromising the duodenal lumen, and a jejuno-jejunal intussusception was described. Gastroscopy confirmed the presence of multiple gastric polyps and complete duodenal obstruction. Citology revealed malignant cells.

The patient underwent pancreticoduodenectomy with a simultaneous resection of 23 cm of jejunum with signs of intussusception. The patient required no blood transfusion and had an uneventful postoperative course except for an episode of self-limited hematochezia.

The histopathological examination revealed what follows: "The main tumor measured 6 cm in diameter and was located in the duodenum. This tumor obstructed the duodenum, infiltrated the pancreas, and showed large cystic areas between 5 and 9 mm in diameter (Fig. 2). The duodenal tumor showed an atypical epithelial glandular growth pattern, which infiltrated the wall of the small bowel and pancreas (Fig. 3). Two other similar infiltrating tumors, which measured between 1.5 and 5 cm in diameter, and occupied the entire intestinal wall, were located in the jejunum. The atypical glands were fre-

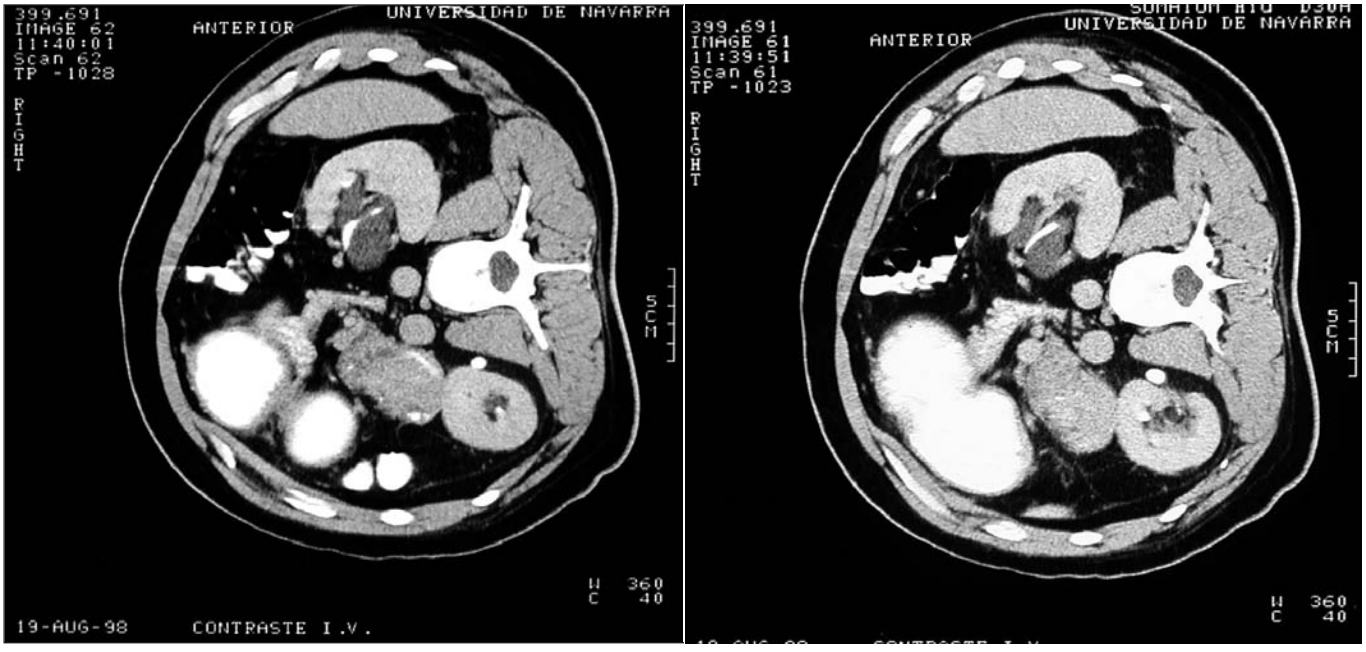

Fig. 1. Axial abdominal CT showing a tumor in the head of the pancreas that obstructs the duodenal lumen.

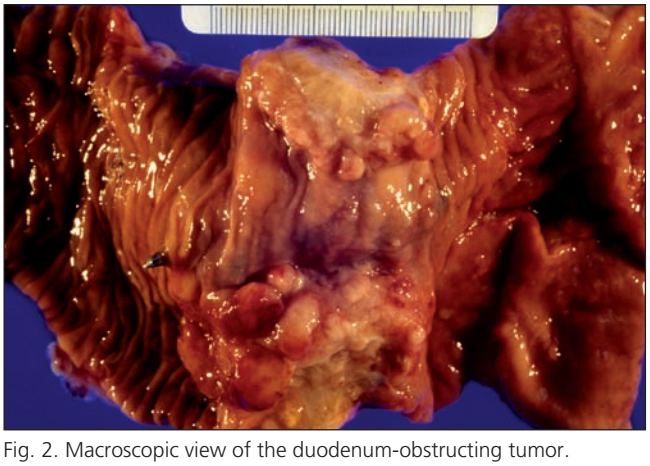

Fig. 2. Macroscopic view of the duodenum-obstructing tumor.

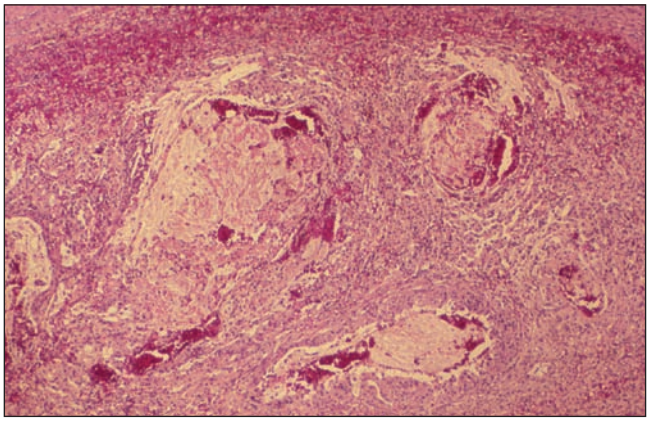

Fig. 3. Microscopic appearance of the tumor showing infiltrating cells into the pancreas.

quently cystic and showed characteristics similar to those in the duodenum. No metastatic tumor was identified in the periportal or peripancreatic lymph nodes. Primary well-differentiated multifocal adenocarcinomas originating from pre-existing polyps were diagnosed.

Multiple polyps in the stomach and jejunum were observed. Gastric polyps were numerous and measured between 1 and 4 mm in diameter. Three pediculated jejunal polyps, which measured up to 3 cm in diameter, were observed. Histologically, these tumors showed either hyperplastic or adenomatous characteristics. The glands were cystic and covered with moderately to severely dysplastic mucosecretory epithelium. Frequent bundles of smooth muscle from the muscularis mucosae were spread among the atypical glands".

A PJS diagnosis had been first established in 1989 when the patient was 29 years old. The patient required and urgent intestinal resection for an intestinal intussusception and subsequent bowel obstruction. Several hamartomatous polyps and phenotypical features – mucocutaneous melanosis – were assessed. There was no family history of "intestinal problems".

The patient has been followed up for 11 years and remains asymptomatic and recurrence-free. A surveillance program was implemented with gastroscopies, double-balloon enteroscopies, two capsule endoscopy studies, and seven colonoscopies. Fifteen gastric hyperplastic polyps and 11 hamartomatous polyps, 9 jejunal hamartomatous polyps without epithelial dysplasia, 7 colon hamartomatous polyps, and 3 adenomatous polyps with

low-grade dysplasia foci were removed without complications.

DISCUSSION

Peutz-Jeghers syndrome (PJS) was first described by Peutz en 1921, and then by Jeghers in 1949 (11,12). In 1954 Bruwer "coined" the eponym "Peutz-Jeghers" (13). PJS is characterized by the presence of multiple adenomatous and hamartomatous polyps along the gastrointestinal tract in association with melanocytic pigmentation around the mouth, but also in the hands and feet and axillary pits. An incidence of 1/8,300 to 1/200,000 live births has been estimated, and the condition is an autosomal dominant disease that affects both males and females, and is found in all racial groups.

Three series reviewed 404 PJS patients and reported jejunal polyps in 78%, colon polyps in 42%, gastric polyps in 38%, and rectal polyps in 28% of patients (1-3,6). Epithelial dysplasia foci and invasive carcinoma have been reported in 26% of polyps (9).

Hemminki was first to describe a deletion in the short arm of a chromosome 19 region, which was later identified as a mutation in the LKB-1 gene (19p 13.3), also known as STK11 (serine/threonine-protein/kinase 11). LKB-1 acts as a tumor suppressor gene and is believed to regulate cell orientation, polarization and apoptosis. A loss of LKB-1 function leads to hamartomatosus polyp formation and tumor formation because of epithelial polarity disruption. This molecular alteration has been reported in 30 to 82% of PJS patients (8-10,14-20).

In addition to the clinical diagnosis and polyp-related complications such as intestinal obstruction (14%), abdominal pain (23%), rectal bleeding (14%), and polyp intussusception (40%) (1-3,6,10), the most challenging clinical aspect is early tumor or preinvasive lesion identification.

Germ-line mutations are present in 70% of families with complete penetrance. The cumulative risk of developing cancer is 93% at 65 years of age, with a median age at presentation of 43 years. There have been no differences in cancer incidence between patients with and without molecular mutations.

The reported case shows a strong correlation with the natural course of the disease. The patient was diagnosed at 29 years of age on presenting with an acute abdominal complication (1-3,6,10,21,22) and developed multiple gastrointestinal cancer at 38 years. It represents the sixth case of intestinal adenocarcinoma in PJS in the Spanish literature, with previous cases being gastrointestinal adenocarcinomas (stomach, jejunum, jejunum-ileum, and colon) and one case of simultaneous renal, rectal and cholangiocarcinoma (23-27).

Dozois et al reported in 1969 eleven cases of gastrointestinal cancer out of 321 PJS patients (4 in the stomach, 3 the in duodenum, 1 in the ileum, and 3 in the colon and rectum) (28).

In 2000 Gianderlo conducted a meta-analysis in order to define cancer risk in a PJS population, and studied 210 patients from 6 case-series published in Holland and the UK. The relative risk of cancer was 15.2 with no gender-specific differences. Age at presentation was 42.9 ± 10.2 years, similar to our reported case (38 years). The cumulative risk of cancer was 93% at 65 years. The highest cumulative incidence was: breast (54%), colon (39%), pancreas (36%), stomach (29%), and ovary (21%) (29).

In a later report of 419 PJS patients the cumulative risk of cancer at age 70 was 85%, four times superior to the general population. Again colo-rectal and breast tumors were most frequent (30). The relative risk of gastric and small-bowel cancer was 84; 213 and 520, respectively, when compared to the general population (95% CI) (29).

In Gianderlo's study, six patients developed pancreatic cancer; age at diagnosis was 41 years with a relative risk of 36% for this tumor, which supports the need for surveillance to facilitate early detection for pancreatic cancer (31-33).

Hearle reported 11 cases of pancreatic cancer in 4,109 individuals with PJS syndrome, but did not report the outcomes of these cases (30).

Today the existence of precursor lesions giving rise to invasive pancreatic cancer is well established, with a pattern similar to the adenoma-carcinoma sequence previously described for colon cancer (34-36). This offers an opportunity to detect local precursor lesions such as pancreatic intraepithelial neoplasia (Pan IN) or early invasive lesions (< 3 cm), which are amenable to curative resection. Screening for invasive pancreatic cancer and its precursors is currently recommended with endoscopic ultrasonography (EUS) and computed tomography (CT) annually, followed by endoscopic retrograde cholangiopancreatography (ERCP) and fine-needle aspiration for suspect lesions (37).

In the Johns Hopkins experience seven patients out of 38 PJS patients underwent pancreatoduodenectomy. One of them had an adenocarcinoma of 2.8 cm, and remains

Table I. Case series of malignant tumors in Peutz-Jeghers syndrome

Author (ref.)	*Year*	*Patients*	*GI(*) cancer*	*Non-GI cancer*
Utsunomiya (42)	1975	102	12	5
Linos (43)	1981	27	1	3
Giardiello (44)	1987	31	4	11
Spigelman (45)	1989	72	10	7
Boardman (46)	1998	34	10	16
Choi (47)	2000	30	4	1
Lim (48)	2004	240	19	35
Hearle (30)	2006	419	40	26
Mehenni (5)	2007	170	17	10
Total		*1,125*	*107*	*114*

*GI: gastrointestinal.

Table II. Surveillance recommendations by age and sex*

Age (years)	*For males*	*For females*
From birth to 12	History/physical exam. Testicle exploration (ultrasounds every 2 years through year 12)	History/physical exam
At age 8	Upper endoscopy. Upper and small bowel follow-through series (if positive, every 2-3 years)	Upper endoscopy. Upper and small bowel follow-through series (if positive, again every 2-3 years)
At age 10	Capsule endoscopy every 2-3 years	Capsule endoscopy every 2-3 years
From age 18 on	Colonoscopy, upper endoscopy every 2-3 years	Colonoscopy, upper endoscopy every 2-3 years. Breast self-examination monthly
From age 21 on	Endoscopic ultrasounds every 2 years (abdominal CT and CA-19.9 optional)	Pelvic exam, transvaginal ultrasounds and serum CA-125 annually. Mammography annually (abdominal CT every 2 years and CA-19.9 is optional)

*Adapted from Giardello (39).

free of disease five years after surgery. The other six had pain with various grades (38).

PJS patients must be included in specific follow-up programs with screening for pancreas cancer (39-41).

Table I depicts the most numerous series and the incidence of cancer in PJS patients, and table II shows screening techniques and surveillance strategies (49-54).

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