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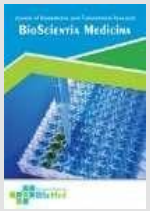

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Unveiling Peutz-Jeghers Syndrome in the Fourth Decade: A Rare Case of Colorectal-Predominant Polyposis and High-Grade Dysplasia without Pathognomonic Pigmentation

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A B S T R A C T

Background: Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant condition characterized by gastrointestinal hamartomatous polyposis and mucocutaneous pigmentation. While typically presenting in childhood with small bowel predominance, adult-onset cases lacking classical phenotypic markers present severe diagnostic challenges. **Case presentation:** A 41-year-old male with no significant family history presented with a six-month history of progressive constipation, altered stool caliber, and hematochezia. Clinical examination revealed an absolute absence of pathognomonic mucocutaneous pigmentation. Abdominal imaging and full colonoscopy demonstrated an extensive colorectal polyposis burden extending from the rectosigmoid junction to the caecum. Histopathology of the resected tissue confirmed hamartomatous polyps featuring arborizing smooth muscle cores alongside focal high-grade dysplasia. The patient successfully underwent an elective total proctocolectomy with an ileal J-pouch anal anastomosis and a diverting loop ileostomy. Postoperative recovery was completely unremarkable. **Conclusion:** This case underscores the profound phenotypic heterogeneity of PJS. The presence of an extensive colorectal burden and high-grade dysplasia in an adult lacking mucocutaneous pigmentation highlights the definitive malignant potential of hamartomatous polyps and the critical necessity for prompt surgical intervention and tailored surveillance in atypical clinical presentations.

1. Introduction

Peutz-Jeghers syndrome represents a rare, highly penetrant, autosomal dominant inherited disorder that stands as a profound paradigm for tumor suppressor gene dysfunction within the realms of clinical gastroenterology and oncology. Initially characterized in the early twentieth century, this complex syndromic entity has continually challenged medical professionals due to its intricate pathophysiology and severe clinical manifestations.[1] It is intrinsically linked to germline mutations in the STK11 (Serine/Threonine Kinase 11) tumor suppressor gene, frequently referred to in foundational molecular literature as LKB1, which is precisely mapped to the chromosomal locus 19p13.3. The identification of this genetic locus was a monumental milestone, providing a molecular basis for the unregulated cellular growth that defines the condition.

The STK11 gene encodes a highly conserved serine/threonine kinase that operates as a master upstream regulatory protein, orchestrating a multitude of critical intracellular signaling cascades. Its primary and most well-elucidated biological

function involves the direct phosphorylation and subsequent activation of AMP-activated protein kinase. AMP-activated protein kinase functions as an essential cellular energy sensor, fundamentally regulating metabolic homeostasis. Under normal physiological parameters, the activation of this kinase network leads to the potent downstream inhibition of the mammalian target of rapamycin signaling pathway. The mammalian target of rapamycin pathway is universally recognized as a central, ubiquitous driver of cellular proliferation, protein translation, neoangiogenesis, and the inhibition of programmed cellular apoptosis.[2] Consequently, the deleterious truncation, missense mutation, or complete loss of heterozygosity of the STK11 gene results in the uninhibited, runaway hyperactivation of the mammalian target of rapamycin. This specific molecular cascade directly and aggressively facilitates the unregulated epithelial and mesenchymal cellular proliferation that ultimately culminates in the massive hamartomatous polyp formation distinctly observed in this condition. Furthermore, the loss of STK11 disrupts cellular polarity, further predisposing the mucosal lining to chaotic architectural distortion and subsequent neoplastic transformation.

The epidemiological landscape of Peutz-Jeghers syndrome remains distinctly difficult to accurately define on a global scale. This difficulty arises primarily from widespread clinical underdiagnosis, variable genetic penetrance, and the heterogeneous nature of the phenotypic presentation.[3] Current epidemiological models provide estimated global incidences ranging broadly from 1 in 25,000 to 1 in 300,000 live births. It is widely postulated that these figures may underestimate the true disease burden, particularly in regions lacking centralized hereditary cancer registries or comprehensive national genetic screening programs. While the disorder follows an autosomal dominant pattern of inheritance, a significant proportion of newly diagnosed patients represent spontaneous, de novo germline mutations in the STK11 gene, meaning they present with absolutely no preceding familial history of the disease. This reality inherently complicates proactive screening efforts and relies heavily on the acute clinical recognition of the syndrome's hallmark features by frontline healthcare providers.

The classical clinical hallmarks of this complex syndrome consist of a recognized dual presentation: the progressive, relentless development of multiple hamartomatous polyps distributed throughout the gastrointestinal tract, paired with the manifestation of distinctive mucocutaneous pigmentation. These dermatological manifestations most commonly present as circumoral, labial, or buccal melanin spots.[4] Histologically, these pigmented macules are entirely distinct from common nevi; they are characterized by a profound increase in melanin pigment production within the basal layer of the epidermis, rather than a quantifiable proliferation in the absolute number of melanocytes. These spots often appear prominently across the vermilion border of the lips, the inner buccal mucosa, and occasionally on the palmar and plantar surfaces of the extremities.

However, the natural history and phenotypic expression of Peutz-Jeghers syndrome are notoriously variable and highly unpredictable.[5] In classical archetypes of the disease, mucocutaneous pigmentation clearly and unmistakably manifests during early pediatric development, often prompting an initial diagnostic evaluation during infancy or early childhood. Yet, a critical and dangerous clinical nuance exists: these pathognomonic dermatological signs may progressively fade into late adulthood. By the time a patient reaches their third or fourth decade of life, the cutaneous stigmata may vanish entirely, establishing a profound and significant risk for diagnostic overshadowing in older patient demographics. When the classical visible markers are absent, the underlying genetic predisposition can easily remain entirely occult until catastrophic abdominal complications or advanced malignancies arise.

Clinically, the acute, non-malignant morbidity associated with Peutz-Jeghers syndrome is predominantly driven by severe mechanical and

hemorrhagic polyp-related complications. The defining gastrointestinal lesions are true hamartomas, characterized pathologically by a distinct arborizing, tree-like branching framework of hyperplastic smooth muscle bundles that originate directly from the muscularis mucosae and interdigitate deeply into the overlying mucosal stroma. While these polyps can theoretically develop anywhere from the gastric cardia to the rectum, they exhibit a powerful anatomical predilection for the upper and middle segments of the small bowel, specifically the jejunum and the ileum.[6]

The physical presence of these often large, pedunculated space-occupying lesions creates a highly unstable intraluminal environment. Over time, these polyps frequently undergo surface ulceration and ischemic necrosis, leading to chronic, occult gastrointestinal bleeding. This insidious blood loss frequently culminates in profound, refractory iron-deficiency anemia, which may serve as the sole presenting symptom in an otherwise asymptomatic patient. More acutely dangerous is the high propensity for large small-bowel polyps to act as lead points, resulting in transient or established entero-enteric intussusception. This catastrophic mechanical event frequently precipitates acute bowel obstruction, severe localized ischemia, and potential hollow viscus perforation, often requiring emergent exploratory laparotomy and resulting in sequential short bowel syndrome from repeated resections over a patient's lifetime.[7]

Furthermore, moving beyond the severe acute mechanical risks, Peutz-Jeghers syndrome is universally recognized by global oncological consortiums as a highly aggressive and complex cancer predisposition syndrome. The historical classification of hamartomatous polyps as purely benign, non-neoplastic entities has been entirely discarded in modern surgical pathology.[8] Affected individuals carry a substantially elevated, lifelong cumulative risk of developing invasive malignancies that dwarfs the baseline risk of the general population. Comprehensive longitudinal cohort studies demonstrate that the overall cumulative lifetime risk for developing any cancer in a patient with Peutz-Jeghers syndrome can exceed ninety percent by the age of sixty-five.

This oncological risk is broadly distributed, encompassing both gastrointestinal malignancies and extra-gastrointestinal solid tumors. Within the alimentary tract, patients face a severe risk of developing colorectal, gastric, and pancreatic adenocarcinomas. The mechanism of oncogenesis within the gastrointestinal tract is a subject of intense academic focus, with current evidence strongly supporting a distinct hamartoma-adenoma-carcinoma sequential pathway.[9] In this model, the foundational STK11 germline mutation creates a highly unstable mucosal field defect characterized by hyperproliferation. Subsequent acquired somatic mutations in other regulatory genes drive focal dysplastic transformation within the pre-existing hamartomatous stroma, eventually culminating in frankly invasive carcinoma.

Beyond the gastrointestinal tract, the neoplastic threat extends deeply into the endocrine and reproductive systems. Female patients harbor a dramatically increased risk for developing early-onset breast carcinomas and highly specific ovarian neoplasms, most notably sex cord tumors with annular tubules. Additionally, they are at risk for adenoma malignum, a rare, highly aggressive minimal deviation adenocarcinoma of the uterine cervix. Male patients similarly face unique extra-intestinal risks, including the development of large-cell calcifying Sertoli cell tumors of the testicles, which can produce excess systemic estrogens leading to prepubertal gynecomastia and advanced bone age.

Given this severe, multifaceted, and lifelong clinical threat, standardized, algorithmic surveillance guidelines have been carefully proposed by international hereditary tumor groups. These proactive protocols generally advocate for aggressive, frequent endoscopic evaluation, utilizing advanced techniques such as video capsule endoscopy and double-balloon enteroscopy to monitor the typically inaccessible small bowel, alongside regular

colonoscopies, upper endoscopies, breast magnetic resonance imaging, and pancreaticobiliary screening.

However, the foundational evidence base for these guidelines relies heavily on retrospective cohort analyses derived largely from highly specialized tertiary referral centers in developed nations. This creates a significant implementation gap. Situated within a resource-constrained clinical environment, the practical execution of such comprehensive surveillance faces immense, systemic logistical barriers. In many global healthcare systems, routine access to advanced molecular genetic sequencing for STK11 confirmation is financially or technologically prohibitive.[10] Furthermore, advanced endoscopic modalities required for deep small-bowel evaluation are often unavailable, and multidisciplinary high-risk cancer screening programs do not exist. In these settings, the diagnostic and therapeutic burden falls heavily on general surgeons and gastroenterologists who must navigate complex, life-threatening presentations without the benefit of extensive preoperative genetic or anatomical mapping.

This profound disparity in healthcare resources fundamentally shapes the trajectory of the disease and necessitates highly customized clinical decision-making paradigms. When patients in these environments present with acute symptoms, the surgical interventions are often forced to be reactive rather than prophylactic, focusing on immediate life preservation and definitive oncological clearance over complex, staged, organ-sparing procedures. The lack of prior surveillance means that diseases are often encountered at an advanced, high-burden stage, demanding extensive resections and highly aggressive surgical management to mitigate the dual threats of mechanical obstruction and malignant progression.

This study aims to present a highly anomalous clinical presentation of Peutz-Jeghers syndrome that fundamentally diverges from established classical patterns documented in mainstream medical literature. The core novelty of this study lies in a unique, highly specific triad of atypical clinical features that directly challenge conventional diagnostic criteria. First, the study details a remarkably delayed, adult-onset clinical presentation in a patient actively traversing their fourth decade of life, a stark contrast to the typical childhood or adolescent onset. Second, the case demonstrates an overwhelming anatomical predominance of severe, extensive colorectal polyposis as opposed to the universally expected small bowel predilection, paired critically with the rare histological confirmation of multifocal high-grade dysplasia embedded deep within the hamartomatous mucosal architecture. Third, this entire severe gastrointestinal phenotype manifested in the absolute and complete absence of any pathognomonic mucocutaneous pigmentation. By documenting this complex case, managed within a distinctly resource-constrained clinical environment where access to advanced molecular genetic sequencing and algorithmic endoscopic surveillance faces heavy systemic barriers, this comprehensive report aims to illuminate critical, under-recognized diagnostic pitfalls, highlight the aggressive oncological potential of non-pigmented hamartomatous polyposis, and provide a framework for navigating complex surgical decision-making paradigms in highly atypical, resource-limited presentations.

2. Case Presentation

Ethical consent statement

This case report was conducted in strict adherence to the fundamental ethical principles outlined in the Declaration of Helsinki regarding medical research involving human subjects. Written informed consent was formally obtained directly from the patient for the publication of this clinical case report and any accompanying radiological or intraoperative images. The patient was thoroughly counseled regarding the nature of the publication, ensuring complete comprehension that all identifiable personal information, including specific geographical identifiers and detailed demographic data, would be strictly anonymized to preserve absolute confidentiality. Furthermore, the institutional review board of Dr. Kariadi General Hospital granted a formal exemption

for this study, as single-case observational reports that do not involve experimental therapeutic interventions fall outside the mandate for full ethical committee review at our institution. The surgical team guaranteed that the dissemination of this clinical data serves purely educational and scientific purposes, aiming to advance the global understanding of atypical polyposis syndromes without compromising patient privacy.

Patient information

A 41-year-old previously healthy male presented to the specialized surgical gastroenterology outpatient clinic of Dr. Kariadi General Hospital in Semarang, Indonesia. The patient reported a progressively worsening six-month history of severe constipation, a distinct and persistent decrease in stool caliber, the frequent passage of intraluminal colonic mucus, and intermittent episodes of fresh hematochezia. An exhaustive systemic inquiry and review of systems revealed no history of unexplained weight loss, clinical anorexia, early satiety, or extra-intestinal manifestations. The patient's past medical and surgical history was entirely unremarkable, with no previously documented colonoscopies, inflammatory bowel disease flares, or prior abdominal surgeries. A rigorous, multi-generation pedigree analysis was conducted; the patient denied any known family history of polyposis syndromes, inherited gastrointestinal malignancies, or characteristic perioral dermatological changes among first or second-degree relatives.

Clinical findings

Upon objective admission assessment, the patient's general physiological condition was fair, with a recorded Body Mass Index of 18.7 kg/m^2, indicative of mild, chronic nutritional depletion likely secondary to his prolonged gastrointestinal disturbances. All primary vital signs were hemodynamically stable. Regional abdominal examination demonstrated mild, generalized tympanic distension. The abdomen was soft and completely non-tender to both superficial and deep systematic palpation, with no discrete solid masses or organomegaly appreciated transabdominally (Table 1).

A digital rectal examination was significantly abnormal. The examination revealed multiple soft, compressible, and pedunculated masses protruding directly along the rectal vault wall. The rectal ampulla was distinctly non-collapsible due to the sheer voluminous burden of the intraluminal polyps, though the overlying palpable mucosa felt smooth and devoid of obvious rigid ulceration or malignant fixation. A dermatological examination specifically targeting the perioral region, lips, buccal mucosa, palmar surfaces, and plantar surfaces yielded absolutely no evidence of typical mucocutaneous pigmentation or lentigines, thereby significantly obscuring the initial clinical suspicion for classical PJS.

Diagnostic assessment

Initial comprehensive serological investigations highlighted a mild, normocytic-normochromic anemia with a measured hemoglobin concentration of 10.1 g/dL, consistent with chronic, low-grade mucosal blood loss. A mild reactive leukocytosis was observed with a leukocyte count of 15.5 × $10^3/\mu L$. All other routine biochemical parameters, including comprehensive serum electrolytes, renal function indices, and hepatic transaminase levels, remained within strict normal physiological limits. Baseline tumor marker profiling revealed a serum carcinoembryonic antigen of 4.2 ng/mL and a carbohydrate antigen 19-9 of 18 U/mL, indicating no systemic biomarker elevation suggestive of advanced, disseminated invasive carcinoma.

Radiological evaluation via a contrast-enhanced multislice computed tomography scan of the abdomen and pelvis elucidated the extensive and severe nature of the localized disease (Table 2). The cross-sectional imaging clearly demonstrated multiple, large, lobulated, and heterogeneously enhancing intraluminal masses forming a near-continuous carpeting effect extending from the rectosigmoid junction proximally up to the caecal pole. The

dominant space-occupying lesion, definitively localized in the sigmoid colon, measured approximately 7.0 × 6.1 × 5.6 cm and caused critical partial luminal narrowing. The scan confirmed the absolute absence of obvious regional mesenteric lymphadenopathy, hepatic parenchymal lesions, or distant peritoneal metastatic seeding.

A full diagnostic colonoscopy was subsequently executed. The advancing endoscope revealed an overwhelming, complex burden of polyposis. The mucosal landscape was entirely obscured by hundreds of sessile and pedunculated polyps of drastically varying sizes and morphologies, carpeting the entire colonic mucosa continuously from exactly 2 cm above the dentate line through to the ascending colon. Multiple endoscopic polypectomies utilizing hot snare techniques were attempted for diagnostic tissue acquisition and immediate symptomatic relief.

Histopathological examination of the retrieved formal-fixed paraffin-embedded polypectomy specimens was clinically definitive. The mucosal architecture displayed the universally recognized, pathognomonic features of hamartomatous polyps. This was characterized by a distinct arborizing, tree-like branching framework of hyperplastic smooth muscle bundles, originating directly from the muscularis mucosae and interdigitating deeply into the polyp stroma. Crucially, extensive and multi-quadrant microscopic sampling identified highly concerning focal architectural and cytological abnormalities consistent with advanced high-grade dysplasia within the glandular epithelium overlying the hamartomatous core. Due to the resource-limited setting of the regional hospital, advanced immunohistochemical staining protocols and immediate in-house molecular sequencing for the STK11 germline mutation were logistically unavailable.

Based strictly on the profound synthesis of clinical, endoscopic, and histopathological findings—despite the confounding absence of classical mucocutaneous pigmentation and genetic confirmation—a definitive working diagnosis of atypical, colorectal-predominant Peutz-Jeghers syndrome was confidently established. The absolute indication for radical, definitive surgical intervention was set, driven equally by the massive obstructing polyp burden and the ominous histological presence of multifocal high-grade dysplasia.

Therapeutic intervention

Following a comprehensive multidisciplinary gastrointestinal tumor board consensus meeting, the patient was extensively counseled and subsequently underwent an elective total proctocolectomy accompanied by a restorative ileal J-pouch anal anastomosis and a protective diverting loop ileostomy (Table 2). The procedure was performed under general endotracheal anesthesia. Intraoperative gross exploration perfectly mirrored the preoperative cross-sectional imaging; the entire anatomical length of the colon and rectum was structurally engorged, dilated, and heavily studded with innumerable large, coalescing polypoid masses. Careful, systematic tactile exploration of the peritoneal cavity, visceral hepatic surfaces, and the entirety of the small bowel mesentery revealed no overt liver lesions or signs of peritoneal carcinomatosis.

The total proctocolectomy was performed utilizing a standardized medial-to-lateral vascular mobilization technique. Following the complete, precise total mesorectal excision down to the levator ani muscle complex, the distal ileal mesentery was aggressively and carefully mobilized to ensure a completely tension-free pelvic reach. A functional restorative J-pouch was fashioned utilizing approximately 40 cm of the healthy terminal ileum. A standardized, double-stapled ileoanal anastomosis was successfully and securely completed. To definitively protect the low pelvic anastomosis from early fecal loading and potential catastrophic anastomotic leakage, a diverting loop ileostomy was matured in the right lower abdominal quadrant. The total operative duration was recorded at 240 minutes, with a highly controlled and minimal estimated blood loss of approximately 350 mL.

TABLE 1. SUMMARY OF CLINICAL FINDINGS ON ADMISSION

Clinical Parameter	Detailed Findings
Patient Demographics	41-year-old Male
Chief Complaints	• Progressive severe constipation (6-month duration) • Persistent decrease in stool caliber • Frequent passage of intraluminal colonic mucus • Intermittent episodes of fresh hematochezia
Medical & Surgical History	Unremarkable. No prior colonoscopies, inflammatory bowel disease flares, or abdominal surgeries.
Family History	Negative for polyposis syndromes, inherited gastrointestinal malignancies, or perioral dermatological changes across a multi-generation pedigree.
Review of Systems	Negative for unexplained weight loss, clinical anorexia, early satiety, and extra-intestinal manifestations.
General Physical Assessment	**Underweight** Fair general condition. Body Mass Index of 18.7 kg/m² (indicative of mild chronic nutritional depletion). Vital signs hemodynamically stable.
Abdominal Examination	Mild generalized tympanic distension. Soft, completely non-tender to superficial and deep palpation. No discrete solid masses or organomegaly appreciated.
Digital Rectal Examination (DRE)	**Abnormal** Multiple soft, compressible, pedunculated masses protruding along the rectal vault wall. Non-collapsible rectal ampulla due to voluminous polyp burden. Overlying palpable mucosa smooth, devoid of rigid ulceration or malignant fixation.
Dermatological Examination	**Negative for PJS Stigmata** Absolute absence of typical mucocutaneous pigmentation or lentigines on the perioral region, lips, buccal mucosa, palmar surfaces, and plantar surfaces.
Initial Laboratory Investigations	• **Hemoglobin:** 10.1 g/dL (mild normocytic-normochromic anemia) • **Leukocytes:** 15.5 × $10^3/\mu$L (mild reactive leukocytosis) • **Comprehensive Metabolic Panel:** Electrolytes, renal function indices, and hepatic transaminases within normal physiological limits

TABLE 2. DIAGNOSIS AND TREATMENT

Clinical Phase	Detailed Parameters & Interventions
Radiological & Endoscopic Assessment	• **CT Scan:** Multiple lobulated, enhancing intraluminal masses from the rectosigmoid to the caecal pole. Largest lesion in sigmoid colon (7.0 × 6.1 × 5.6 cm) causing partial luminal narrowing. No distant metastasis. • **Colonoscopy:** Hundreds of sessile and pedunculated polyps carpeting the colonic mucosa continuously from 2 cm above the dentate line through the ascending colon.
Histopathology	High-Grade Dysplasia • Pathognomonic hamartomatous architecture with arborizing, tree-like branching hyperplastic smooth muscle bundles from the muscularis mucosae. • Focal architectural and cytological abnormalities confirming advanced high-grade dysplasia within the glandular epithelium.
Definitive Diagnosis	Atypical Presentation Atypical, colorectal-predominant Peutz-Jeghers Syndrome with multifocal high-grade dysplasia in the absolute absence of classical mucocutaneous pigmentation.
Surgical Intervention	• **Procedure:** Elective total proctocolectomy with restorative ileal J-pouch anal anastomosis (IPAA) and a protective diverting loop ileostomy. • **Anesthesia:** General endotracheal anesthesia. • **Technique:** Total mesorectal excision. J-pouch fashioned from ~40 cm of healthy terminal ileum. Double-stapled ileoanal anastomosis. Right lower quadrant loop ileostomy.
Intraoperative Details	• **Duration:** 240 minutes • **Estimated Blood Loss:** ~350 mL • **Gross Findings:** Entire colon and rectum structurally engorged with large coalescing polyps. No liver lesions or peritoneal carcinomatosis.

Follow-up and outcomes

The patient's immediate postoperative physiological trajectory in the specialized surgical ward was excellent, characterized by progressive, early mobilization and a carefully structured, stepwise diet advancement protocol. Pelvic drains were safely removed on postoperative day 4 following the strict confirmation of low-volume, serous, non-bilious output (Table 3). The newly formed stoma function was closely monitored and deemed highly adequate. The patient experienced absolutely no immediate major surgical complications and was successfully discharged to outpatient community care on postoperative day 9 in excellent overall condition.

At the initial 3-month postoperative follow-up clinic visit, the patient reported normal, easily manageable stoma output and a complete, welcome resolution of all preoperative obstructive symptoms and hematochezia. The planned reversal of the loop ileostomy is strategically scheduled for 8 to 10 weeks post-operatively, strictly contingent upon a highly favorable endoscopic visualization and evaluation of

the J-pouch mucosal integrity. The patient's long-term management strategy involves a rigorous, lifelong surveillance plan. This encompasses annual enteroscopic review to closely monitor the retained small bowel mucosa, serial cross-sectional imaging specifically targeting pancreaticobiliary and extra-intestinal solid organ malignancies, and comprehensive genetic counseling offered to the patient's immediate relatives, while formal STK11 mutational analysis remains pending formal referral to a centralized national tertiary genetics center.

TABLE 3. FOLLOW-UP AND OUTCOME

Clinical Phase	Detailed Parameters & Interventions
Immediate Postoperative Course	**Uncomplicated Recovery** • Progressive, early mobilization and structured diet advancement. • Pelvic drain safely removed on postoperative day 4 (serous output). • Adequate stoma function established early. • No major surgical complications. Discharged to outpatient care on postoperative day 9.
Short-Term Follow-up (3 Months)	• Complete resolution of preoperative obstructive symptoms and hematochezia. • Normal, easily manageable stoma output.
Long-Term Management & Surveillance Plan	**Lifelong Surveillance Required** • **Planned Surgery:** Loop ileostomy reversal scheduled at 8 to 10 weeks post-operatively, contingent upon favorable endoscopic evaluation of J-pouch integrity. • **Endoscopy:** Annual enteroscopic review to monitor retained small bowel mucosa. • **Imaging:** Serial cross-sectional imaging targeting pancreaticobiliary and extra-intestinal solid organ malignancies. • **Genetics:** Comprehensive genetic counseling for the patient's immediate relatives.

3. Discussion

The fundamental pathophysiology driving the clinical manifestations of Peutz-Jeghers syndrome is intimately and inextricably tied to the profound loss of function within the STK11 tumor suppressor gene.[11] This critical genetic locus, which precisely maps to the chromosomal region 19p13.3, encodes the highly conserved liver kinase B1 protein. In the realm of cellular biology, liver kinase B1 operates as a master upstream serine/threonine kinase that plays a profoundly pivotal role in orchestrating a multitude of intracellular signaling cascades. Its primary responsibilities include regulating cellular energy homeostasis, establishing essential cellular polarity, and modulating programmed apoptotic pathways to prevent unchecked cellular immortality. Under normal, healthy physiological conditions, the direct phosphorylation and subsequent activation of AMP-activated protein kinase by liver kinase B1 serve as a critical metabolic checkpoint. When cellular energy levels fluctuate, this activated protein kinase complex leads directly to the potent downstream inhibition of the mammalian target of rapamycin signaling pathway. This specific regulatory pathway acts as a central, ubiquitous governor of cellular proliferation, protein synthesis, and mucosal neoangiogenesis.[12]

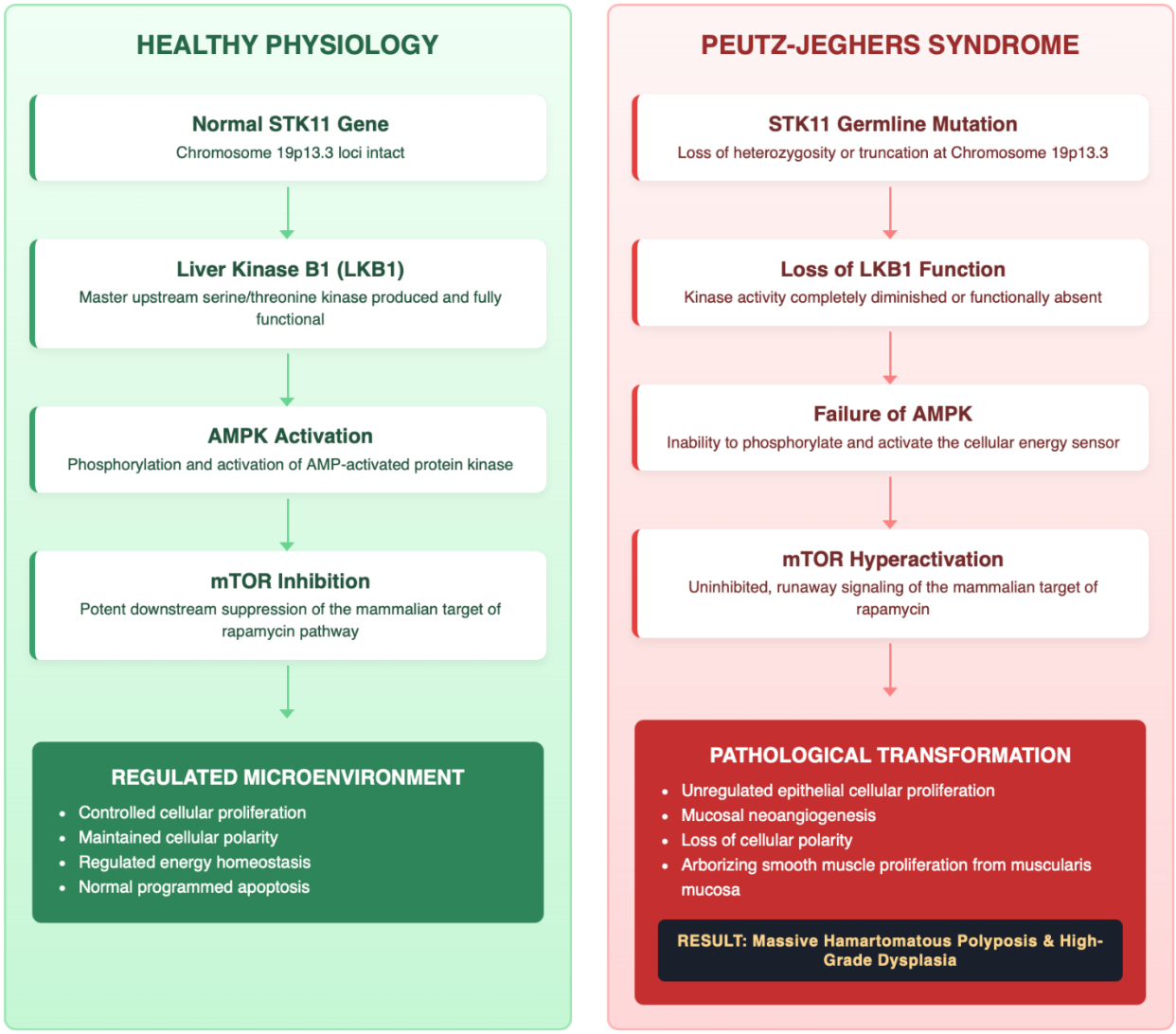

Figure 1. Pathophysiology and cellular microenvironment of Peutz-Jeghers syndrome.

The deleterious truncation, complete genomic deletion, or functional loss of liver kinase B1—which stands as the defining molecular hallmark of this inherited polyposis syndrome—results in an uninhibited, runaway hyperactivation of the mammalian target of rapamycin.[13] Without the regulatory braking mechanism normally provided by the STK11 gene product, the cellular environment shifts permanently into an anabolic, highly proliferative state. This highly specific molecular cascade directly and aggressively facilitates unregulated epithelial cellular proliferation and pathological mucosal neoangiogenesis. Concurrently, the loss of cellular polarity further disrupts the normal architectural constraints of the gastrointestinal lining. This combination of unchecked growth and structural disorganization directly drives the subsequent massive hamartomatous polyp formation distinctly observed in this clinical condition. The unique microscopic architectural distortion, specifically the hallmark arborizing smooth muscle proliferation originating directly from the muscularis mucosae and driving deeply into the overlying mucosal polyp stroma, is a direct, physically measurable phenotypic consequence of this severely disrupted microenvironmental signaling network.[14]

This specific clinical case powerfully and definitively illustrates the profound phenotypic heterogeneity intrinsic to the syndrome, challenging rigidly held diagnostic paradigms. While the disorder is classically and historically diagnosed within pediatric or early adolescent patient cohorts—often triggered by early intussusception or visible dermatological changes—adult-onset clinical presentations extending deep into the fourth decade of life remain exceedingly rare and statistically highly uncommon in the published medical literature. The significantly delayed clinical penetrance observed in our patient is a complex phenomenon that is likely multifactorial in origin. It may directly relate to the specific, inherently lower biological penetrance of his underlying, unmapped genetic variant.[15] Alternatively, it could reflect an inherently slower biological trajectory of polyp growth occurring silently over several decades, or the distinct absence of secondary environmental or epigenetic triggers that typically accelerate the disease process in younger demographics.

The total, absolute absence of classical perioral or generalized mucocutaneous pigmentation in this adult patient serves as a critical and highly illuminating clinical focal point. Mucocutaneous pigmentation is a primary, foundational hallmark utilized heavily in established clinical diagnostic criteria globally. These pigmented macules arise from an alteration in melanin synthesis and transport within the basal epidermal layers, driven by the same underlying kinase dysregulation that affects the gastrointestinal tract.[16] The complete absence of these pathognomonic dermatological signs significantly masks the underlying genetic syndrome and directly, dangerously contributes to prolonged and potentially fatal diagnostic delays. This case highlights the vital clinical reality that mucocutaneous manifestations are neither universally present nor strictly biologically requisite for the severe pathogenesis of the underlying gastrointestinal hamartomatosis. When frontline clinicians rely too heavily on the presence of visible lentigines to trigger suspicion, patients with atypical phenotypes are inevitably miscategorized until catastrophic luminal obstruction or advanced malignancy occurs.

Furthermore, while the overwhelming majority of associated hamartomatous polyps predictably and characteristically localize to the proximal and middle segments of the small bowel, specifically the jejunum and the ileum, our patient demonstrated a radical, highly unusual anatomical divergence. The patient presented with an extensive, physically obstructive colorectal-predominant disease burden, featuring massive, coalescing lesions carpeting the distal gastrointestinal tract. This distinct anatomical shift fundamentally challenges conventional, rigid surveillance paradigms. Current guidelines heavily prioritize and mandate intensive upper small bowel evaluation via video capsule enteroscopy or balloon-assisted enteroscopy, while potentially under-evaluating the colonic mucosa in suspected but unconfirmed cases. The sheer volume of the colorectal burden in this instance dictates that complete anatomical visualization of the entire gastrointestinal tract is absolutely imperative, regardless of the presumed classical distribution patterns of the disease.[17]

Moving beyond the benign mechanical complications of polyposis, the oncological implications of this syndrome represent its most lethal threat. Historically, in the early eras of surgical pathology, hamartomatous polyps were erroneously and broadly categorized as completely benign developmental anomalies carrying a negligible malignant potential. However, contemporary, high-level oncological consensus now strongly and unequivocally supports a specific, highly aggressive sequence of malignant transformation unique to this disease process, commonly referred to as the hamartoma-adenoma-carcinoma sequence. Extensive global cohort data and longitudinal survivorship analyses clearly indicate a staggering cumulative cancer risk approaching fifty-five percent by the time a patient reaches the age of sixty. This reflects a severe relative oncological risk that is greater than sixty times

that of the healthy, unaffected general population.[18]

While the direct, observable malignant transformation of colorectal hamartomatous polyps into advanced high-grade dysplasia or frank invasive adenocarcinoma is well documented in broad epidemiological studies, capturing this transitional phase histologically in a resected surgical specimen remains a remarkably rare event. The definitive histological identification of multifocal high-grade dysplasia deeply embedded within the branching smooth muscle arbors of the hamartomatous polyps in our patient represents a critical, life-altering juncture in the natural history of his specific disease process. It confirms biologically that the liver kinase B1 dysregulation not only drives benign physical overgrowth but also establishes a highly volatile, unstable mucosal field defect across the entire length of the affected bowel.

This specific, hyperproliferative microenvironment is acutely susceptible to acquiring secondary oncogenic driver mutations.[19] As the unregulated cellular turnover continues unabated, the mucosal cells inevitably accumulate additional genetic errors, which immediately precipitate rapid dysplastic progression toward invasive carcinoma. Because diagnostic facilities in resource-limited settings often face barriers to conducting advanced molecular profiling or targeted mutational analysis on excised tissue, the purely morphological identification of high-grade dysplasia serves as the ultimate, definitive warning sign of impending malignancy. Consequently, this histologically verified high-grade dysplastic transformation strongly and absolutely validates the aggressive, prophylactic surgical approach taken by the multidisciplinary team. By executing a complete removal of the at-risk colonic and rectal mucosa, the surgical team completely mitigated the impending, otherwise inevitable progression to invasive, metastatic carcinogenesis.

While this detailed clinical case provides profound, actionable insights into highly atypical presentations, it is fundamentally constrained by the inherent, recognized limitations of single-case observational reporting. This singular, highly specific data point naturally precludes the establishment of definitive, broad epidemiological incidence rates for this non-pigmented, colorectal-dominant phenotype within the larger global population.[20] Future collaborative, multi-center, international registry-based studies are strictly imperative to systematically catalogue, sequence, and analyze these highly atypical genotypic-phenotypic correlations on a much larger scale. Furthermore, prospective translational research focusing intently on delineating the specific molecular pathways and microenvironmental factors that differentiate small-bowel versus colorectal predominant disease could eventually yield highly targeted, organ-specific chemopreventive agents. The development of localized, targeted mammalian target of rapamycin inhibitors tailored for the gastrointestinal mucosa could potentially suppress polyp growth medically, potentially altering the severe surgical landscape and reducing the lifetime burden of operative morbidity for future generations of patients affected by this syndrome.

4. Conclusion

This comprehensive report elucidates a highly rare, profoundly atypical adult-onset presentation of Peutz-Jeghers syndrome, distinctly characterized by a severe, dominant colorectal hamartomatous polyposis burden and histologically verified, dangerous high-grade dysplasia. The complete absence of both a supportive, documented familial history and classical mucocutaneous pigmentation critically underscores the dangerous phenotypic heterogeneity of this inherited genetic syndrome. This variability can easily and silently mask profound, life-threatening underlying oncological risk until the disease reaches a critical, obstructive, or malignant stage. The confirmed presence of multifocal high-grade dysplasia directly within the architecture of these hamartomas firmly and definitively reiterates their aggressive malignant potential, completely dispensing with the antiquated notion that such polyps are purely benign developmental anomalies.

For frontline clinicians, interventional endoscopists, and gastrointestinal surgeons, particularly those operating in resource-limited or non-tertiary healthcare settings without immediate access to comprehensive genetic sequencing panels, this clinical case strictly enforces a vital diagnostic lesson. It highlights the absolute necessity of maintaining a remarkably high index of clinical suspicion for underlying hereditary polyposis syndromes when encountering severe, unexplained, high-volume polyposis at any age, regardless of the patient's dermatological presentation or chronological age at symptom onset. When faced with such extensive, high-risk disease, definitive and timely radical surgical intervention currently remains the absolute cornerstone of effective medical management. Complex, restorative operative strategies, such as the total proctocolectomy with restorative ileal J-pouch reconstruction performed successfully in this instance, are absolutely essential. This proactive, aggressive surgical philosophy is definitively required to preserve long-term patient quality of life, alleviate severe obstructive morbidity, and simultaneously achieve crucial, definitive oncologic clearance in the face of high-burden, highly dysplastic disease.

5. References

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