

Original Article

Large polypoid perineurioma of the transverse colon without crypt serration (NPS)

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Abstract: Intestinal perineuriomas without crypt serration are mainly polypoid lesions characterized by a proliferation of stromal cells expressing perineurial markers. These lesions morphologically differ from those with serrated crypts because of the serrated/hyperplastic architecture in addition to the disorganization of the crypts. These tumors, despite both expression of perineurial cell markers (epithelial membrane antigen, claudin-1, GLUT-1, and collagen type IV), show well-characterized molecular differences such as BRAFV600E mutation, suggesting that they might represent two distinct variants of a single lesion. In this report, we describe a polypoid intestinal perineurioma without crypt serration of the transverse colon, showing an unusual large size compared with other reported polypoid lesions ranging from 0.2 to 0.6 cm in size.

Keywords: Intestinal perineurioma without crypt serration, transverse colon, large size

Introduction

Colorectal perineuriomas are benign lesions mainly located in the recto-sigmoid area. About 70% of these tumors show serrated/hyperplastic architecture (SPs) of the glands and are characterized by mucosal proliferation of benign stromal cells expressing perineurial markers leading to separation and/or disorganization of the crypts [1]. In 2004 Eslami-Varzaneh et al. identified SPs as an entity distinguished from fibroblastic colonic polyps based on expression of the epithelial membrane antigen and claudin-1 [2], but subsequently these lesions were reconsidered as the same entity [3]. The current nomenclature identifies colorectal fibroblastic polyp and SPs as two synonyms for a benign mucosal lesion with a predilection for the rectosigmoid colon [1].

Much less frequent colorectal perineuriomas are represented by tumors lacking serrated crypts (NPS). They are rarely reported in literature and their relation to serrated ones remains unclear [4]. Several studies showed that most SPs have a high prevalence of BRAFV600E

mutation but this molecular alteration is never present in NPS [5], suggesting that this subset of perineuriomas represent a unique type of hybrid epithelial/neurogenic polyp.

However, despite well-defined morphological and molecular differences, common features of polypoid intestinal perineuriomas are represented by the small size (ranged from 0.2 to 0.6 cm) and the rectosigmoidal location with only few cases reported in transverse colon [4, 6].

We describe a case of a 53-year-old male with a clinical diagnosis of a colorectal polyp subsequently diagnosed by morphological, immunohistochemical and molecular investigations as "polypoid intestinal perineurioma without Crypt Serration" (NPS) in the transverse colon. The peculiarity of this case is also represented by its unusual large size.

Case description

A 53-year-old Caucasian male without comorbidities underwent to INT Fondazione Pascale Hospital (Naples, Italy) for colorectal cancer screening. He was to an EGD with endoscopic

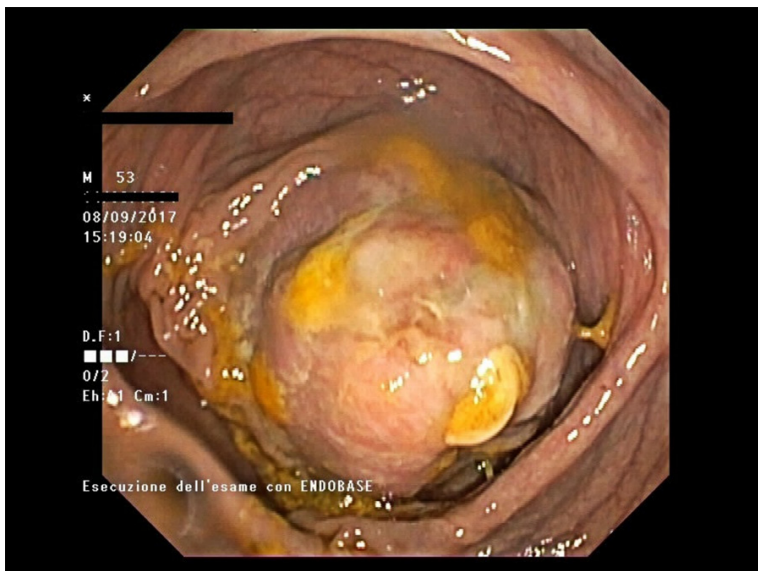


Figure 1. Endoscopic examination revealed a polypoid lesion covered by normal pink but focally ulcerated mucosa and a normal submucosal vascular pattern.

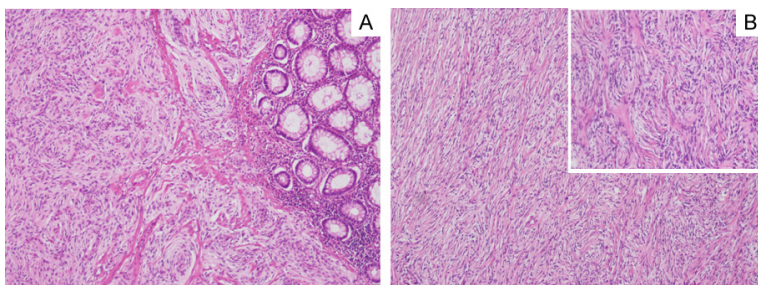


Figure 2. Histological findings. A. Overview of the intestinal mucosa without crypt serration overlying a moderately cellular mesenchymal proliferation (20 ×); B. Overview of slightly elongated cells without any atypia (20 ×) sometimes forming neuroid whorls (40 ×).

ultrasound (EUS) which highlighted a solid dishomogeneous area of 6.6 × 4.6 cm in size surrounded by peri-visceral adipose tissue in the transverse colon. The suspected polypoid mass was covered by normal pink but focally ulcerated mucosa and a normal submucosal vascular pattern (**Figure 1**). The following endoscopic biopsy showed only fragments of fibrous tissue with high fibroblastic reaction but with intestinal glandular elements without proliferative anomalies. However, because of the strong clinical suspicion of a colonic cancer, the patient underwent to a right hemicolectomy.

The surgical specimen was composed of an intestinal segment of 32 cm in length, including terminal ileum with ileocecal valve and appen-

dix. A polypoid sessile 4 cm in maximum diameter lesion, covered by focally eroded mucosa, was present at 2 cm from the distal resection margin. From the peri-visceral adipose tissue, along the main vascular trunks, 25 lymph nodes were isolated.

Under microscopic observation, the lesion was mainly represented by a moderately cellular mesenchymal proliferation, consisting of slightly elongated cells without any atypia, forming neuroid whorls (**Figure 2**). A large ulcerated area with underlying granulation tissue was present on the surface; the remaining colonic glands were normal without serrated/hyperplastic features (**Figure 2**). All lymph nodes were negative for cancer.

The panel of immunohistochemical markers showed a positive strong and diffuse cellular reaction for claudin1 (CLDN1, 1:50, Cell Marque, Rocklin, California, USA), EMA (E29, 1:75, Dako, Carpinteria, CA, USA) and collagen IV (M0785, 1:35, Dako, Carpinteria, CA, USA), less diffuse for GLUT1 (Anti-GLUT1, pre-diluted, Cell Marque, Rocklin, California, USA) and CD34 (QEnd/10, pre-diluted, VentanaMedical Systems, Inc.) (**Figure 3**). Indeed, CD117/c-Kit (CD117, 1:50; Dako, Carpinteria, CA, USA), S100 (1:3,000; Dako, Carpinteria, CA, USA), DOG1 (K9, 1:100, Leica Microsystems, Wetzlar, Germany), MSA (HHF35, pre-diluted, Cell Marque, Rocklin, California, USA) and STAT6 (M-20, pre-diluted, Santa Cruz Biotechnology, Santa Cruz, CA) were all negative.

Following indications from the literature showing that most perineuriomas with crypt serration harbor a BRAFV600E mutation whereas those without crypt serration do not, a molecu-

Polypoid intestinal perineurioma

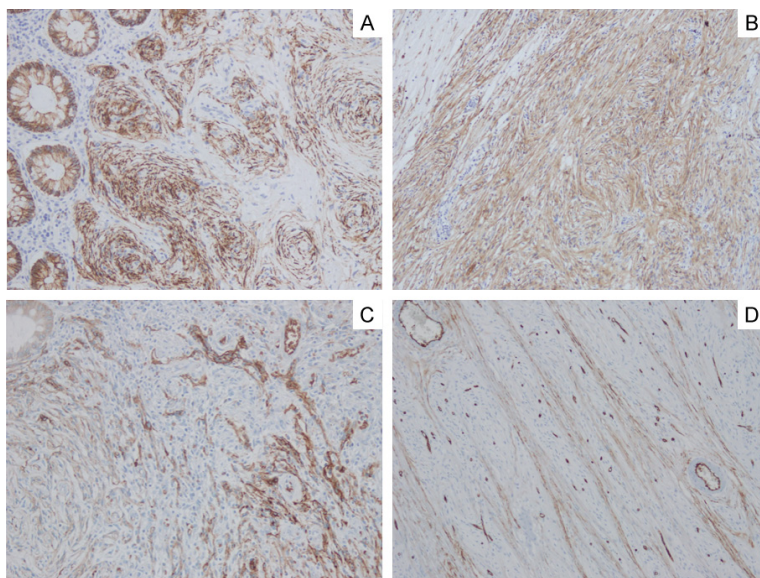


Figure 3. Immunohistological findings showing strong and diffuse positive expression for Claudin1 (A) and EMA (B), less diffuse for GLUT1 (C) and CD34 (D) (20 ×).

lar analysis was carried out to evaluate the V600E mutation of exon 15 of the BRAF gene. A representative formalin-fixed, paraffin-embedded (FFPE) sample of the case was selected and following DNA purification (QIAamp DNA FFPE Tissue kit; Qiagen, Valencia, CA, USA), polymerase chain reaction (PCR) was performed on 25-50 ng of isolated genomic DNA in a 9700 Thermal Cycler (Applied Biosystems, Foster City, CA, USA). The analyses were performed using a commercial kit (BRAF Mutation Analysis Kit, EntroGen, Tarzana, CA, USA), containing a distinct primer/probe in order to detect, by Real Time PCR system, V600 point mutations. No BRAF gene mutations were detected in the sample.

The microscopic features, in association with the immunohistochemical and molecular findings, were conclusive of a final histological diagnosis of polypoid intestinal perineuriomas without crypt serration. Currently the patient is well and is still undergoing follow-up at the INT Fondazione Pascale Hospital.

Discussion

In this report we describe a case of a 53-year-old male who underwent surgery for a colonic polyp, with a final diagnosis of intestinal perineurioma without crypt serration (NPS). The

peculiarity of this case is also represented by the very unusual large size of the lesion presenting as a polyp.

The benign polyps derived from perineurial cells, presented in the colon or rectum as sessile lesions, and were characterized by proliferation of bland spindle cells within the mucosa, leading to separation and architectural distortion of the crypts. The cells had fusiform nuclei, pale eosinophilic cytoplasm, and an immunoprofile characterized by a negative staining for S-100, a weak staining for epithelial membrane antigen (EMA) and strong diffuse expression of collagen IV, vimentin, CD56, claudin-1,

and glucose transporter 1 (GLUT1). CD34 was expressed in approximately 20% of cases. Also in our case, immunohistochemistry was done with particular effort to prove perineurial differentiation (EMA, claudin1, GLUT1 and collagen type IV), and this allowed us to make the correct diagnosis.

These lesions frequently display a serrated/hyperplastic architecture and for this reason they are also defined as perineuriomas with serrated crypts (SPs) to distinguish them from the much less frequent ones without crypt serration (NSPs). The latter are rare lesions and currently the mechanisms related to the lacking of serrate crypts and the relations with the SPs are poorly understood. The morphological differences could be due to the fact that serrated crypts were destroyed by the stromal component [4]. Moreover, whereas most SPs are characterized by the presence of several mutations known to be involved in serrated colorectal epithelial polyps, in particular BRAFV600E mutation in 63% and KRAS in 4% of cases, these molecular alterations have never been described in NSPs [5].

A recent comparative study analyzed clinical, histological, immunohistochemical, and molecular features of a large series of NSPs and SPs showing that the prevalent location of both

lesions was rectosigmoid colon and microscopically both displayed a subepithelial zone of uninvolved slightly inflamed lamina propria [4]. Moreover regarding immunophenotype, no differences were highlighted for IHC expression of claudin1, GLUT1, EMA, and collagen IV in both lesions. Molecular analysis confirmed the high prevalence of V600E mutation of the BRAF gene only in SPs. Nevertheless, an important clinical finding was that the median size for both these polypoid lesions was about 3 mm [4]. Only the even rarer submucosal tumors are of large size [6]. They are also usually located in the rectosigmoid area with a few cases in other segments of the colon [4, 6]. The interesting findings of our case are the unusual location and the size of the polypoid lesion, about 4 cm, which has never been reported in the literature.

It is now defined that whereas SPs represent a unique type of mixed epithelial-stromal polyps (hybrid hyperplastic polyp/mucosal perineurioma) with a well-defined and favorable clinical course, very little is known about the NSPs. These appeared as a distinct type of mucosal polyp unrelated to the serrated variant [5] and could represent a true neoplastic stromal tumor. Considering the large size of our lesion, it would be interesting to better molecularly characterize these lesions and our data suggest an appropriate patient follow-up is warranted to verify the true benign nature and indolence of these tumors.

Disclosure of conflict of interest

None.

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