Case Report

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A rare case of Colorectal Cancer in a patient with polyposis and an NTHL1 gene mutation

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ABSTRACT

NTHL1 polyposis syndrome (or FAP-3 syndrome) is a rare familial polyposis syndrome with only 72 reported cases worldwide from 50 different families. A 54-year-old male presented with a change in bowel habits and an incidence of blood in the stools. Colonoscopy demonstrated over 60 polyps and a suspicious cecal lesion with high grade dysplasia on biopsy. Genetic panel testing tested positive for NTHL1 mutation. Subsequently he was operated on with a subtotal colectomy in order to manage the cecal lesion and the polyposis syndrome. A colorectal adenocarcinoma with a squamous feature of the cecum was diagnosed. The patient was the first of his family with a cancer diagnosis. Finally, he was released after 10 days with no major complications. His family was informed about the inheritance characteristics of the syndrome and was advised properly. This is a rare case of familial polyposis syndrome with an NTHL1 gene mutation. APC and MUTYH are the most common gene mutations among patients with FAP. Clinicians should be aware of such mutations and advise patients and families properly.

Key Words: *Case Report; polyposis; NTHL1; colorectal cancer*

INTRODUCTION

The protein encoded by NTHL1, endonuclease III-like protein 1 (NTHL1), is a DNA glycosylase of the base excision repair pathway that removes endogenously damaged nucleotides in DNA [1].Mutations in this gene cause NTHL1 tumour syndrome (or NTHL1 polyposis syndrome, or FAP-3 syndrome) which is an autosomal recessive syndrome characterised by an increased lifetime risk for colorectal cancer (CRC), breast cancer, and colorectal polyposis, as well as endometrial cancer [3], urothelial carcinoma of the bladder, meningiomas [8], unspecified brain tumours, basal cell carcinomas, head and neck squamous cell carcinomas, and haematologic malignancies [5]. Colorectal polyps can be adenomatous, hyperplastic, and/or sessile serrated. Duodenal polyposis has also been reported. NTHL1 tumour syndrome has been described in 50 families with 72 affected individuals.The cumulative lifetime risk of developing extracolonic cancer by age 60 years has been estimated at 35% to 78% [5]. Almost all (93%) homozygous patients have colonic adenomas on colonoscopy, while among heterozygous carriers the percentage is 38% [3]. These patients are at high risk of developing CRC as half of the patients (37 out of 72) developed CRC with a median age of onset at 51 [2]. In most cases it was a right-sided cancer but cancers in the rest of the colon were also found. Heterozygotes do not seem to have an increased risk [4]. To date, diagnostic criteria for NTHL1 tumour syndrome have not been established. Individuals in whom the syndrome should be suspected include those with presence of multiple primary cancers before the age of 50, colorectal cancer (CRC) diagnosed

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before the age of 40, one or more colorectal adenomas in an individual aged ≤40 years, a personal cumulative lifetime history of ten or more colorectal adenomas in an individual aged ≤60 years, a personal cumulative lifetime history of any combination of 20 or more colorectal adenomas, hyperplastic polyps, and/or sessile serrated polyps in an individual of any age or a family history of NTHL1 syndrome [5]. Molecular genetic testing should be performed in these individuals [6].

NARRATIVE

Patient Information

A 54-year-old male individual presented with a reported recent incidence of blood in the stools and a change in his bowel habits. Medical history included hypertension under medication, and he did not report any family history of bowel cancer. He had undergone an appendicectomy at a young age. Endoscopic assessment revealed more than 60 polyps in total from 2mm to 40mm, one of which was located at the cecum and raised a high suspicion of malignant transformation. Biopsies were taken from several polyps.

The biopsies summarised in Table 1 resulted as follows: (A) Cecum lesion biopsies: Parts of a villotubular adenoma with high-grade dysplasia. B-catenin with a pathological expression pattern. (B) Transverse colon polyp: Pedunculated polyp with low grade dysplasia and at some spots high grade dysplasia, excluded within healthy limits. B-catenin with a pathological expression pattern. (C) Rectal polyps: 8 small parts of rectal polyps that originated from a hyperplastic polyp and a sessile serrated lesion with no dysplasia but with a change in the crypt architecture. The above lesions were checked for microsatellite instability and were found to be MSI stable.

The patient had a staging CT of the thorax and the abdomen with IV contrast. The thoracic CT was normal with no findings compatible with metastatic lesions. The CT of the abdomen showed the polyps in the colon, specifically the 35-mm cecum lesion, a 15-mm sessile polyp in the sigmoid colon and a 20-mm pedunculated polyp in the rectum. Some lymph nodes less than 7-mm were found next to the inferior mesenteric artery and on branches of the superior mesenteric artery. No findings of metastatic or peritoneal disease were reported.

TABLE 1. Endoscopic biopsy results.

Type of biopsy	Location	Result
Parts of villotubular adenoma	Cecum	High grade dysplasia
Pedunculated polyp	Transverse colon	Low grade and at some spots high grade dysplasia
8 small parts of rectal polyps	Rectum	Parts of hyperplastic polyps – no dysplasia
Sessile serrated lesion	Rectum	No dysplasia – change in crypt architecture

Finally, the patient had molecular genetic testing from a blood sample as FAP was a probable diagnosis. As the patient had more than 10 polyps on colonoscopy, a multigene panel including genes causing Polyposis or associated with a high risk for CRC was considered necessary [14]. A test including 52 of them was performed, including those suggested by the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer [10]. Twenty-eight of them are mentioned in Table 2. APC, MUTYH, BRCA1, BRCA2, EPCAM, MLH1, MSH2, MSH6, PMS2, NTHL1 and several other genes were included in the panel. In the NTHL1 gene the individual was found homozygous for a NM_002528:c.268>T,p.(Gln90*) mutation. This is a mutation in the 268th nucleotide base of the NTHL1 gene that causes an alteration in which glutamine is substituted by a termination codon. The protein produced is an inactive protein [7]. This mutation has been described in individuals with attenuated polyposis and colorectal cancer [8]. He was also found heterozygous for a mutation in the NF1 gene. The mutations in this gene cause Neurofibromatosis type 1 (NF1), an autosomal dominant disorder with several clinical features that include benign and malignant tumours [9]. As mentioned above there was no clinical feature indicative of neurofibromatosis type 1. Furthermore, NF1 is generally not associated with colonic adenocarcinomas.

Multidisciplinary discussion suggested proceeding to surgical intervention taking into consideration the clinical presentation and imaging.The objective was the management of the polyposis syndrome and the excision of the suspicious cecum lesion. Surgical options discussed with the patient were as follows:

1. Right hemicolectomy
2. Subtotal colectomy with IRA (ileorectal anastomosis)
3. Total proctocolectomy with IPAA (ileal-pouch anal anastomosis) with J-Pouch
4. Total proctocolectomy with end ileostomy

Therapeutic Intervention

After a detailed discussion with the patient all the therapeutic choices were reviewed. The patient and his family were also informed about the inheritance pattern of the gene, and they were advised to speak with an expert geneticist. A laparoscopic subtotal colectomy with an ile-

TABLE 2. Sample of genes tested for mutations.

Gene	Reference Sequence	Result	Zygosity	Clinical significance
APC	NM_000038	No Mutation	-	-
ATM	NM_000051	No Mutation	-	-
AXIN2	NM_004655	No Mutation	-	-
BMPR1A	NM_004329	No Mutation	-	-
BRCA1	NM_007294	NoMutation	-	-
BRCA2	NM_000059	NoMutation	-	-
CDH1	NM_004360	NoMutation	-	-
CDK4	NM_000075	NoMutation	-	-
CHEK2	NM_007194	NoMutation	-	-
EPCAM	NM_002354	NoMutation	-	-
MEN1	NM_000244	NoMutation	-	-
MLH1	NM_000249	NoMutation	-	-
MSH2	NM_000251	NoMutation	-	-
MSH3	NM_002439	NoMutation	-	-
MSH6	NM_000179	NoMutation	-	-
MUTYH	NM_001128425	NoMutation	-	-
NF1	NM_000257	NM_000267:c.49992G>A, p.(Trp1664*)	Heterozygous	pathogenic
NTHL1	NM_002528	NM_002528:c268C>T, p.(Gln90*)	Homozygous	pathogenic
PALB2	NM_024675	NoMutation	-	-
PMS2	NM_002528	NoMutation	-	-
PTEN	NM_000314	No Mutation	-	-
RAD50	NM_005732	NoMutation	-	-
RET	NM_020975	NoMutation	-	-
RAD51C	NM_058216	NoMutation	-	-
RAD51D	NM_002878	NoMutation	-	-
SMAD4	NM_005359	No Mutation	-	-
STK11	NM_000455	No Mutation	-	-
TP53	NM_000546	NoMutation	-	-

orectal anastomosis was performed.The rationale behind this decision was that this operation is a safe choice, less radical than other interventions. As no malignancy was detected in the rectum, sparing of the rectum can provide acceptable functional outcomes for a patient of his age. It also achieves excision of all the colon, reducing the risk for a future incidence of CRC and does not include the creation of a stoma, either permanent or temporary. The patient was informed of the need for frequent rectoscopies and the possibility of the need for a more radical intervention in the future.

Outcomes

According to the pathologist's report of the surgical specimen, the cecum tumour was a pT3N1b adenocarcinoma of intermediate differentiation, with a squamous feature in less than 50% of the total mass. The tumour, infiltrating the pericolic fat, was 5 x 4.5 cm, and 2 out of 46 lymph nodes were found positive. Perivascular infiltration was detected. The rest of the colon was found to contain numerous polyps sized from 0 to 18mm (Figures 1 - 2) that were listed according to the distance from the surgical boundaries and the size of the polyp.

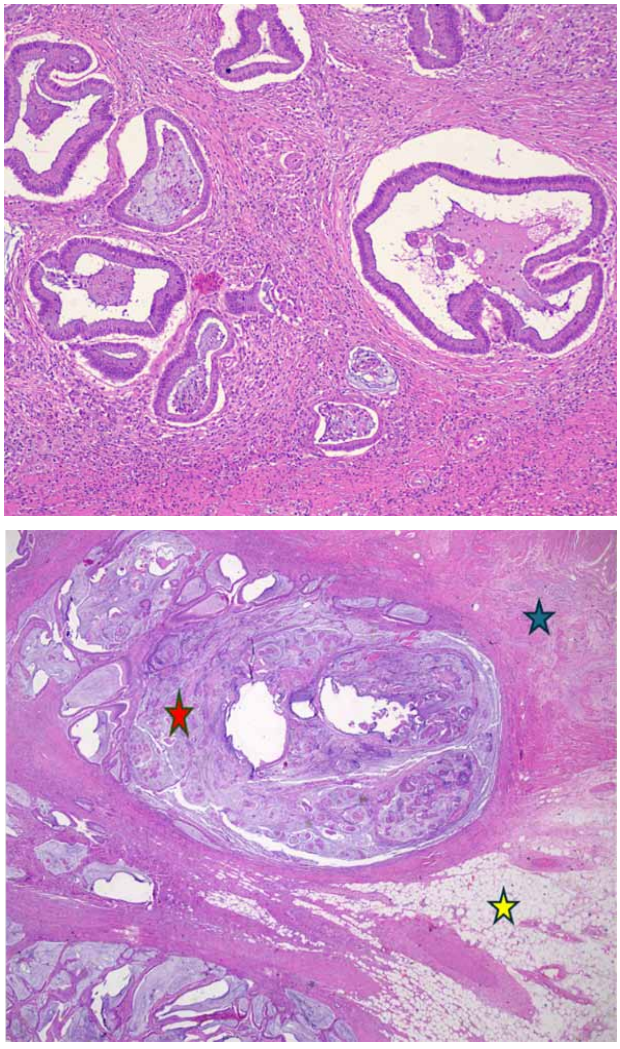

FIGURE 1. Colorectal adenocarcinoma composed of neoplastic gland invading muscular propria ★ and the pericolic fat tissue ☆. Presence of extracelular mucin in <50% of the adenocarcinoma ★.

The pathologist report was discussed in the oncological MDT, and the administration of adjuvant chemotherapy was suggested.

DISCUSSION

This is a case report of a rare case of familial adenomatous polyposis and colorectal cancer in an individual with a homozygous NTHL1 mutation, which is called NTHL1 polyposis syndrome or FAP-3. Our purpose is not to suggest guidelines or diagnostic and therapeutic approaches, but to raise awareness of this syndrome as up to now it is reported to affect only 72 individuals among 50 families [2]. These patients are at high risk of developing colorectal cancer. From our experience patients with more than 10 polyps, or young patients less than 40 years old with polyps on a colonoscopy should

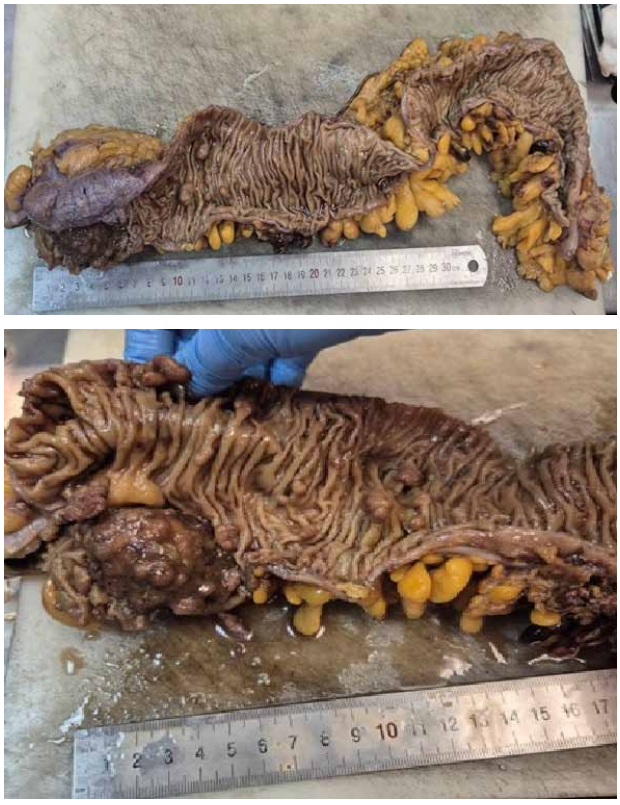

FIGURE 2. Up: Surgical specimen of subtotal colectomy. Numerous polyps can be detected throughout the colon and a cecum lesion on the left of the figure. Down: Ascending colon. The cecum lesion can be seen more closely. Several polyps can also be detected.

be suspected of having a familial polyposis syndrome. Thus, they should be candidates for molecular genetic testing [14). Except for the most common APC and MUTYH gene mutations, there are other less frequent mutations [8) like those of NTHL1, that can cause such syndromes. In such patients it is reasonable to take endoscopic biopsies from several lesions across all parts of the colon and rectum, with more attention to more suspicious lesions. Gene testing should be the next step. A multigene panel is a reliable way of molecular genetic testing with the advantage of the inclusion of several possible mutations that may cause the same phenotype [10). Patient and family consultation is of utmost importance firstly because such syndromes need radical surgical intervention that can affect the quality of life, and secondly because they have a hereditary pattern and they can affect other family members [2). An oncological MDT including surgeons, geneticists, oncologists and pathologists could amplify this process. As far as therapeutic intervention is concerned radical colectomy should be the first option including Right hemicolectomy, subtotal colectomy, total proctocolec-

tomy with IPAA with J-Pouch, and total proctocolectomy with end ileostomy. The patient's characteristics such as age, comorbidities, way of life and preferences should be seriously considered in the decision making and options should be discussed with the patient. Possible dangers, the way quality of life is affected, and the need for future follow-up related to each therapeutic choice should be analysed for the patient. In general, such syndromes are diagnosed in younger patients, with NTHL1 polyposis syndrome affecting patients less than 60 years old in most cases, who have an active way of life [3]. In these cases, subtotal colectomy with ileorectal anastomosis and regular endoscopic evaluation of the rectum afterwards, or total proctocolectomy with J-pouch anastomosis could be reasonable solutions, as they exclude all or most of the colon and provide a good quality of life.

In our case, subtotal colectomy with ileorectal anastomosis was chosen as it was considered safe and with the optimal functional results for the patient. As mentioned above, sparing of the rectum can provide an acceptable functional outcome for a patient of his age.It also achieves excision of all the colon, reducing the risk for a future incidence of CRC, and does not include the creation of a stoma either permanent or temporary. The patient was informed and agreed with a close follow-up with frequent rectoscopies and accepted the possibility of the need for a more radical intervention in the future.

Squamous features in colorectal adenocarcinomas represent a rare subtype of colorectal cancer accounting for 0.06-0.18% of cases. Due to its rarity, immunohistochemical and biological profiles have not been well investigated, anda specific percentage cut-off necessary for each componentto characterise it as adenosquamous has not been established, as with other gastrointestinal adenosquamous malignancies. This feature predisposes to an aggressive clinical course in several case series, often diagnosed at later stages and with lower overall survival than typical adenocarcinomas [13). To our knowledge, there is no other case of NTHL-1 colorectal adenocarcinoma with a squamous feature reported.

Regarding the heterozygous NF1 variant, Neurofibromatosis type 1 is a soft-tissue autosomal dominant condition. Individuals with NF1 are at high risk of several malignancies [9). Some molecular mechanisms may indicate a connection between NF1 gene mutations and sporadic colorectal cancers [12). Yet, there has not been any association described between this condition and colorectal cancer including several cohort studies [11). Consequently, in this case, this mutation was considered incidental.

CONCLUSIONS

Not all familial polyposis syndromes are caused by the most described genes APC and MUTYH. There are more genes, like NTHL1, with such a phenotype. Therefore, molecular genetic testing in proper candidates is important to determine the responsible gene which helps clinicians give proper therapeutic advice as well as appropriate family guidance. NTHL1 polyposis syndrome is a newly described syndrome, so clinicians should be informed about it. Subtotal colectomy and close follow-up due to the risk of other malignancies in the future seem like a reasonable approach. Such cases should be reported as they are uncommon. More data are necessary to better determine its clinical manifestations and therapeutic approach.

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The authors declare no conflict of interest.

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