CASE REPORT

A case report of hamartomatous polyposis in an individual with Neurofibromatosis type 1

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Key Clinical Message
Even in well-described genetic syndromes, such as neurofibromatosis type 1, expansion of the phenotype should be considered as a possible explanation for atypical presentations. However, it is critical to complete the evaluation for a potential dual diagnosis, as there could be significant prognostic and management implications.

KEYWORDS
colonic polyposis, dual diagnosis, hamartomatous polyps, hereditary polyposis syndrome, juvenile polyposis syndrome, neurofibromatosis type 1, *PTEN* hamartoma syndrome

1 | INTRODUCTION

Neurofibromatosis type 1 (NF1) is a neurocutaneous syndrome that manifests with cafe-au-lait macules (CAL), axillary and inguinal freckling, cutaneous neurofibromas, Lisch nodules, and specific bone dysplasias. NF1 is caused by pathogenic variants in *neurofibromin*, a tumor suppressor gene, which encodes for a guanosine triphosphate hydrolase-activating protein involved in the modulation of mechanistic target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) pathways. NF1 is a classic tumor predisposition syndrome and is associated with an increased risk of developing numerous benign and malignant tumors. Whereas significantly elevated risk of developing peripheral nerve sheath tumors and gliomas of the optic nerves and the brain are pathognomonic features of the disease, recent studies have shown increased risk for breast cancer, pheochromocytoma, and gastrointestinal tumors.[1,2]

While not part of the classic presentation of NF1, gastrointestinal manifestations have been described 5%-25% of individuals with NF1, though the full gastrointestinal phenotype is not well described.[3] Approximately 5% of gastrointestinal findings are symptomatic, with the lack of symptoms making the presence of manifestation difficult to discern.[3]

Gastrointestinal stromal tumors (GIST) are a common GI manifestation in individuals with NF1, seen in 3.9%-25% of patients[4,5]. When polyposis is present, it is usually in the form of submucosal neurofibromas limited to the stomach and small intestine.[6] Neuroendocrine tumors, in particular those of the periampullary duodenum, are also reported.[3] While an isolated case report suggested possible association between NF1 and juvenile-type polyposis,[7] other data suggests no known association between NF1 and juvenile-type intestinal polyps.[8] As there is limited literature regarding the risk for GI manifestations in individuals with NF1, we present an individual with NF1 who presented with extensive colonic polyposis. We discuss the challenges in evaluation of an individual with such a clinical presentation and review the literature regarding gastrointestinal manifestations in NF1.

2 | CLINICAL REPORT

The proband, a 60-year-old Caucasian male, was evaluated at the Adult Genetics Clinic of Baylor College of Medicine, Houston, TX. All procedures outlined in the report were performed as a part of the clinical care. Informed consent was obtained to publish de-identified clinical information. The proband had been diagnosed with NF1 at age of 15 years

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based on the presence of multiple CAL, numerous subcutaneous neurofibromas (face, upper and lower limbs, and trunk), and axillary freckling. The medical history was also significant for gastroesophageal reflux, Hashimoto's thyroiditis, osteoporosis, and prostate cancer. Current physical examination was also remarkable for macrocephaly (FOC 60 cm). No mucocutaneous pigmentation was identified around the oral mucosa or fingertips. There were no hyperpigmentation spots on glans penis; however, small hyperpigmented spots were identified on the shaft of the penis akin to elsewhere on the skin. During a screening colonoscopy performed at 60 years of age, over 50 colonic polyps were found. The proband denied any history of abdominal pain, weight loss, and bleeding or mucoid discharge per rectum. Histopathological examination of the excised polyps demonstrated features consistent with hamartomatous polyps. The polyps (stained with tryptase) did not contain any significant neural component and no significant clustering of mast cells. The pathology report did not state the presence of other microscopic findings, such as specific juvenile histology. Polyp pathology was suggestive of a hamartomatous polyposis syndrome such as Cowden syndrome, juvenile polyposis syndrome (JPS), or idiopathic Cronkhite-Canada syndrome. Upper gastrointestinal endoscopy was unremarkable and showed no evidence for polyps.

Cancer family history was significant for one sister who expired because of bilateral breast cancer at 45 years of age. No family members had a diagnosis of NF1. There was no family history of colonic or intestinal polyposis, gastrointestinal cancers, and other early-onset cancers. There was no history of recurrent epistaxis or AVMs that was concerning for HHT.

As numerous colonic polyps are not a typical presentation of NF1, alternative diagnoses were considered. The differential included the well-known Mendelian disorders that present with intestinal polyposis as well as *PTEN*-hamartoma syndrome. The a priori risk of carrying a pathogenic variant in *PTEN*, as assessed by the Cleveland Clinic *PTEN* risk calculator, was 67% based on the presence of macrocephaly, personal history of cancer, thyroid disease, and more than five hamartomatous gastrointestinal polyps.[9]

After detailed counseling, the proband elected to pursue testing with a comprehensive hereditary colorectal/GI cancer panel to evaluate for a genetic etiology of the polyposis. The genes interrogated by the panel, which included sequencing and duplication and deletion analysis, were *APC, ATM, BMPR1A, BRCA1, BRCA2, CDH1, CDK4, CDKN2A, CHEK2, ENG, EPCAM* (deletion analysis only) *MLH1, MSH2, MSH6, MUTYH, PALB2, PMS1, PMS2, PTEN* (including *PTEN* promoter region analysis), *SMAD4, STK11,* and *TP53*. The panel methodology utilized a capture-based method and sequenced using Illumina platform. Deletion/duplication analysis was completed using array comparative

genomic hybridization. As molecular testing did not identify any known pathogenic variants or variants of uncertain significance in the interrogated genes, the molecular basis for the hamartomatous polyposis remains unknown.

3 | DISCUSSION

Here, we describe an individual with NF1 who presented with over 50 asymptomatic hamartomatous colonic polyps. The diagnostic considerations for such a clinical presentation include the following: (a) the individual has two distinct disorders, NF1 and a hamartomatous polyposis syndrome, and (b) the polys are a rare manifestation of NF1. Multiple hamartomatous polyps are observed in Peutz-Jeghers syndrome, *PTEN* hamartoma syndrome, Juvenile polyposis syndrome, and Cronkhite-Canada syndrome. Gastrointestinal tumors and colonic polyps have also been reported in NF1. The tumors of the gastrointestinal tract in NF1 include neurofibromas of the small bowel and colon, gastric schwannoma, diffuse mucosal/submucosal neurofibromatosis, malignant peripheral nerve sheath tumors, ganglioneuromas, and embryonal tumors.[3,5] Neuroendocrine tumors such as pheochromocytomas, periampullary somatostatinoma, insulinoma, gastroma, gangliocytic paraganglioma, and carcinoids, non-neurogenic gastrointestinal stromal tumors (GIST) have also been reported, along with multifocal interstitial cell of Cajal hyperplasia.[3]

Juvenile polyposis syndrome (JPS) is characterized by the occurrence of multiple juvenile polyps (typically 1-100) in the stomach, small intestine, colon, and rectum.[10] Juvenile-like polyps are a subtype of hamartomatous polyps. A diagnosis of JPS is established in proband with any one of the following clinical criteria: (A) having greater than five juvenile polyps of the colon or rectum, (B) having multiple juvenile polyps of the upper and lower GI tract, and (C) having any number of juvenile polyps and a family history of juvenile polyposis.[11,12] Thus, the individual in this case has a history suggestive of juvenile polyposis syndrome based on his pathology report.

Some manifestations of JPS have been reported in individuals with NF1. Juvenile-like polyps have been reported in 15 individuals with NF1.[13] Individuals with these polyps presented with abdominal pain or anemia. Six of 15 reported individuals were above 50 years of age and the majority had only one polyp. However, in one individual, 13 inflammatory polyps of the small intestine that required resection of the ileum and cecum was reported.[14] While isolated juvenile polyps are typically considered benign, it is unknown whether the juvenile polyps observed in NF1 are more likely to undergo malignant transformation. There is one reported case of a patient with clinical and molecular diagnosis of both NF1 and JPS. This patient demonstrated CAL, axillary

freckling, a parent with NF1, neurofibromas, and 27 colorectal juvenile polyps, two tubular adenomas, and 11 gastric hyperplastic polyps by age 39.[8] Unlike these previous reports, our patient was found to have more extensive polyposis (>50 polyps). CAL macules have been reported at an increased rate in individuals with JPS and familial adenomatous polyposis, and two of eight patients examined were found to have genital lentigines.[15]

PTEN hamartoma-related syndromes should be included in the differential for patients presenting with a similar phenotype to our proband. Cowden syndrome (CS) is one of the *PTEN*-hamartoma syndromes and is associated with an increased risk for benign and malignant tumors, most commonly of the thyroid, breast, and endometrium. Macrocephaly has been reported in 84% of patients with CS and is considered a hallmark of the syndrome.[16] Clinical diagnosis is based on a combination of major criteria (breast cancer, epithelial thyroid cancer (non-medullary), macrocephaly (occipital frontal circumference ≥97th percentile, and endometrial carcinoma) and minor criteria (thyroid lesions, intellectual disability (IQ ≤75), hamartomatous intestinal polyps, fibrocystic disease of the breast, lipomas, fibromas, genitourinary tumors, genitourinary malformation, and uterine fibroids).[9,16] Despite a high a priori risk of Cowden syndrome, this patient does not meet clinical criteria for the diagnosis of Cowden syndrome.[16]

Cronkhite-Canada syndrome (CCS) is an acquired disorder that is associated with gastrointestinal hamartomatous polyposis, alopecia, onychodystrophy, hyperpigmentation, and diarrhea. The average age of onset is 59 years old and most affected individuals exhibit all of the cardinal manifestations of the symptoms.[17] Our patient did not report symptoms consistent with CCS.

The germline genetic testing for a hereditary polyposis syndrome did not identify any pathogenic sequencing or copy number variants. While there exist possible molecular explanations for the connection between these polyps and NF1, we must also consider the possibility of two separate etiologies for this presentation. It is becoming increasingly recognized that there are many patients with mild phenotypes that do not come to clinical attention[18] and dual diagnoses may explain supposedly expanded phenotypes.[19] As molecular testing did not identify a second genetic etiology for our patient's symptoms, the etiology for his polyp burden is unclear. A hereditary polyposis syndrome is still in the differential; however, the patient's presentation may be due to an expansion of the clinical phenotype for NF1.

The correct classification and diagnosis of these polyps have important prognostic implications. A second diagnosis could confer a significantly increased risk of cancer regardless of age. For this reason, further studies to clarify the risk status such as a molecular diagnosis of NF1 would be recommended, though have not yet been pursued for logistic reasons. We have recommended follow-up colonoscopies annually until no new polyps are identified and then every 3 years after that point.

4 | CONCLUSION

We report on an individual with NF1 diagnosed in childhood and 54 hamartomatous colonic polyps found in late adulthood. While these findings could be explained by two distinct genetic disorders, we also consider that this history could be explained by the expansion of the NF1 phenotype.

AUTHOR CONTRIBUTIONS

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