ORIGINAL ARTICLE

Nasal polyposis in Peutz–Jeghers syndrome: a distinct histopathological and molecular genetic entity

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Background: Peutz–Jeghers syndrome (PJS) is an autosomal dominant hamartomatous polyposis syndrome of the gastrointestinal tract, caused by a germline *STK11/LKB1* mutation. Nasal polyposis was described in the original report by Peutz. Recently, a molecular–genetic association between nasal polyposis and PJS has been reported.

Objective: To further explore the occurrence and pathogenesis of PJS-related nasal polyposis.

Methods: 51 patients with PJS, 84 unaffected family members and 36 spouses from 18 families with PJS were questioned for the presence of nasal polyposis. 12 PJS-related nasal polyps, 1 carcinoma of the nasal cavity and 28 sporadic nasal polyps were analysed for loss of (wild type) *STK11/LKB1*, eosinophilia, squamous metaplasia, dysplasia and expression of cyclo-oxygenase 2 and p53.

Results: Nasal polyps occurred in 8 of 51 patients with PJS, and were not reported by non-affected family members ($p < 0.001$). Germline *STK11/LKB1* mutations were identified in all patients with PJS and nasal polyposis. Loss of heterozygosity was found in four of eight PJS-related nasal polyps, but not in sporadic nasal polyps ($p = 0.002$). PJS-related nasal polyps showed less eosinophilia than sporadic nasal polyps ($p < 0.001$). Expression of cyclo-oxygenase 2 was found in 11 of 12 PJS-related nasal polyps and 19 of 28 sporadic nasal polyps ($p > 0.05$). Overexpression of p53 was not found.

Conclusions: Nasal polyposis occurs in a significant number of Dutch patients with PJS, one of whom developed a carcinoma in the nasal cavity. The loss of heterozygosity, and the absence of eosinophilia suggest a distinct pathogenesis compared with sporadic nasal polyposis.

Peutz–Jeghers syndrome (PJS) is a rare autosomal dominant disorder, characterised by hamartomatous polyposis of the gastrointestinal tract and melanin pigmentation of the skin and mucous membranes.^{1–2} Patients with PJS have an increased risk of developing gastrointestinal and extraintestinal cancer at a relatively young age.^{3–6} PJS is caused by a germline mutation in the *STK11/LKB1* tumour suppressor gene on chromosome 19p13.3.^{7–8} Molecular analysis of tumours from patients with PJS has shown loss of heterozygosity (LOH) at chromosome 19p13.3, indicating inactivation of wild-type *STK11/LKB1*.^{9–11}

In 1921, the Dutch physician Peutz described the first family with PJS with both nasal and gastrointestinal polyposis.¹ Evaluation of this original family revealed that 6 of 22 patients had nasal polyposis, and one of these individuals developed a nasopharyngeal carcinoma.¹² Nasal polyposis associated with PJS has also been described by others.^{13–19} In addition, we reported LOH at the *STK11/LKB1* locus in PJS-related nasal polyps; haplotype analysis, indeed, confirmed that this resulted in loss of wild-type *STK11/LKB1*, providing genetic support for the association between nasal polyposis and PJS.²⁰

In the general population, nasal polyposis is common,²¹ and thought to be an allergic inflammatory disorder with common pathogenesis to asthma.²² This is reflected by extensive infiltration of eosinophilic leucocytes in most cases.²³ Nasal polyps are not considered as a pre-neoplastic entity. To the best of our knowledge, reports about malignant degeneration are lacking, and oncogenic mutations have not been described. However, there are case reports of nasal polyposis associated with PJS.^{13–18} LOH in nasal polyps of patients with PJS,²⁰ and the co-occurrence of nasal polyposis and a carcinoma of the

nasal cavity in a patient with PJS,¹² suggest that these nasal polyps follow a distinct pathogenesis and could be part of the PJS.

This study further investigates the relationship between nasal polyposis and PJS. The presence of nasal polyposis in Dutch families with PJS was assessed. PJS-related and sporadic nasal polyps were studied for LOH at 19p13.3, and for eosinophilia, squamous metaplasia and dysplasia. Also, the expression of cyclo-oxygenase (COX) 2 and p53 was evaluated. A carcinoma of the nasal cavity from a patient with PJS having nasal polyposis was investigated for inactivation of *STK11/LKB1*.

METHODS

Patients and tissue specimens

A total of 51 patients with PJS, from 18 families with PJS^{11 12 24 25} were included. The clinical diagnosis was confirmed by histopathological review of gastrointestinal hamartomas by an experienced pathologist (GJAO). In all but one family, germline *STK11/LKB1* mutations were identified.

From the above study group, 35 patients with PJS were questioned about a medical history of nasal polyposis. In addition, data from 16 deceased patients with PJS from the original family, described by Peutz, were used. Clinical information about these patients was obtained from medical charts, previous publications^{1 12 25} and interviews with first-degree relatives. As controls, 84 non-affected (genetically related) family members, and 36 spouses were questioned about the occurrence of nasal polyposis. The protocol was

Abbreviations: COX, cyclo-oxygenase; LOH, loss of heterozygosity; PJS, Peutz–Jeghers syndrome

Table 1 Germline *STK11/LKB1* mutation, number of patients with Peutz–Jeghers syndrome (PJS), and number of patients with PJS having nasal polyposis from families with PJS having nasal polyposis

Family	<i>STK11</i> mutation	Exon/intron; codon	Nucleotide change	Alteration mRNA	Patients with PJS (n)	Patients with PJS with nasal polyposis (n)
1*	Deletion	Exon 2–3; codon 98–150	Loss of 57 codons	Deletion of 57 amino acids	1	1
2	Missense	Exon 7; codon 297	4016 G/A	AGG/AAG	1	1
3	Insertion	Exon 1; codon 66	535 ins T	Frameshift 162 TGA/stop	22	6†

PJS, Peutz–Jeghers syndrome.

*Not previously published mutation.

†Including a patient who developed a carcinoma of the nasal cavity.

approved by the medical ethics committee of the University Hospital Rotterdam. Informed consent was given by all participating individuals.

From 4 patients with PJS with nasal polyposis, 12 nasal polyps and 1 carcinoma of the nasal cavity were available for study. The specimens were collected from several hospitals in The Netherlands. A control group consisted of 28 randomly selected sporadic nasal polyps from age- and gender-matched patients without PJS, cystic fibrosis, Kartagener's syndrome or aspirin hypersensitivity, removed between 1996 and 1998 at the Academic Medical Center in Amsterdam, The Netherlands.

Tissue preparation and DNA isolation

Formalin-fixed paraffin wax-embedded samples were cut into 5 µm thick sections, and stained with H&E for histopathological examination. Polyp and carcinoma epithelium were carefully microdissected from haematoxylin stained slides. For wild-type DNA, stromal tissue from the same sample was used. DNA was isolated from microdissected tissue as described previously.¹¹

LOH at 19p13.3, mutation analysis, CpG-island hypermethylation

LOH was analysed as described previously,²⁰ comparing DNA from polyp or carcinoma tissue with normal tissue from the same patient. Polymorphic microsatellite markers (D19S886 and D19S565) flanking the *STK11/LKB1* gene on chromosome 19p13.3 were used. If a marker was homozygous in normal DNA, polyps of this patient were defined as non-informative for the tested marker. DNA from a PJS-related carcinoma of the nasal cavity was also studied for somatic *STK11/LKB1* mutations by exon sequencing using reported primers,²⁶ and for silencing the promoter region of *STK11/LKB1* by CpG-island methylation using a methylation-specific PCR as described previously.²⁷

Histopathological examination

H&E-stained slides of nasal polyps were examined for the presence of eosinophils, squamous metaplasia and dysplasia by two observers (JJK and GJAO) in a coded fashion. The presence of eosinophils in the stroma underneath the surface epithelium was assessed in a semiquantitative manner (0, none/only a few eosinophils; +, moderate number of eosinophils; and ++, large number of eosinophils). Squamous metaplasia and dysplasia were assessed as either present or absent.

Immunohistochemical analysis for COX 2 and p53

Immunohistochemical analysis was performed as described previously.¹¹ Primary monoclonal antibodies used were: antibody 160112 against COX 2 (Cayman Chemical Co, Ann Arbor, Michigan, USA) at a dilution of 1:100; and DO7 (Dako, Glostrup, Denmark) against p53 at a dilution of 1:200. For antigen retrieval, slides were boiled for 10 min in 0.01 M citrate buffer, pH 6.0, incubated with the primary antibody overnight at 4°C (COX 2) or for 1 h at room temperature (p53). As

positive control, a known positive colorectal carcinoma was used.

Immunostained slides were scored by two observers (JJK and GJAO) in a coded fashion. Epithelial COX 2 staining was assessed as negative or positive (ranging from weak to intense staining²⁸). p53 staining was considered positive if >10% of nuclei were positive. Nuclear p53 staining restricted to the basal (proliferative) compartment of squamous metaplasia was not considered positive.

Statistics

Comparisons between groups were made using the Mann–Whitney U test or Fisher's exact test. A p value of <0.05 was considered significant; p values were two sided.

RESULTS

Nasal polyposis in patients with PJS

Nasal polyposis occurred in 8 out of 51 (16%) patients with PJS, whereas none of the non-affected family members or spouses of patients with PJS reported nasal polyposis ($p < 0.001$).

The eight patients with PJS having nasal polyposis were from three different families with established germline *STK11/LKB1* mutations (table 1). Nasal polyposis did not occur in patients with PJS from 15 other families. Clustering of nasal polyposis and PJS was found in one family. In this well-documented family,^{1 12 25} 6 out of 22 (27%) patients with PJS had nasal polyposis. Detailed clinical information was available from four patients with PJS having nasal polyposis, from three different families with PJS. Three of these patients had recurrent and serious nasal polyposis for which multiple polypectomies were performed. Of note, nasal polyposis was symptomatic and diagnosed at a young age in four patients aged 7, 8, 11, and 14 years. One patient with PJS who first presented with (recurrent) nasal polyposis in infancy developed a moderately differentiated carcinoma of the nasal cavity at the age of 52 years.¹² The patient had also had a pulmonary adenoma at the age of 38 years.

Inactivation of *STK11*

A total of 12 nasal polyps from 4 patients with PJS and 28 sporadic nasal polyps were studied for LOH at polymorphic markers flanking the *STK11/LKB1* locus 19p13.3. As reported previously,²⁰ LOH was found in four of eight informative nasal polyps from two patients with PJS from different families. Markers were non-informative in one patient from whom two polyps were selected for study. DNA from two polyps from different patients did not amplify consistently. LOH was not found in 23 informative sporadic nasal polyps from the controls. The difference in frequency of LOH in PJS-related nasal polyps compared with sporadic nasal polyps was significant ($p = 0.002$; table 2).²⁰

DNA isolated from a carcinoma of the nasal cavity from a patient with PJS having nasal polyposis was studied for inactivation of *STK11/LKB1*. Markers used for LOH analysis

Table 2 Loss of heterozygosity at 19p13.3 (informative cases), eosinophilia, squamous metaplasia, expression of cyclo-oxygenase 2 and overexpression of p53 in nasal polyps from patients with Peutz-Jeghers syndrome having sporadic nasal polyps

	LOH 19p p<0.01	Eosinophilia* p<0.001	Sq metaplasia p>0.05	COX 2 p>0.05	P53 p>0.05
PJS	4/8	1/12	1/12	11/12	0/12
Sporadic	0/23	23/28	6/28	20/28	0/27

COX, cyclo-oxygenase; LOH, loss of heterozygosity; PJS, Peutz-Jeghers syndrome; Sq, squamous.

*Moderate or strong infiltration of eosinophils.

were non-informative (see above). However, sequencing revealed that tumour DNA contained wild-type *STK11/LKB1* in addition to known germline mutant *STK11/LKB1* DNA (insert T at codon 66, exon 1), indicating the absence of LOH at 19p13.3. No somatic mutation in *STK11/LKB1* or CpG-island hypermethylation within the promoter region of *STK11/LKB1* was found.

Histological comparison of PJS and sporadic nasal polyps

A total of 12 nasal polyps from 4 patients with PJS were compared with 28 sporadic nasal polyps. There were significantly less eosinophils in nasal polyps of patients with PJS compared with sporadic nasal polyps ($p<0.001$; table 2). Only 1 of 12 nasal polyps from patients with PJS showed a moderate number of eosinophils, whereas 23 of 28 sporadic nasal polyps showed moderate ($n=8$) or large ($n=15$) numbers of eosinophils (table 2; figs 1A,B and 2). No other histological differences were encountered. Squamous metaplasia was found in 1 polyp of a patient with PJS (8%), and in 6 sporadic polyps (21%; $p=0.65$; table 2). No dysplasia was found in any of the polyps.

Figure 2 Distribution of eosinophilia in nasal polyps from patients with Peutz-Jeghers syndrome (PJS) and sporadic nasal polyps, assessed in a semiquantitative manner as weak/absent, moderate or strong. Eosinophilia was significantly more common in sporadic than PJS-related nasal polyposis ($p<0.001$).

Immunohistochemical analysis for COX 2 and p53

PJS-related and sporadic nasal polyps were evaluated for the immunohistochemical expression of COX2 and p53. Expression of COX2 is upregulated in PJS-related gastrointestinal hamartomatous polyps,^{28,29} and could be a target for chemoprevention in pre-malignant neoplastic disorders. Also, dysregulated expression of COX2 occurs in sporadic nasal polyposis.³⁰ Expression of COX2 (ranging from weak to intense staining) could be found in the cytoplasm of epithelial cells of 11 of 12 nasal polyps of patients with PJS, and 20 of 28 sporadic nasal polyps (fig 1C). Expression of COX2 was also found in a PJS-related carcinoma of the nasal cavity (fig 1D). p53 staining was assessed because overexpression was reported in 96% of nasopharyngeal carcinomas and 79% of adjacent dysplastic lesions,³¹ suggesting a potential as marker for (pre-) malignant growth of nasopharyngeal epithelium. Nuclear overexpression of p53 (>10% positive nuclei) was not found in PJS-related or sporadic nasal polyps.

Figure 1 Histology and immunohistochemical cyclo-oxygenase (COX) 2 expression of nasal polyps and a Peutz-Jeghers syndrome (PJS)-related carcinoma of the nasal cavity. H&E staining of a sporadic nasal polyp with strong infiltration of eosinophils (A); and a PJS-related nasal polyp lacking eosinophilia (B). Expression of COX 2 in a PJS-related nasal polyp (C) and a carcinoma of the nasal cavity of a patient with PJS having nasal polyposis (D). Of note, expression of COX 2 was also found in sporadic nasal polyps.

DISCUSSION

This study investigates the association between nasal polyposis and PJS, first reported by Peutz in 1921.¹ Our findings suggest a different pathogenesis for PJS-related nasal polyps compared with sporadic nasal polyps. LOH of the non-mutated *STK11/LKB1* locus at 19p13.3 was found in some of the PJS-related nasal polyps, but not in sporadic lesions.²⁰ To date, no report of genetic alterations in sporadic nasal polyps exists. In general, nasal polyps are characterised by extensive infiltration of eosinophilic inflammatory cells, consistent with an allergic/inflammatory pathogenesis.²² Nasal polyps from patients with PJS had significantly fewer eosinophils than sporadic nasal polyps ($p < 0.001$). Similar observations are reported in nasal polyps associated with other specific syndromes. For example, those from patients with cystic fibrosis or Kartagener's syndrome also lack extensive eosinophilia.^{23–32}

In our study, only 16% of the patients with PJS had nasal polyposis, found in 3 of 18 families with PJS studied. In the family originally described by Peutz, 6 of 22 patients with PJS had nasal polyposis, but not their 54 non-affected family members and spouses, making a PJS-independent cause unlikely. Familial clustering seems to occur, but large genotype–phenotype investigations would be necessary to elucidate whether nasal polyposis is correlated with a specific genotype. The relatively low incidence of nasal polyposis in PJS presumably explains the limited number of reports of this association. Nasal polyposis is common in the general population with an estimated incidence of 0.627 patients per 1000 persons per year. Of note, nasal polyposis in the general population is rare at a younger age.²¹ In contrast, nasal polyposis occurred at a very young age in several patients with PJS. Thus, although nasal polyposis cannot serve as a marker for PJS in the general population, an early onset of nasal polyposis in a patient from a family with known PJS suggests that the person is affected. Also, PJS should be considered in the differential diagnosis of a patient with nasal polyposis under the age of 12 years. The early onset of the nasal polyps in patients with PJS is certainly yet another argument that nasal polyposis can indeed be considered as part of the syndrome.

One patient with PJS, recurrent nasal polyposis beginning at a young age and carcinoma of the nasal cavity at the age of 52 years was identified. Genetic analysis of this carcinoma could not prove inactivation of *STK11/LKB1* by LOH, somatic mutation or CpG-island hypermethylation in the promoter region of *STK11/LKB1*. However, inactivation could have occurred by an intronic mutation resulting in alternative splicing, or by large deletions⁶ not detected by exon sequencing of short strands of DNA isolated from paraffin wax-embedded tissue. Taken together, the association between the development of this nasopharyngeal carcinoma and the PJS in this patient remains uncertain.

The finding of LOH in nasal PJS polyps is consistent with clonal growth. At the microscopic level, no pre-neoplastic features such as dysplasia were seen. Thus whether or not nasal PJS polyps carry an intrinsic neoplastic potential needs to be seen. The observed overexpression of COX 2 could provide a rationale for experimental chemopreventive treatment with non-steroidal anti-inflammatory drugs or COX 2 inhibitors in patients with PJS having (severe) nasal polyposis.

In conclusion, nasal polyposis associated with PJS should be considered as extraintestinal hamartomas. The absence of eosinophils compared with sporadic nasal polyps and the early onset indicate a distinct pathogenesis, in which LOH at the *STK11/LKB1* locus 19p13.3 could be involved. Whether or not the polyps in PJS carry a neoplastic risk needs to be seen, but in the clinical management of these patients careful examination is warranted.

Take-home messages

- Nasal polyposis should be considered as an extraintestinal manifestation of Peutz–Jeghers syndrome (PJS), although it occurs in a minority of patients.
- Nasal polyposis in patients with PJS can occur at a very young age and cause serious morbidity.
- The early onset, the absence of eosinophils and the loss of heterozygosity in PJS-related nasal polyps suggest a distinct pathogenesis compared with sporadic nasal polyps.

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