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Peutz - Jeghers Syndrome: A Rare Familial Syndrome

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Abstract: ***Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant inherited disorder characterized by mucocutaneous hyperpigmentation, intestinal and extraintestinal hamartomatous polyps with increased risk of gastrointestinal and extraintestinal malignancy. We report on a case of 16 years old male who presented with colicky abdominal pain, associated with nausea, vomiting for 4 days, which was relieved spontaneously. Patient also had 6 episodes of similar complaints in the past one year. The imaging studies revealed intussusception and large intestinal wall thickening. Intra operative findings show multiple polyps in both small and large intestine. A diagnosis of Peutz - Jeghers syndrome was made on characteristic histopathological examination of polypectomy specimens and presence of characteristic prominent mucocutaneous pigmentation.***

Keywords: Peutz - Jeghers syndrome; Hamartomatous polyps; intussusceptions; melanotic macules

1. Introduction

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant condition determined by a mutation localized at19p13.3; characterized by mucocutaneous hyperpigmentation, intestinal and extraintestinal hamartomatous polyps with increased risk of gastrointestinal and extraintestinal malignancy[1],[2]. The diagnosis of PJS is mainly based on clinical findings and histopathological patterns of polyps. Peutz Jeghers syndrome is associated with significant morbidity, variable clinical course and considerable predisposition to gastrointestinal and non-gastrointestinal malignancies. An overall recommendation for PJS patients includes not only gastrointestinal multiple polyps resolution, but also regular lifelong cancer screening. Early detection and proper surveillance are vital to minimize the risk of carcinoma.

2. Case Report

16 year old male patient presented with colicky abdominal pain, associated with nausea, vomiting for 4 days. Patient had 6 similar episodes in the past one year, which were relieved by taking symptomatic treatment (oral medication).On general examination patient is moderately built and moderately nourished with pallor, melanotic macules on the lip and hard palate (Fig 1). Per abdominal examination revealed a vague lump in right hypochondrium and right paraumbilical region which was non tender and elastic in consistency. The patient's younger brother also had similar complaints.

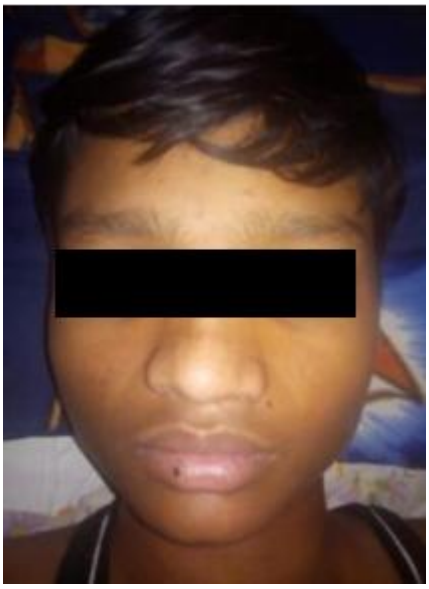

Figure 1: Melanotic macules

Laboratory investigations revealed low hemoglobin concentration: 9.2gm% and peripheral smear shows microcytic hypochromic anemia. Routine blood chemistry reports were unremarkable.

USG and Barium meal follow through were compatible with jejunojejunal intussusception (Fig2). CT shows long segment wall circumferentially thickened (?polyp) and calcified from subhepatic segment to mid level with no significant lumen narrowing, transverse colon and sigmoid colon wall thickened, lumen dilated (Fig3a, Fig3b).

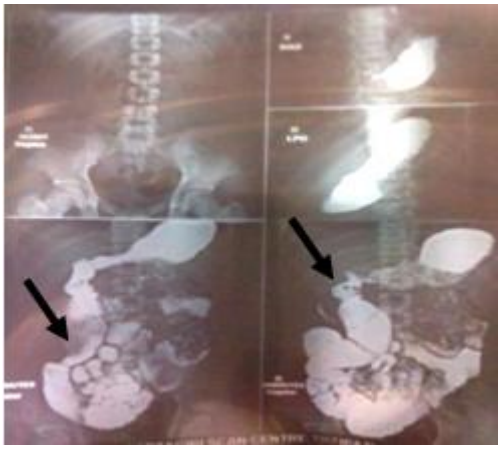

Figure 2 : Barium meal follow through

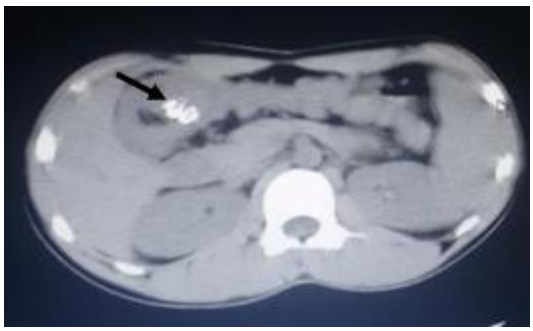

Figure 3 (a)

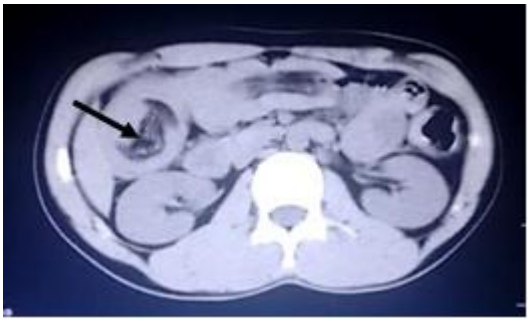

Figure 3 (b)

Figure 3: CT images showing calcification (3a) and polyp (3b).

Patient underwent an exploratory laparotomy, total four jejunojejunal, jejunoileal intussusceptions were noted (Fig: 4a, 4b). Total 7 Palpable polyps identified one each at the site of intussusception, one 30cm distal from duodenojejunal junction, one 20cm proximal to ileocecal junction showing calcifications, and another in middle 1/3rd of transverse colon. Enlarged mesentric lymph nodes were noted. Enterotomies done at the site of polyps and polypectomies done. (Fig: 4c)

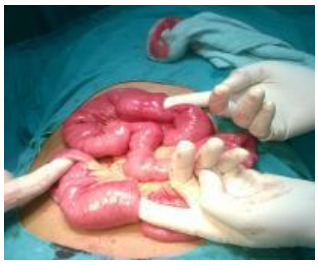

Figure 4 (a)

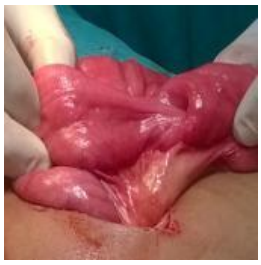

Figure 4 (b)

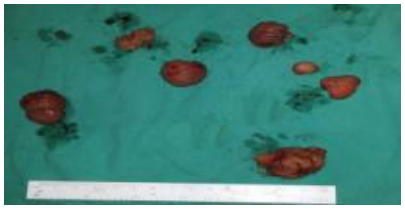

Figure 4(c)

Figure 4: Intra operative findings showing intussusceptions (4a &4b) and polypectomy specimens (4c)

Histopathology

We received multiple (7) cerebriform polypoidal masses, largest mass measuring 2.5x2.5x1cm. Cut section of all masses showed gray tan with focal mucoid areas, in addition larger mass showed focal chalky white areas (Fig: 5). Microscopically, sections from the polyp showed intestinal mucosa with tubular glands lined by tall columnar epithelium and goblet cells , focal cystic areas filled with mucin (Fig: 7a) and focal surface ulceration. Lamina propria shows smooth muscle proliferation with characteristic arborisation, traversing between crypts and chronic inflammatory cell infiltrate (Fig: 6a, 6b). Sections from one polyp also show areas of calcification in submucosa (Fig: 7b). No evidence of malignancy/ dysplasia. Histological features were consistent with hamartomatous –Peutz Jeghers polyp.

On the basis of characteristic hamartomatous small intestinal polyposis and clinical manifestation of mucocutaneous pigmentation the diagnosis of peutz-jeghers syndrome was rendered.

Figure 5 (a)

Figure 5 (b)

Figure 5: Gross - multiple polypoidal masses (5a) and cut section shows gray tan with focal calcifications (5b)

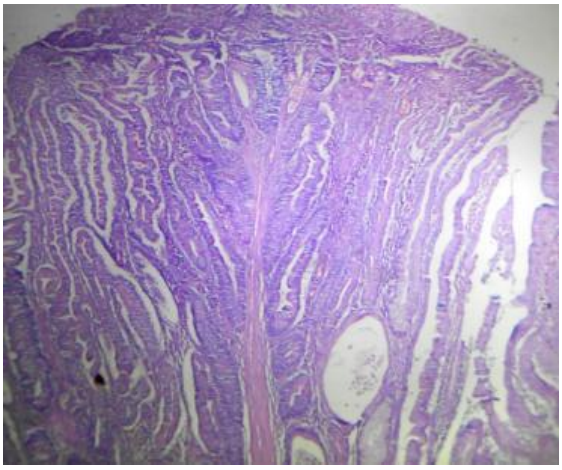

Figure 6 (a)

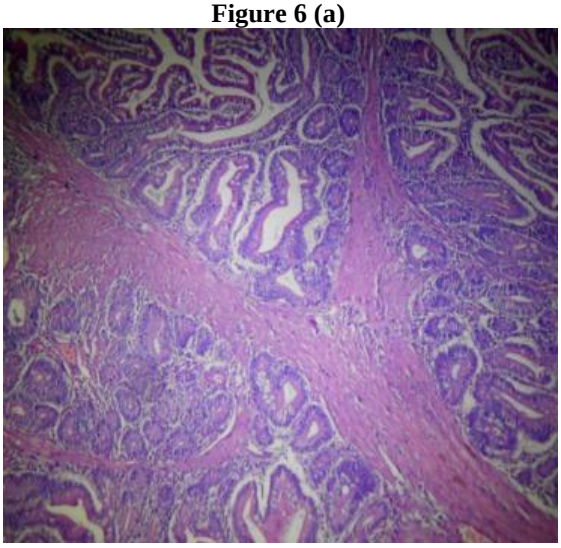

Figure 6 (b)

Figure 6: Small intestinal polyps with characteristic smooth muscle arborisation (6a and 6b)

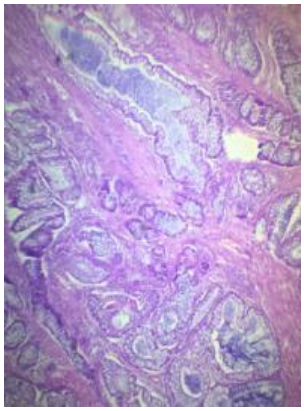

Figure 7 (a)

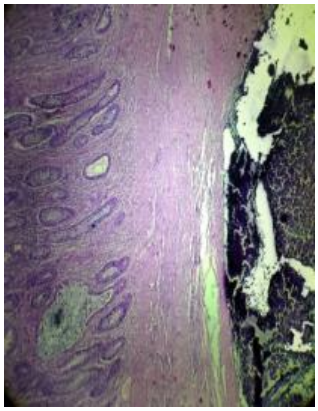

Figure 7 (b)

Figure 7: Polyp with mucinous areas (7a) and polyp with calcifications (7b)

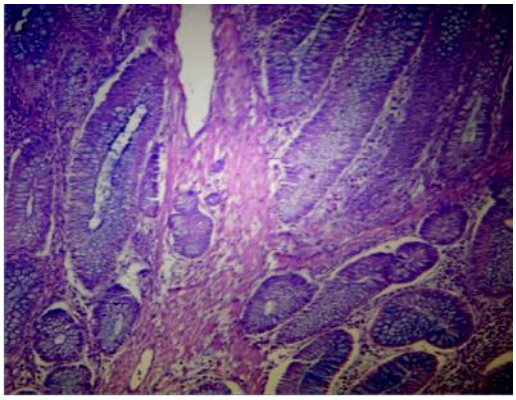

Figure 8: Colonic polyp with smooth muscle arborisation

3. Discussion

The original link between hyperpigmentation and gastrointestinal polyposis was described by Peutz in 1921in his study on one Dutch family, however, it was not until 1949 that Jeghers associated those clinical findings with the risk of invasive carcinoma, approximately in study by Jeghers half of his patients suffered from gastrointestinal malignancy [2],[3],[4]. The eponym PJS was first used in 1954[4]. The estimation of population prevalence of PJS differs between studies. The widest estimated range is from 1 in 8300 to 1 in 280 000 individuals. Probable prevalence is around 1 in 100 000 people [2], [4]. The first histological description of hamartomatous polyps was made in 1957 by Horrilleno and colleagues [4]. Since this time, descriptions have appeared of several different syndromes with the propensity to develop these polyps in the upper and lower gastrointestinal tracts. The hamartomatous polyposis syndromes are a heterogenous group of disorders, which are inherited in autosomal dominant fashion. These syndromes include familial juvenile polyposis syndrome, PJS, phosphatase and tensin homolog gene (PTEN) hamartoma tumour syndromes (Cowden's and Bannayan-Riley-Ruvalcaba syndromes), multiple endocrine neoplasia syndrome 2B, hereditary mixed polyposis syndrome, Cronkhite-Canada syndrome, basal cell nevus syndrome, and neurofibromatosis 1.

Nowadays, the only identifiable mutation causing PJS is a serine-threonine kinase, the tumour suppressor gene; located on chromosome 19p13.3. Hemminki and coworkers and Jenne and associates independently identified the gene in this region as LKB1/STK11 (serine/threonine-protein kinase 11, which is also known as LKB1). This gene has been reported in 80% of patients with PJS. Up to 25% of recorded cases of PJS do not have family history. Those sporadic cases probably arise due to new mutation of STK11 gene or low penetration. In the present case, there was positive family history that his elder brother has similar complaints but not investigated yet [2], [4].

The average age at the time of diagnosis is 23 years in men, and 26 years in women and has a male to female ratio of 1:1. [5].The Peutz-Jeghers syndrome consists of two major components: hamartomatous polyposis of the gastrointestinal tract and mucocutaneous pigmentation.

Mucocutaneous pigmentation is a characteristic finding of PJS and most characteristic pigmentations are present in 95% of patients [4] but not all, very rarely patient presented without mucocutaneous pigmentation [5]. The hyperpigmented lesions contain melanotic deposits and commonly manifest in infancy and childhood. Pigmented lesions could fade during puberty and adulthood. The pigmented lesions are often seen on the lips, around the mouth, eyes, nostrils, on the buccal mucosa; and sparsely on the fingers, soles of the feet, palms, anal area and intestinal mucos. The mucocutaneous lesions of PJS are considered to be hamartomatous in origin and without potential of becoming malignant.

Gastrointestinal hamartomatous polyps are another classic finding of Peutz-Jeghers syndrome. Although these polyps are most commonly found in the small intestine, they can occur anywhere from stomach to rectum. The topographic distribution and frequency of polyps is as follows: small intestine (64%), colon (53%), stomach (49%) and rectum (32%) [6].The median time to first presentation with polyps is about 11-13 years of age and approximately 50% will have experienced symptoms by the age of 20 years [4]. Clinically, the presenting complaints of Peutz-Jeghers syndrome are intestinal obstruction (43%), abdominal pain (23%), blood in the stool (14%) and anal extrusion of polyp (7%). One of the most frequent forms of presentation in the first decade is intussusception. Nearly half of the patients experience an intussusception during their lifetime, most often in the small intestine ileoleal type. Peutz-Jeghers polyps can also ulcerate, leading to acute blood loss or chronic anemia. Although Peutz-Jeghers polyps are most commonly found in the gastrointestinal system, they can also occur in extraintestinal sites such as kidney, ureter, gallbladder, bronchial tree, nasal passages etc.

WHO diagnostic criteria for diagnosis of PJ syndrome is any one of below

a) Three or more histologically confirmed Peutz-Jeghers polyps; or
b) Any number of PJ polyps with a family history of PJ syndrome; or
c) Characteristic prominent mucocutaneous pigmentation with a family history of PJS; or
d) Any number of PJ polyps and characteristic prominent mucocutaneous pigmentation [5], [6], [7].

PJS-associated polyps can be differentiated from sporadic hamartomatous polyps and hamartomatous polyps associated with other syndromes by a unique smooth muscle core that arborizes throughout the polyp. PJS-type polyps do not have specific endoscopic features and can only reliably be distinguished from other types of polyps by histopathology. The unique PJS polyp pathology is best appreciated in PJS small intestine polyps.This framework which is essential in making the proper diagnosis is easily recognized at low power, the polyp has a christmas tree or arborescent like appearance[5],[7].

Diagnostic difficulties found in PJ polyps may be because of extensive ischemic changes, solitary gastric and colonic polyps, colonic, rectal prolapse – with arborization, Pseudo invasion. Characteristic arborization is not seen in most of gastric and colonic polyps. Gastric syndromic polyps are often indistinguishable from non specific gastric hyperplastic polyps [8]. Characteristic arborisation of PJS polyps is seen in only a minority of colonic Peutz-Jeghers polyps (41%).Furthermore, as virtually all colonic polyps—of all types—are prone to prolapse, the presence of smooth muscle fibers within the lamina propria must be considered a nonspecific feature and cannot be used as a diagnostic criterion. Instead, the hallmark of a colonic Peutz-Jeghers polyp is the lobular organization of colonic crypts, a feature that was identified in the majority of cases (68%). [6], in our study colonic polyp shows characteristic arborisation (Fig: 8).

Individuals with PJS have an increased risk for numerous malignancies. The cumulative risk for developing any type of cancer has been estimated to be between 81%-93% [9], [10] with mean age of cancer onset at 40years and a 20year interval between the diagnosis of PJS and cancer development [3]. The greatest specific cancer risk is female breast cancer (45%-54%) [5], [9], [10]. Approximately 57%-68% of affected individuals will develop some type of GI cancer [9]. While polyps occur most commonly in the small intestine, the colon is the most frequent site for GI malignancy (39%) and followed by stomach (29%) of all malignancies. Cancer may also be seen in the pancreas (adenocarcinoma and cystadenocarcinoma), gallbladder and biliary tree and there is an increased association with carcinoid syndrome and malignant melanoma. Sex cord tumors with annular tubules (SCTAT) of the ovary are a classic feature of PJS. Up to 36% of women who develop SCTAT have PJS. Adenoma malignum, also called minimal deviation adenocarcinoma, is also characteristic PJS-related gynecological cancer. Sertoli cell testicular tumors occur in males. These tumors pathologically resemble SCTAT tumors and often present prior to adolescence together with gynecomastia and accelerated physical growth. [5], [9], [10], [11].

Tuberos sclerosis is a frequent neurologic problem in PJS patients and it is characterized by hamartomatous polyp, mental retardation, and epilepsy and adenoma cebaceum [5]. As stated above there is risk of carcinoma in patient and also in their family so the significance of identifying a Peutz-Jeghers polyp cannot be underestimated and the implications for both the patient and their family are significant. Importantly, the diagnosis of Peutz-Jeghers syndrome rests primarily on the histological identification of the polyps, and while sequencing for a germline mutation in STK11 may provide irrefutable evidence, such mutations are not demonstrable in 10% of affected individuals. In fact, in the absence of a family history or mucocutaneous pigmentation, the diagnosis is dependent on documenting three diagnostic polyps.

Typical imaging features of Peutz-Jeghers syndrome consist of multiple polypoid lesions involving the stomach, small bowel and colon. Although the polyps are often detected with barium studies, they can also be identified with US or CT. Some authors have suggested using US or magnetic resonance (MR) imaging for follow-up imaging to reduce the lifetime radiation burden. Another important imaging finding in Peutz- Jeghers syndrome is intussusception.

Over the years, the standard therapy for Peutz-Jeghers syndrome has been laparotomy and bowel resection to remove symptomatic gastrointestinal polyps that cause persistent or recurrent intussusceptions. However, some patients require multiple surgical resections, which can lead to short gut syndrome. Because of this, it has been recommended that endoscopy should be performed to remove all polyps. During each laparotomy, the small bowel should be examined by means of intraoperative enteroscopy (IOE). Nowadays, double balloon enteroscopy (DBE) in combination with capsule enteroscopy are the gold standard for the diagnosis and treatment of the small bowel hamartomatous polyps.

4. Conclusion

Although the incidence of PJS is low, it is important for clinicians to recognize these disorders to prevent morbidity and mortality in these patients and to perform presymptomatic testing in patients at risk. Histological evaluation of polyps in PJS is necessary as its characteristic histological feature is one of the criteria for disease diagnosis and as PJS is associated with increased risk of malignancy, it is important to determine the presence of dysplasia and foci of adenocarcinoma.

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Author Profile

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