Peutz-Jeghers syndrome: Skin manifestations and endocrine anomalies (Review)

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Abstract. Peutz-Jeghers syndrome (PJS), a rare autosomal dominant serine/threonine kinase 11 (*STK11)*/ liver kinase B1 (*LKB1)* gene-related genodermatosis, is characterized by oral hyperpigmentation (OHP); multiple gastro-intestinal mucosal benign hamartomatous polyps causing local bleeding, occlusion, intussusception, post-resection small bowel syndrome, associated increased risk of small intestinal cancer (incidence during the third decade); and 76% cumulative higher risk than the global population of developing non-gastrointestinal tumors (female predominance) including ovarian/testicular neoplasia, pancreatic and gynecologic (breast, uterus, ovarian) cancers. Suggestive PJS-associated OHP requires STK11 genetic testing. Abdominal pain in an OHP patient may be related to PJS-associated polyps. Other features include focal depigmentation followed by hyperpigmentation, and xeroderma pigmentosum-like lesions. The severity of the dermatological findings is correlated with gastrointestinal polyps. The *STK11* gene is linked to reserve of primordial follicles, polycystic ovary syndrome, female fertility, and spermatogenesis. PJS is associated with 2 types of ovarian sex-cord stroma tumors (SCSTs): annular tubules (SCTATs) and pure Sertoli cell tumors. SCSTs accounts for 8% of ovarian cancer and SCTATs represents 2% of SCST, which may be associated with the overproduction of progesterone. PJS-SCTAT vs. non-PJS-SCTAT reveals bilateral/multifocal, small tumors with a benign behavior vs. a unique ovarian, large tumor with increased malignant/metastasis risk. Male precocious puberty is due to large cell calcifying Sertoli cell tumors (LCCSCTs). Notably, 30-40% of LCCSCTs are caused by PJS or Carney complex. PJS-LCCSCT is not aggressive, but it may be bilateral/multifocal, with the ultrasound hallmark being micro-calcifications. Testicular, intra-tubular large cell hyalinizing Sertoli cell tumor is the second testicle neoplasia in PJS. The skin and mucosal lesions are useful markers of PJS, assisting with the early identification of hamartomatouspolyps and initiation of serial surveillance of ovarian, or testicular neoplasia.

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Abbreviations: AD, Addison disease; ACTH, adrenocorticotropic hormone; AMH, anti-Mullerian hormone; FSH, follicle stimulating hormone; LKB1, liver kinase B1; LCCSCT, large cell calcifying Sertoli cell tumor; LHS, Laugier-Hunziker syndrome; MMR, DNA mismatch repair; MAS, McCune-Albright syndrome; MEN, multiple endocrine neoplasia; MSH, melanocyte-stimulating hormone; OPL, oral pigmented lesions; PJS, Peutz-Jeghers syndrome; STK, serine/threonine kinase; SCTAT, sex cord tumors with annular tubules; SCT, Sertoli cell tumors; WHO, World Health Organization

Key words: Peutz-Jeghers syndrome, oral hyperpigmentation, *STK11/LKB1* gene, gastrointestinal polyp, ovarian tumor, ovarian neoplasia, sex-cord stroma tumors, Sertoli cell ovarian tumors, annular tubules, testicular tumor

Contents

1. Introduction

Peutz-Jeghers syndrome (PJS), a rare genodermatosis with an autosomal dominant inheritance of a high-penetrance profile, is caused by serine/threonine kinase (STK)11 gene mutation on chromosome 19p13.3 (1). This is a tumor-suppressor gene, also known as liver kinase B1 (*LKB1*) gene, which involves master serine-threonine protein kinase activity that communicates with different growth and angiogenesis factors representing tumorigenic pathways of associated neoplasia (2). *STK11/LKB1* is also involved in signaling pathways involved in the DNA damage response to sun ultraviolet radiation as a contributor to skin cancer and it has been connected to other non-PJS-related epithelial cancers (3,4). In addition, control of certain immune cells has been reported to be under the influence of the *STK11/LKB1* gene (5).

The syndrome, with a reported incidence of 1/25,000-1/280,00 persons/year, includes multiple gastro-intestinal mucosal lesions including benign hamartomatouspolyps causing local bleeding, occlusion and intussusception, post-resection small bowel syndrome; hyperpigmentation of the skin and mucosa especially at the oral and lips levels, and a higher risk of developing other non-gastrointestinal tumors including ovarian/testicular, pancreatic, breast, and uterine neoplasia (6,7) (Fig. 1). The cumulative risk of cancer is higher with 76% in the general population and with females being more exposed (8). Cancer of the small intestine usually occurs during the third decade of life making early assessment and serial follow-up crucial, once the skin lesions or gene anomalies are identified in a carrier or a specific family (9). Esophago-gastro-duodenoscopy screening and further surveillance are essential (10). Familial genetic consult is useful since the digestive disease may be asymptomatic for years (11). Lifelong follow-up is required (12).

The need for multidisciplinary teams of surveillance in PJS patients is essential, from dermatology to gastroenterology, from endocrinology to oncology, in both the pediatric and adult patients. Muco-cutaneous hyperpigmentation (deposits of melanin in skin and mucosa) represents an essential dermal clue for assessment of this multi-system condition (13,14).

2. Aim of the review

This is a systematic, narrative review of the literature conducted based on two main aspects in PJS: on the one hand, skin and mucosa anomalies and, on the other hand, endocrine manifestations. Additional genetic and neoplasia data are provided in order to integrate the general multidisciplinary, complex image of this hereditary syndrome.

The research of the review started from the PubMed database with respect to the following key words: 'Peutz-Jeghers syndrome' and 'skin', 'mucosa', 'oral', 'endocrine, 'puberty', 'ovary', 'testes', and 'polyps'. A total of 101 references were cited between January 2010 and May 2021. Full-length original papers of different types were exclusively introduced due to the rarity of the publications in areas of interest. The selection was based on clinical relevance.

3. Skin and mucosal manifestations

Dermatological findings may be identified before gastro-intestinal polyps and other PJS-related tumors; skin and mucosal manifestations being a valuable clue of this hereditary syndrome (15,16). In some cases, vitiligo (usually focal depigmentation) may be followed by focal hyperpigmentation in the skin, oral mucosa, lips, and labia (17,18). Pigmentation features may mimic xeroderma pigmentosum in the early stages (xeroderma pigmentosum is an extreme sun sensitivity-associated high risk of skin cancer) (19). Melanin hyperpigmentation present on a patient who is not previously known to have the syndrome must be biopsied in order to obtain a clear diagnostic (20). Previous findings have revealed a certain genotype-phenotype correlation of the *STK11/LKB1* gene involving the fact that more severe dermatological findings are correlated with a more aggressive profile of gastro-intestinal hamartomatous polyps (21). A total of 90% of subjects with positive PJS criteria have *STK11/LKB1* mutations; an oral hyperpigmentation suggestive for PJS is an indication of *STK11* genetic testing and further familial genetic assessment (22). Abdominal pain in a patient with oral pigmentations is suggestive of a complication of a digestive PJS polyp (23). Except for a digestive field, specific protocols of investigations and follow-up regarding skin and mucosal PJS lesions remain suboptimal (24).

4. Differential diagnosis of oral hyperpigmentation

Skin and mucosa hyperpigmentation need to be differentiated from other conditions that are indicated by hyperpigmentation: Addison disease (AD), McCune-Albright syndrome (MAS), and Laugier-Hunziker syndrome (LHS) (25).

AD, a chronic primary adrenal insufficiency, requiring lifelong glucocorticoid and mineralocorticoid substitution, is accompanied by hyperpigmentation at general level or at the level of scars, areolas, and skin-fold, a hyperpigmentation that is reversible to some extent under adequate endocrine therapy (26). The areas that are more exposed to the sun are also more sensitive to hyperpigmentation (26). The underlying mechanism involves high adrenocorticotropic hormone (ACTH) in addition to increased levels of melanocyte-stimulating hormone (MSH) (26). Concurrent focal or general depigmentation may also be found since vitiligo is associated with poly-glandular autoimmune syndrome, especially with chronic autoimmune thyroiditis (26).

MAS, an underlying endocrine condition usually accompanied by hyper-function, presents focal hyperpigmentation including 'café au lait' spots, similar to type 1 neurofibromatosis (27,28).

LHS is an exceptionally rare, acquired condition (the level of evidence is case reports) associated with idiopathic hyperpigmentation at the level of the lip, acral area, oral mucosa, and even nails (29). The skin color changes are due to diffuse spreading of black macules with dimensions that vary from 1 to 5 mm (29,30). Longitudinal melanonychia has been described in both children and adults (30). To date, the cause is unknown (31). It seems that skin anomalies are not associated with a higher risk compared to general manifestations including endocrine conditions or non-endocrine

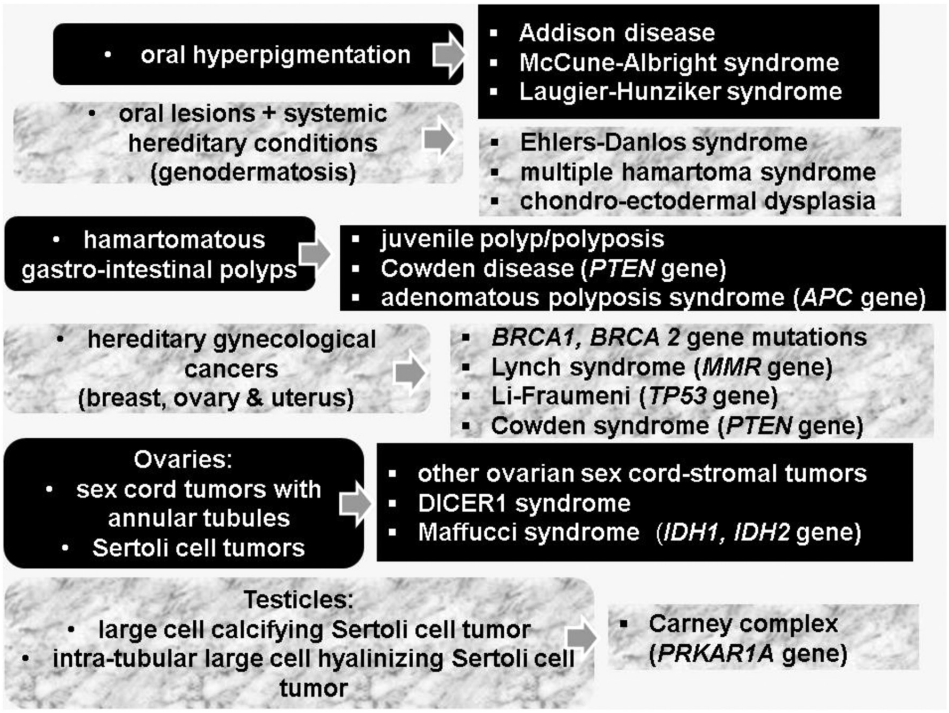

Figure 1. Differential diagnosis of the pathological elements associated with Peutz-Jeghers syndrome as discussed in the review.

tumors/cancers, as observed in PJS (32). The overall prognosis is a favorable one (33). Melanonychia striata, caused by higher melanocyte activity and secondary hyperplasia at the nail level, is also described in constitutional circumstances (individuals with dark skin), after local traumatisms or infections, in conditions such as alkaptonuria, hemochromatosis, porphyria, and LHS (34). Since LHS is a benign, rather harmless condition when it comes to general complications, the endocrine assessment is necessary to exclude the diagnosis of AD and MAS (35).

5. Hereditary syndromes associated with oral lesions

PJS is a type of genodermatosis representing a complex cluster of hereditary syndromes with cutaneous-mucosal manifestations in addition to systemic complications of tumor and non-tumor type (for instance, Ehlers-Danlos syndrome, multiple hamartoma syndrome, and chondro-ectodermal dysplasia) (36,37). Non-genodermatoses involve lesions such as acanthosis nigricans associated with insulin resistance, diabetes mellitus, and polycystic ovary syndrome (38). Other hereditary syndromes that involve lesions of the oral region are associated predominantly with cutaneous manifestations (Brooke-Spiegler syndrome, Muir-Torre syndrome) or predominant endocrine complications such as multiple endocrine neoplasia (MEN) type 1 (*MEN* gene) and type 2 (*RET* gene) syndrome, Carney complex (*PRKAR1A* gene), or head and neck tumors (Cowden syndrome-*PTEN* gene) or systemic tumors (neurofibromatosis type 1) (39,40). In many cases, the skin lesions are less important in regards to the overall prognosis even though they represent the obvious mark of the syndrome or the first step in its identification (41,42). So-called familial lentiginosis dermato-endocrine syndromes include PJS, Carney complex, Cowden disease and Noonan syndrome (43). A study published in 2021 that analyzed the published papers focusing on oral pigmented lesions (OPL) introduced 9 different syndromes in individuals with a mean age at diagnosis of 35 years and female predominance (68%) (44). Multiple lesions were more frequent than single (73.15% vs. 26.85%); lip followed by buccal mucosa were the more affected sites, in 75% of cases, OPL preceded the recognition of the syndrome (44).

6. Endocrine aspects in females

Multiple endocrine anomalies have been reported in PJS as mentioned subsequently. Individuals presenting with PJS have a lifelong higher risk of gynecological cancers with endocrine components, so-called hereditary gynecological cancers (breast, ovarian and uterine), also including those related to Lynch syndrome (mutations of the *MMR* gene), Li-Fraumeni (mutations of the *TP53* gene), and Cowden syndrome (45). Similarity with hereditary conditions with an identical malignancy pattern includes mutations of *BRCA1* and *BRCA2* genes, respectively (46). Lynch syndrome is mostly related to endometrial cancer, while Cowden syndrome and Li-Fraumeni are related to breast cancer (Li-Fraumeni syndrome is also an important cause of adrenocortical carcinoma especially in the pediatric population) while PJS is equally associated with all three mentioned malignancies (47).

Conditions with benign behavior have been reported in PJS including breast hyperplasia and ovarian cysts, the *STK11* gene being related to primordial follicles reserve and female fertility (48). Another potential link involves *STK11* gene polymorphism in polycystic ovary syndrome that has been reported in PJS subjects, although an incidental overlap cannot be excluded (49).

PJS constitutes two types of ovarian tumors, namely sex cord tumors with annular tubules (SCTAT) and pure

Sertoli cell tumors (SCT), both originating from ovarian sex cord-stroma (50,51). Overall, ovarian sex-cord stromal neoplasia accounts for 8% of all cases diagnosed with ovarian cancer (the most frequent cause of ovarian malignancy among sex-cord stromal tumors is due to granulosa cell tumors) (52). Hereditary syndromes that have been related to this large group of ovarian sex cord-stromal tumors includes, besides PJS, DICER1 syndrome, Maffucci syndrome and Ollier disease (52). The most important hereditary syndromes in ovarian cancer are PJS, Lynch syndrome and BRCA1 and BRCA2- related disease, overall accounting for 1 out of 4-5 females with ovarian cancer (53).

SCTAT, representing 2% of all sex cord-stromal tumors, are considered very rare neoplasias (54). An increased progesterone production has been revealed in some cases (55). In non-PJS cases, one in five are malignant; thus, candidates are subjected to chemotherapy and/or surgical resection (56). Overall, the risk of malignancy is higher compared to other sex cord stromal tumors (55,57). Surgical removal remains the first-line therapy, regardless of the presence of PJS (58). The presentation of SCTAT-PJS vs. SCTAT-nonPJS reveals bilateral or multifocal tumors of small size with a rather benign behavior vs. a unique ovarian tumor usually with increased diameters and a higher malignant profile, including the risk of developing distant metastases (59). Previous findings have shown synchronous detection of SCTAT and SCT in the same PJS patient (60). Other data suggest a poorer prognosis of SCTAT-PJS because of the associated higher risk of non-ovarian malignancies (61). SCTAT has also been associated with co-presence of dysgerminomas and gonadoblastomas or with Turner syndrome or endometriotic cysts, most probably incidental-based (62). The association of PJS with Sertoli-Leydig cell ovarian tumor has been reported in a very limited number of cases and it seems atypical (63,64). The first recurrent Sertoli-Leydig cell tumor of the ovary was reported in 2016 in an African-American female with PJS diagnosed at the age of 3 years due to precocious puberty followed by recurrence at age of 17 years (65).

7. Endocrine aspects in males

Murine experiments have revealed a role of the *LKB1/STK11* gene in spermatogenesis (66). Males with PJS may have low levels of follicle stimulating hormone (FSH) and high anti-Mullerian hormone (AMH), the product of testicular Sertoli cells that is inhibited by androgens under normal circumstances and escapes these mechanisms in PJS based on less understood connections (67). Gynecomastia in pre-pubertal boys and precocious puberty have been reported (68). Most cases are related to hormonally active testicular tumors, also causing precocious puberty with advanced bone age and tall stature (69). These aspects are caused by a male-specific tumor named large cell calcifying Sertoli cell tumor (LCCSCT) (70). A total of 30-40% of cases are associated with hereditary syndromes such as PJS and Carney complex while 60-70% of all LCCSCT represent sporadic forms (71).

This is an extremely rare entity derived from sperm cord cells (70). Despite the fact that the neoplasia typically does not have a very aggressive profile, one out of five men may have a bilateral/multifocal presentation (70). The presence of specific PJS skin-mucosal lesions helps the syndromic diagnosis (70). The hallmark of LCCSCT is testicular ultrasound showing micro-calcifications (72). In addition, inhibin A assays are useful for diagnosis and during follow-up (72,73). Surgical removal is the standard therapy and testes-sparing procedures or partial orchiectomy are encouraged especially in very young patients (74). Aromatase inhibitors for gynecomastia and control of advanced bone age may also be useful (75,76). Since 2016, WHO (World Health Organization) has recognized another distinct PJS-related group, namely intra-tubular large-cell hyalinizing Sertoli cell tumors (77).

8. Gastro-intestinal polyps

The specific manifestation of PJS at the digestive system level is the presence of hamartomatous polyps, which otherwise are described as single lesion (outside PJS), juvenile polyp/polyposis or as clinical manifestation of Cowden disease (78,79). Solitary Peutz-Jeghers polyp is a distinct entity and it does not underline PJS; similarly, *LKB1/STK11* mutations (80,81). Their evaluations combine family medical history, endoscopy findings, histological and immunohistochemistry report (after biopsy or after resection) and serial endoscopic follow-up because of post-polypectomy recurrence and increased malignancy risk (78,82). The clue at first endoscopic evaluation is the number of polyps; multiple polyps generally have a genetic background and require further dermatological and endocrine workup if PJS is suspected (78). A polyp takes time to grow, thus its detection is less likely to occur during the first decade of life (83).

The most frequent sites are the small intestine as well as the colon and stomach, with the duodenum and appendix being rare sites (84). Recent findings indicate the duodenum as the most frequent location of complicated polyps (85). PJS-related polyps at the level of the small bowel need to be differentiated from other benign tumors including lipomas, leiomyomas, neurofibromas or syndromic circumstances such as adenomatous polyposis syndromes (caused by *APC* gene mutations) (86,87). The PJS-related polyp histological profile includes peripheral edema, mucin-filled, dilated cystic glands (88).

Not all PJS polyps have the same malignant potential of transformation because it seems that an underlying cell population is not homogenous and the exact mechanisms and prevalence of PJS polyps are not fully known at present (89). Recent findings show that hypo-methylation of the *LKB1/STK11* promoter is correlated with a more aggressive profile (90). *STK11* genotype-phenotype correlations regarding malignant potential remain a subject of discussion (91). Other authors suggest that sporadic PJS polyps are less malignant than familial cases (92). Non-*STK11* gene mutations have been found in hamartomatous PJS polyps such as the *MMR* (DNA mismatch repair) gene (93).

9. Future considerations

Another potential role of the *STK11* gene involves a higher risk of lung cancer in PJS subjects, albeit this remains an open question (94). Scalp metastases (the general rate of malignancy spreading at this level is of 0.22 to 12% in all cancer types) from

lung cancer have been reported in a male patient with PJS (95). KRAS-positive lung adenocarcinoma has been reported in some PJS patients (96). One third of pulmonary adenocarcinomas are related to *LKB1* gene mutations (independently of PJS) (97). In addition, sporadic cases of non-PJS colonic cancer may be associated with *STK11* gene anomalies (98). Overall, PJS is an example of the genomics approach in syndromes involving multiple cancer types and non-malignant lesions together and several medical and surgical domains are placed together in search of early clinical tools to improve the overall prognosis (99-101).

10. Conclusions

Specific multidisciplinary guidelines and protocols for the dermatological manifestations in addition to gastro-intestinal, endocrine and oncologic complications in PJS are sub-optimal. The skin and mucosal lesions are useful markers of the syndrome, assisting in early identification of hamartomatous polyps and serial surveillance concerning the associated higher risk of breast, uterine, ovarian, and pancreatic neoplasia.

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Authors' contributions

FS drafted the manuscript and critically revised the final form, AP researched the literature and generated the figure, MCD drafted the manuscript, RCP researched the literature, MC drafted the manuscript and approved the final form. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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