MULTIDISCIPLINARY APPROACH TO PEUTZ-JEGHERS SYNDROME – DISCUSSIONS ON A CLINICAL CASE

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Summary

Peutz-Jeghers syndrome, first described in 1921 by Peutz and later on, in 1949, by Jeghers, is a relatively rare condition characterized by the association between cutaneous-mucosal pigmentation alterations with a specific distribution and multiple hamartomatous colonic polyps with an onset during the first 10 years of life and with a 10-18 times higher risk of malignant degeneration than that of the general population [1,2,3,4,5,6,7].

Clinically, Peutz-Jeghers syndrome is characterized by cutaneous lesions consisting of brown-black or bluish pigmented macules similar to ephelides that are predominantly distributed on the cephalic extremity, as well as on the palmo-plantar and perianal regions, and are associated with gastrointestinal disorders (gastrointestinal hamartomatous polyps, occlusions and intestinal intus-susceptions) and various neoplasms (digestive, thyroid, breast, genital and lungs) [7].

Taking into account the multiorgan involvement and the increased risk of severe complications, the multi-disciplinary approach of these patients is essential for therapeutic success.

In the present paper we present the case of a 53-year-old patient who requested a dermatological consultation for multiple pigmented labial macules of brownish-black color, affirmatively evolving since childhood. Anamnestically, the patient stated irregular bowel habits with diarrhea-constipation alternations, so that the patient was referred to the general surgery service, where a laparoscopic sigmoidectomy was performed for multiple suspicious-looking polyps that were discovered colonoscopically. The histopathological examination of the biopsy material established the diagnosis of Peutz-Jeghers syndrome.

Keywords: *genodermatoses, Peutz-Jeghers syndrome, colonic polyposis.*

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Introduction

Peutz-Jeghers syndrome represents a disease with genetic determinism, that is caused in about 90% of cases by familial or sporadic mutations with autosomal dominant transmission of the STK11/LKB1 gene located on chromosome 19p13.3, which encodes serine/threonine kinase 11, a tumor suppressor enzyme with a major role in cell cycle regulation; to date, there haven't been identified other genes responsible for this disorder [12,13,14].

Worldwide, a variable **incidence** between 1:25.000-300.000 births has been estimated, with a relatively equal sex distribution and without racial predispositions [1,2,3,5].

Regarding the **etiopathogenesis** of this condition, following several studies conducted among patients diagnosed with Peutz-Jeghers syndrome, it was noted that the STK11/LKB1 gene encodes an ubiquitous protein with a tumor suppressor role and also with a regulatory role for some enzymes from the kinase family [5,12]. Thus, the overexpression of the STK11 gene causes the cell cycle to stop in the G1 phase and it was also observed that the healthy allele of the STK11 gene was inactivated in biopsy samples taken from colonic polyps of patients with Peutz-Jeghers syndrome, regardless of whether the studied lesion was benign or malignant [5,15 ,16]. On the other hand, it has been proved that there are interactions between p53 tumor suppressor pathways and the LKB1 gene pathway, which has the function of regulating kinases of the adenosine monophosphate-activated protein kinase family, with a role in regulating cellular metabolism and the cellular response to stress [5,15,16]. Given the variable penetrance and phenotypic expressivity, there is a wide spectrum of clinical expressions of these mutations that are responsible for the appearance of specific skin macules and colonic polyps, as well as tumorigenesis [5,15,16,17,18].

From a **clinical** point of view, the mucocutaneous lesions of Peutz-Jeghers syndrome frequently have an onset before the age of 5 and are represented by pigmented macules of brown, blackish or dark blue color, of round-oval shape or with an irregular outline, varying in size between 1-5 mm, diffusely distributed on the cephalic extremity, especially on the oral mucosa and on the labial, perioral and perianal areas, but also on the nails, palmo-plantar and perianal regions and in some cases, on the intestinal mucosa [5,12,13]. Oral mucosal lesions tend to be permanent, while other skin macules may be transient, with improvement or complete disappearance after adolescence, although there have also been reported rare cases with an onset during adulthood [5,12,13].

Pathognomonic gastrointestinal hamartomatous polyps most frequently affect the jejunum, are often formed in the first decade of life, become symptomatic in about 50% of cases by the age of 20-30 years and can generate multiple potentially life-threatening complications, such as chronic gastrointestinal hemorrhages with anemic syndromes or intussusceptions of the small intestine and repetitive intestinal obstructions that affect up to 70% of patients between the ages of 6-18 years, resulting in repetitive intestinal resections [5,7,12].

The malignant complications of Peutz-Jeghers syndrome represent another cause of increased morbidity and mortality in this category of patients for which there has been estimated an 81-93% risk of polyps transforming into gastrointestinal adenocarcinomas, with the mention that approximately 48% of cases of malignant degeneration tend to occur by age 57 [1,3,19,20]. At the same time, Peutz-Jeghers syndrome is associated with an increased risk of pancreatic tumors, thyroid papillary carcinomas, breast cancer, genital tumors (cervical, uterine, ovarian, testicular Sertoli tumors associated with gynecomastia) and lung tumors [1,2 ,3,4,5,6,7].

Clinical Case

In the current paper we present the case of a 53-year-old patient of rural provenience, affirmatively known to have undergone segmental enterectomy around the age of 30 for intestinal polyposis (no supporting documents) and that is suffering from essential hypertension (TAs max = 160 mmHg) in treatment with perindopril/-indapamide 5/1.25 mg 1 cp/day, who requested a dermatological consultation for multiple hyperpigmented lesions of the perioral area and

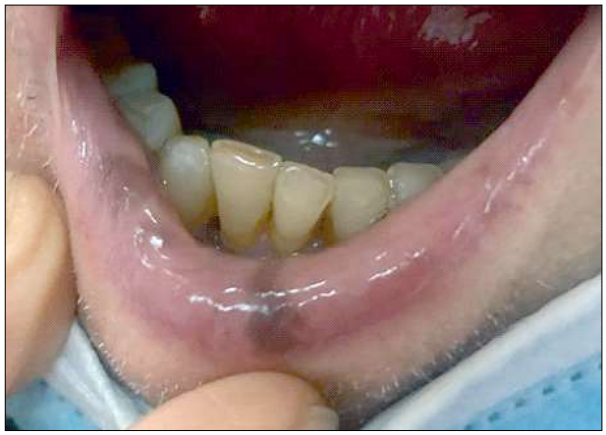
oral mucosa, affirmatively evolving since childhood.

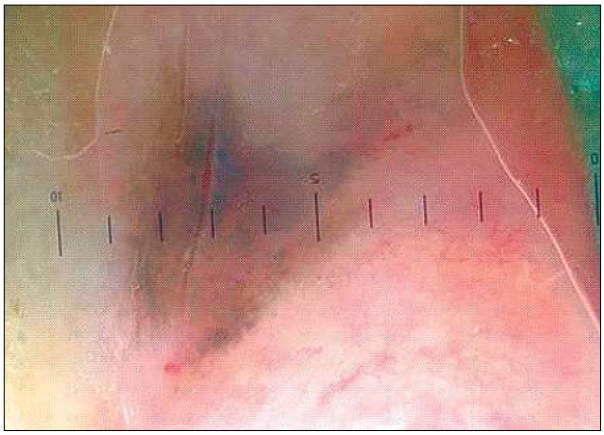
The patient denies significant heredocollateral history.

Regarding lifestyle and hygienic-dietary regime, it should be noted that the patient is a smoker (30 PY), consumes coffee and alcohol, occasionally, and does not work in a toxic environment.

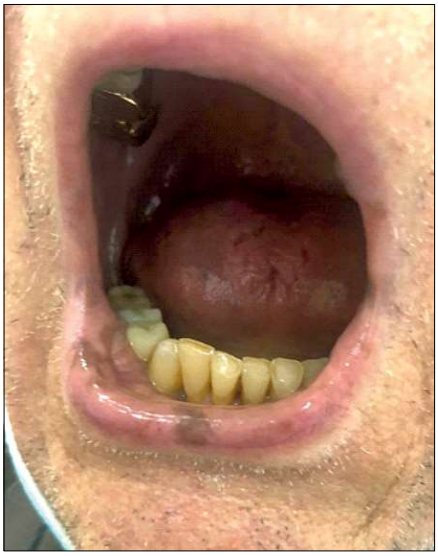
Upon dermatological clinical examination, there could be observed multiple oval or irregular brownish-black well-defined macules with sizes between 0.2 - 1 cm, located on the oral mucosa and lips, predominantly affecting the lower lip (figure 1,3,4). Dermoscopy revealed a relatively homogeneous pigment network with paler areas showing punctate granulations and a more intensely colored peripheral region with multiple confluent pigment globules (Figure 2).

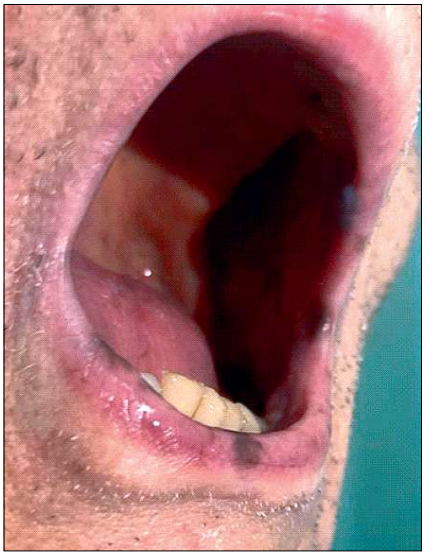
The general clinical examination showed a kyphotic thorax, a bilaterally present vesicular murmur with a rough tonality and without rales, an increased cardiac dullness, rhythmic heart sounds without valvular murmurs, BP = 130/90





Figures 1 and 2. Peutz-Jeghers syndrome, macroscopic (1) and dermatoscopy (2) appearance - labial hyperpigmented macules





Figures 3 and 4. Peutz-Jeghers syndrome - hyperpigmented macules of the lips and oral mucosa

mmHg, AV = 68 bpm. The clinical examination of the digestive system revealed a supple median post-laparotomy scar, a supple and elastic abdomen mobile with breathing, discreetly painful both spontaneously and upon palpation (diffusely and accentuated in the left iliac fossa), affirmative irregular bowel habits with diarrhea-constipation alternation with predominance of constipation, and without signs of peritoneal irritation. Otherwise, the general clinical examination was within normal limits.

Regarding laboratory analyses, the complete blood count showed biological inflammatory syndrome with leukocytosis (10,650/µl) without changes in the leukocyte formula and an accelerated erythrocyte sedimentation rate (ESR 45 mm/h).

Following the anamnesis and the objective clinical examination, the presumptive diagnosis of Peutz-Jeghers syndrome was established, and the patient was referred to the general surgery service for clinical-paraclinical investigation and establishment of a specialized treatment.

Colonoscopy up to the ileocecal valve revealed colonic polyposis with an aspect suspicious of malignant degeneration, so that a thoraco-abdominal CT examination and pelvic MRI with contrast substance were performed, through which the etiology of the lesions detected upon colonoscopy was not elucidated, although other pathologic alterations were excluded.

Therefore, the multidisciplinary committee consisting of an oncologist, a general surgeon and a gastroenterologist proposed a sur-gical therapeutic to the patient. The patient underwent laparoscopic sigmoid resection with T-T colo-rectal anastomosis (figure 5) without intra-operative incidents and accidents, and with a favorable postoperative evolution lacking complications.

Histopathological examination of the biopsy material confirmed the diagnosis of hamartomatous polyps in Peutz-Jeghers syndrome (images 6, 7 and 8).

The patient was discharged in surgical recovery, hemodynamically and cardio-respiratory stable, with a good physical condition and with recommendations to stop smoking and to abide by a low-sodium, hypolipidemic and fiber-rich

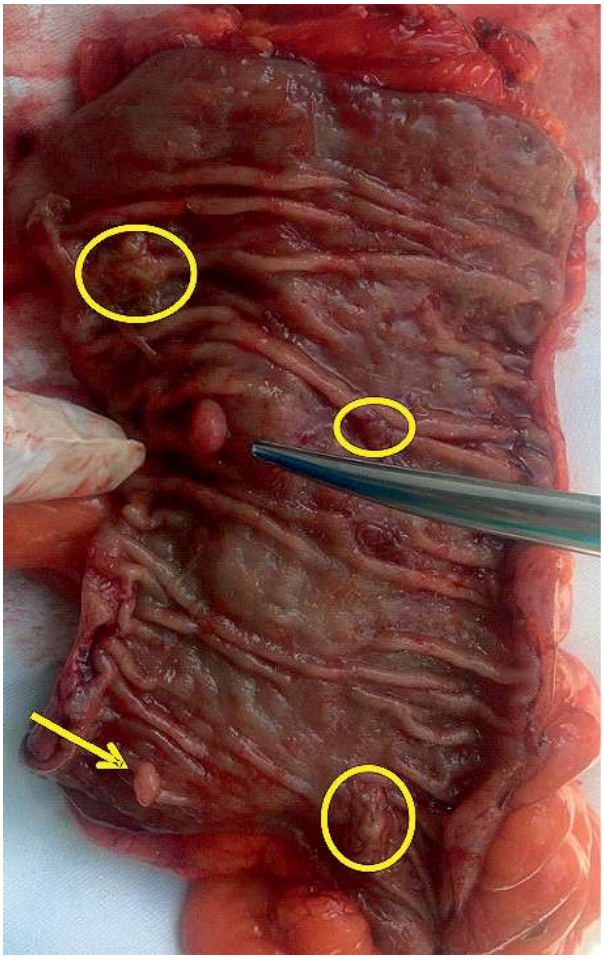
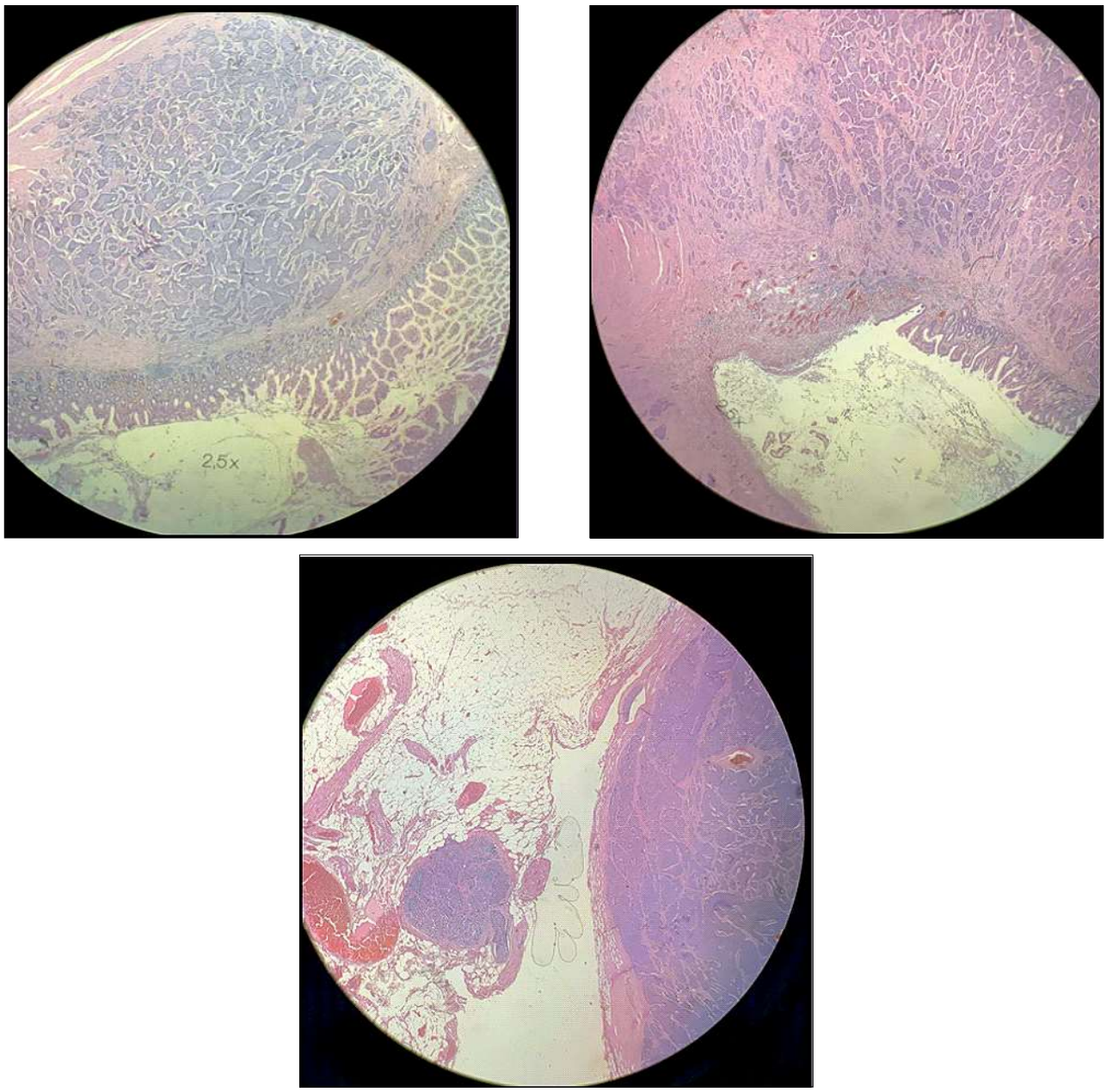


Figure 5. Sectioned sigmoidectomy specimen – colonic polyposis and hypertrophy of some folds of the colonic mucosa in a patient with Peutz-Jeghers syndrome

hygiene-dietary regime, to consume at least 2 liters of liquids/day, to use permanent photo-protection, to avoid exposure to UV radiation, adverse climatic conditions and intercurrent infections, trauma and psycho-emotional stress, as well as to perform periodic dermatological, gastroenterological and surgical reevaluations.

At the same time, the patient was informed about the genetic determinism, evolution and possible complications of Peutz-Jeghers syndrome, more precisely about the fact that he suffers from a disease that can be passed on to offspring and has a chronic evolution of variable severity that can change with age, with the improvement of clinical manifestations having been reported in some cases, while in other cases



Figures 6, 7 and 8. Histopathological aspect of hamartomatous polyp (hematoxylin-eosin)

it was found that the disease had aggravated over time and multiple oncological or surgical gastrointestinal complications had developed. Therefore, genetic testing of the patient was recommended, as well as family investigation, genetic testing of blood relatives and genetic counseling for descendents that desired to procreate.

Discussions

The **paraclinical evaluation** of patients suspected of Peutz-Jeghers syndrome includes a complete set of laboratory tests, genetic testing if possible, histopathological examination of biopsy samples taken from patients upon indication, as well as complex imaging studies performed

periodically, adapted to individual symptomatology and clinical manifestations.

Histopathological examination of skin biopsy specimens taken from patients with Peutz-Jeghers syndrome reveals increased melanin within the basal cells and proliferation of melanocytes at the dermoepidermal junction [1,4]. The histopathological examination of gastrointestinal polyps shows hyperplasia of smooth muscle fibers and a tree-like pattern of polyp formation towards the epithelial layer, with epithelial islands in the muscle layer, frequently associated with chronic inflammatory edema of the lamina propria and deposits of eosinophilic mucin at the level of dilated cystic glands [5,21,22,23].

Starting from the age of 18, it is recommended to carry out the following laboratory analyses annually: blood count, liver and kidney samples, ionogram, sideremia, transferrin, total iron binding capacity, ESR, C-reactive protein, tumor markers - CEA, CA19-9 and CA125, as well as occult bleeding test [1,5].

Imaging investigations recommended for patients with Peutz-Jeghers syndrome include upper and lower gastrointestinal endoscopy every 1-3 years starting at age 12, video capsule enteroscopy in symptomatic patients without endoscopically detectable changes, endoscopic ultrasound and/or MR-cholangiopancreatography every 1-2 years starting at the age of 25-30, mammography and/or breast ultrasound every 1-2 years starting at the age of 25, transvaginal ultrasound and annual Babeș-Papapanicolau test starting at the age of 18, annual testicular ultrasound starting at the age of 10 years, as well as thoraco-abdominal computed tomography completed by pelvic MRI with contrast and CT enterography in selected cases [1,5,7].

In order to establish the diagnosis of Peutz-Jeghers syndrome, at least one of the following **diagnostic criteria** established by WHO (World Health Organization) is required [5,24]:

- at least 3 histopathologically-confirmed Peutz-Jeghers polyps;
- at least one histopathologically-confirmed hamartomatous polyp associated with heredocollateral history of Peutz-Jeghers syndrome or pathognomonic cutaneo-mucosal lesions;
- pathognomonic cutaneo-mucous lesions associated with hereditary Peutz-Jeghers syndrome.

In the case of the presented patient, the second WHO diagnostic criteria was fulfilled, so that the diagnosis of Peutz-Jeghers syndrome could be established.

The **differential diagnosis** of Peutz-Jeghers syndrome includes familial juvenile polyposis, Cowden syndrome, Bannayan-Riley Ruvalcaba syndrome, and Laugier-Hunziker syndrome [7,25].

The **management** of Peutz-Jeghers syndrome requires clinical-paraclinical reevaluation according to the previously mentioned protocol and interdisciplinary collaboration for the early detection of malignant and/or acute gastrointestinal complications.

Regarding the hygienic-dietary regime and the rules of prophylaxis, it is indicated to avoid products that cause photosensitisation, the use of permanent photoprotection with SPF 50 + photoprotectors against UVA and UVB ultraviolet radiation associated with wide-brimmed hats, glasses with dark lenses and natural, wide clothes, to cover as much of the body surface as possible, even if the transformation of the pigmented cutaneo-mucosal lesions has not been reported in the specialized literature [1,5,12].

The therapeutic approach to gastrointestinal polyps depends on their number, size, location and appearance and varies from endoscopic polypectomies of polyps up to 1 cm in size, performed in the gastroenterology or general surgery service, respectively to segmental enterectomy for multiple polyps with dimensions over 1 cm and suspicious macroscopic appearance, performed predominantly laparoscopically in general surgery services [3,26]. Endoscopic treatment of colonic polyposis is preferred whenever possible, due to its minimally invasive nature, which limits peri- and postoperative complications [5,21]; a non-negligible risk in the case of repeated laparotomies and intestinal resections is represented by the adhesion-related disorder that can be complicated by intestinal obstructions requiring new surgical interventions and new enterecto-

mies, and over time these patients can suffer from short bowel syndrome associated with intestinal malabsorption, hydroelectrolytic imbalances and protein-caloric malnutrition.

Recent studies have reported promising results with reductions in the size and number of gastrointestinal polyps after the use of mTOR inhibitors like rapamycin in experimental animal models with STK11 mutations, as well as cyclo-oxygenase 2 inhibitors like celecoxib in both experimental animal models with LKB-1 mutations, as well as in studies on human subjects [5,21].

Acute gastrointestinal complications require emergency surgical treatment, and neoplastic complications benefit from standard oncological treatment.

Peutz-Jeghers syndrome is an incurable condition, with a chronic **evolution** of variable severity, and the **prognosis** of these patients depends on the severity of the clinical manifestations; in severe cases, the quality of life and life expectancy of the patients, who may also suffer from depression, are significantly affected.

In the case of the presented patient, a good vital prognosis can be estimated in the absence of malignant or acute gastrointestinal complications.

Conclusions

Peutz-Jeghers syndrome represents a genodermatosis with multi-organ involvement and increased neoplastic risk, so that it is mandatory to carefully monitor these patients according to the latest international protocols, with the collaboration of a multidisciplinary team consisting of a geneticist, a dermatologist, an internist, a gastroenterologist, a general surgeon, a gynecologist and an urologist.

Given the genetic determinism of Peutz-Jeghers syndrome, genetic testing and counseling are of particular importance in the management of these patients, the later aiming to explain complex information regarding genetic risks, methods of anamnestic and clinical-paraclinical investigation, stages of diagnosis and therapeutic options, as well as having the role of providing psycho-emotional support and directing patients towards modern medical services specialized in this regard and adapted to individual needs.

The current case was presented due to the rarity of the disease and the peculiarity of the onset of gastrointestinal manifestations at an older age than that usually reported in the specialized literature.

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Conflict of interest
NONE DECLARED

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