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Review

The histomorphological and molecular landscape of colorectal adenomas and serrated lesions

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Summary
The 2019 WHO classification of digestive system tumors significantly reformed the classificatory definition of serrated lesions of the colorectal mucosa and added new essential diagnostic criteria for both conventional adenomas and hereditary gastrointestinal polyposis syndromes. Histopathological examination of colorectal adenocarcinoma precursors lesions represents an important segment of daily clinical practice in a pathology department and is essential for the implementation of current colorectal adenocarcinoma secondary prevention strategies. This overview will focus on a schematic histopathological and molecular classification of precursor lesions arising within colorectal mucosa.

Key words: colorectal adenomas, *KRAS*, *BRAF*, dysplasia, serrated lesions

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Introduction

Histopathological examination of colorectal adenocarcinoma precursors lesions represents an important segment of daily clinical practice in a pathology department and is essential for the implementation of current colorectal adenocarcinoma secondary prevention strategies.
The 2019 WHO classification of digestive system tumors significantly reformed the classificatory definition of serrated lesions of colorectal mucosa and added new essential diagnostic criteria for both conventional adenomas and hereditary gastrointestinal polyposis syndromes. This overview will focus on schematic histopathological and molecular classification of precursor's lesions arising within the colorectal mucosa.

Conventional adenomas

General definition

Conventional adenomas are benign, premalignant neoplastic lesions characterized by dysplastic epithelium. They can arise throughout the

colorectal mucosa, from the ileocaecal valve to the anorectal junction, and can have a pedunculated, sessile protuberant, slightly elevated/flat, or depressed appearance. Most lesions are clinically silent, but superficial erosion/ulceration is common and, thus, occult bleeding may occur [1].

The seminal work of Fearon and Vogelstein pinpointed an adenoma-carcinoma genetic model of colorectal carcinogenesis [2,3] in which the normal colon mucosa epithelium evolves into full-blow adenoma due to the alterations of a small number of driver genes, such as *APC*, *KRAS*, *SMAD4* and *TP53* [4,5].

Clinical picture

As mentioned above, most patients are asymptomatic and can for occult bleeding is fundamental for the diagnosis, especially in screening programs [1]. Lesions with large dimension can manifest with evident bleeding, abdominal pain and occlusion symptoms. Secretory diarrhoea with electrolyte imbalance (McKittrick - Weelock Syndrome) can occur occasionally in distant large polyps.

Histologic elementary lesions

Three subtypes of conventional adenomas can be differentiated on the basis of villi formation. Despite the poor intra-observer concordance in subtyping conventional adenomas, this approach is historically accepted and used clinically [6,7]. However, its prognostic role is not yet well defined.

Tubular adenomas

Tubular adenomas are the most common phenotype of conventional adenomas detected during population screening [8]. Tubular adenomas are polyps with largely conserved normal crypt architecture, with variable elongation of the crypts and an increase in the number of glands. The epithelium shows enlarged, hyperchromatic nuclei, with different degrees of nuclear atypia and stratification, with loss of nuclear polarity. There is a pseudo-stratification and a de-differentiation with decreased numbers of goblet cells. A small villous component (< 25%) is acceptable in tubular adenomas.

Tubulo-villous adenomas

In tubulo-villous adenomas, > 25% of the architecture is composed of structures resembling small intestinal villi, with cellular atypia similar to the tubular ones (Fig. 1A-B).

Villous adenomas

If > 75% of the adenoma has a villous architecture, it is diagnosed as villous adenoma.

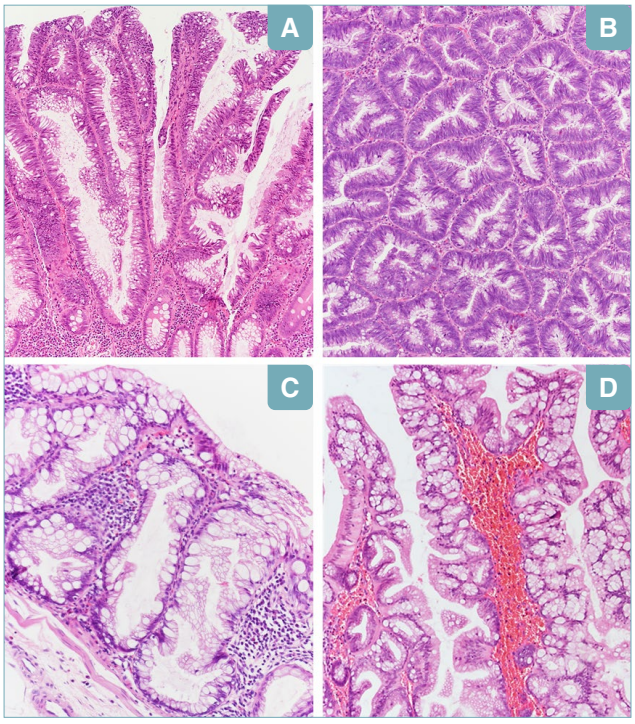

Figure 1. Histological aspects of polypoid lesions. Tubulo-villous adenoma with low-grade dysplasia, magnification 100x (A). Tubular adenoma showing a characteristic pseudoserrated pattern, magnification 100x (B). Sessile serrated lesion of the ascending colon, magnification 200x (C). Traditional serrated adenoma of the sigmoid colon, magnification 100x (D).

Rare morphological subtypes

Rare morphological variants of conventional adenomas have been described. The most common is the Paneth cell-rich subtype, in which Paneth cells can be identified in > 20% of adenomas, that is more common in proximal adenomas and in younger patients [9,10]. Squamous component (either as morules or as true squamous metaplasia) is present in < 0.1% of adenomas [11]. Clear cells are present in < 0.1% of adenomas [12].

Histological grading

Grading of conventional adenomas is defined using a two-tiered scoring system that subdivided the lesions into low-grade dysplasia (LGD) and high-grade dysplasia (HGD). HGD is characterized by marked complex glandular crowding and irregularity of glands, cribriform architecture, and intraluminal necrosis. These architectural features are accompanied by cytological atypia, including substantial loss of cellular polarity, markedly enlarged nuclei with prominent nucleoli and

dispersed chromatin, often with atypical and apical mitosis [13]. Typically, the interobserver concordance is low, although its prognostic value is fundamental for follow-up and treatment of conventional adenoma. In a polyp identified during screening, a small area with high-grade dysplasia within the lesion is enough to define the entire high-grade lesion. In other contexts, it is useful to report the presence of both dysplasia pictures.

Molecular background

Sequencing studies have traced the evolution of most conventional adenomas and sessile serrated polyps into carcinomas through one of two major pathways: the chromosomal instability pathway or the microsatellite instability pathway. In both pathways, approximately 25 genes that are commonly affected by somatic mutations become the major drivers of most cancers. These genes include *APC* and *TP53*, the most commonly mutated tumour-suppressor genes, and *KRAS*, *PI3KCA*, *BRAF*, and *NRAS*, the most commonly mutated oncogenes. Approximately 85% of colorectal cancers are thought to evolve from conventional adenomas through a median of approximately 60 mutations per tumor that go beyond the genes that are major drivers; this process is referred to as the adenoma-to-carcinoma sequence [14]. The earliest changes involve aberrations of the WNT signalling pathway, most frequently altering APC function, usually by mutations that truncate the APC protein that reduces degradation of beta-catenin allowing it to accumulate and dysregulate WNT signalling [15]. The resultant altered morphology becomes histologically detectable as dysplasia. The enlargement of the dysplastic lesions occurs through accumulation of further molecular abnormalities affecting a small number of key signalling pathways such as *KRAS*, *SMAD*4 and *PI3KCA*. A small subset of adenomas acquires defects in DNA mismatch repair genes, sporadically due to hypermethylation of the *MLH1* promoter, with a very small number of cases of inherited mutations in *MLH1* or *MSH2* (or rarely *MSH6*) in Lynch syndrome families, and these may evolve into detective mismatch repair adenocarcinomas.

Serrated lesions and polyps

General definition

Colorectal serrated lesions and polyps are characterized by a serrated (sawtooth or stellate) architecture of the epithelium and gland [16]. Serrated polyp is like an “umbrella term” that includes different histological and clinic entity as hyperplastic polyps (HPs), sessile serrated lesions (SSLs), and traditional serrated adenomas (TSAs). Nowadays, a significant level of confusion surrounding serrated polyps in terms of classification and risk assessment is still present. In part, this is due to confusing nomenclature, varied and changing pathology criteria, and uncertainties about prognosis. Although 25% of sporadic colorectal cancers (CRCs) arise through the serrated molecular pathway, many clinicians and pathologists still consider the serrated lesions as harmless hyperplastic polyps. New edition of the WHO classification system has been changed the definitions of these entities and has been increased our insight on distributions and clinical impact of them.

Clinical picture

Most serrated lesions are asymptomatic and therefore an incidental finding at endoscopy is frequent. Endoscopically they present as sessile polyps, with low risk of bleeding, so the faecal blood-based test is not an effective screening method [17].

HPs of the distal tract are usually small (< 5 mm) and sessile. Proximal HPs and SSLs are poorly defined, sessile to flat lesions covered with a mucus cap and a rime of debris. Instead, TSA are usually broad-based polyps with a surface texture with a coral pattern.

Histologic elementary lesions

The last WHO edition extensively revised the serrated lesions classification.

Hyperplastic polyps

HPs consist of serrated epithelium which can cover the upper two-thirds of the funnel-shaped, evenly spaced crypts with proliferative zones confined to the basis. As it can be considered a diagnosis of exclusion, and the characteristics of SSLs are mainly observed in the deeper parts of the crypts, the orientation of biopsies is essential for adequate diagnosis. Two variants of HPs are recognized: the microvesicular type (MVHP) and the goblet cell-rich hyperplastic polyps (GCHP). GCHPs have fine morphologic alterations, such as surface tufting and increased numbers of goblet cells. MVHP are easily recognized and characterized by microvesicular epithelial cells with abundant cytoplasm, with stellate lumina inside of the crypts. In the past a third subtype was described (the mucin-poor type), but it is no longer considered a separate histotype because these lesions are considered to be caused by regenerative changes in other HPs [16].

Sessile serrated lesion

Sessile serrated lesions (SSLs) have bland cytology with variable amount of goblet cells and cells with microve-

sicular mucin droplets as HP, and crypts with prominent serration. The characterizing feature of SSL is an overall distortion of the crypt profile, probably resulting from alterations of the proliferative zone. Crypt distortion can be present in different forms, such as horizontal growth of the crypts along the muscularis mucosa, dilated crypts (basal third of the crypt), and/or crypts that have serrations extending in the basis (Fig. 1C). According to the updated WHO criteria, the presence of a single unequivocally distorted crypt is considered diagnostic for SSL. Mucosal prolapse or herniation through the *muscularis mucosae* (also known as inverted crypts) and lipomatosis of the lamina propria are phenomena resulted strongly associated with SLL. The new WHO edition recommends use of the term sessile serrated lesion vs other terms, such as sessile serrated adenoma, sessile serrated polyp, or sessile serrated adenoma/polyp. The application of the "at least one crypt" criterion resulted in a 7% increase in the proportion of serrated polyps classified as SSLs [18]. An additional benefit of this new definition is improved inter-observer agreement compared with previous WHO edition [19]. Other crucial factors capable of improving inter-observer variability are the training of expert gastrointestinal pathologists and the orientation of biopsies.

Sessile serrated lesion with dysplasia

Only 4 to 8% of SLLs evolve versus the dysplastic phenotype. Multiple morpholgical pattern of dysplasia may develop, also in the same polyp. At least 3 different morphologic types of dysplasia have been described: intestinal and serrated pathway and the minimal deviation dysplasia. Stratification of dysplasia into low-grade vs high-grade is not recommended [16]. The intestinal one is similar to the dysplasia observed in conventional adenomas but is almost rare. It is characterized by maintaining the expression of MLH1, and there seems to be no progression to CRC in these lesions, especially when there is low-grade dysplasia [20]. Serrated dysplasia is more common and is characterized by eosinophilic cytoplasm and small crowded glands with pronounced nuclear atypia and mitotic activity. Loss of MLH1 staining is infrequent and it can be considered an intermediate step for the evolution in TSA [21]. Minimal deviation dysplasia, which, as the name implies, differs little from the LSS architecture, is typically characterised by the loss of MLH1. Immunohistochemical analysis for MLH1 is important for determining the presence of clinically important dysplasia in SSLs because the loss of MLH1 staining confirms the presence of dysplasia. However, it is a sufficient but not necessary condition and the normal staining pattern can be retained in some cases of manifest dysplasia.

Traditional serrated adenoma

TSA may have different clinical presentations: it may present in the distal colon as frankly polypoid lesions or as sessile, flat lesions in the proximal tract. TSAs are villous polyps with tall cells that contain prominent eosinophilic cytoplasm and pencillate nuclei [16]. Ectopic crypts, defined as epithelial islets developed orthogonally to the main crypt axis and not related to the *muscularis mucosa,* are another typical feature of this lesion, although it most distinguishes the larger and distally located TSAs (Fig. 1D). In more than 50% of cases, an adjacent precursor lesion (HPs or SSLs) could be present. Areas of dysplasia (intestinal or serrated type) could be found, but no specific surveillance guidelines currently exist for these lesions, although they may represent a worst progression of TSA. The recent WHO edition advised to report these cases separately, especially when the high-grade dysplasia is documented.

Unclassified serrated adenoma

The differential diagnosis between different serrated lesions is not always easy, especially as diagnostic criteria are still evolving. However, there may be histological pictures that show mixed characteristics between either serrated and conventional polyps. Included in this group are the recently described serrated tubulovillous adenomas [22,23]. At a genetic level, polyps may switch phenotype as they accumulate genetic changes, evolving from a serrated pathway to a more conventional one, which could be the basis for a spectrum theory starting out with a TSA with serration evolving into a TSA with conventional dysplasia and, eventually, to a well-developed conventional adenoma. Nevertheless, other studies will be necessary to provide further connections in our present understanding. Another recently described type of colorectal polyps showing mixed morphological features of both conventional adenomas and serrated lesions is the so called superficially serrated adenoma. This polyp shows intermixed histological features with straight adenomatous gland. Unlike low-grade tubular adenomas, however, proliferative cells localize to the middle and lower layers of the mucosa while the superficial epithelium exhibits serration. The lesions exhibit nuclear accumulation of β-catenin and MYC overexpression, suggestive of WNT pathway activation [24].

Molecular background

The serrated pathway is characterized by a continuum of genetic and epigenetic alterations that attend polyp progression, followed by histologic features. The first step of the pathway is the acquisition of a mutation in a gene such as *KRAS* or in most cases *BRAF*. Acti-

vating mutations in *BRAF* result in widespread methylation of CpG islands, representing the a CpG island methylator phenotype (CIMP). CIMP results in silencing of many genes, including some tumor suppressor genes such as CDKN2A (which encodes P16) that occurs more frequently in TSAs than SSLs, in particular in the advanced lesions with *BRAF* mutations [21]. Hypermethylation of MLH1 promoter occurs specifically in SSLs and approximately 75% of SSL with dysplasia have microsatellite instability (MSI), resulting from this specific hypermethylation. Thus, immunostaining for MLH1 protein can identify dysplasia [25]. Progression of serrated polyps is associated with activation of the WNT signaling pathway. TSA shows differences from SSL, including more frequent mutations in the *RNF43-ZNRF3* complex [26,27] and fusions of genes in the R-spondin family (*RSPO* fusions) resulting in down-regulation of *RNF43* [28]. Colorectal carcinomas (CRCs) originating from serrated lesions typically are grouped in three different patterns according to the molecular hallmarks: *BRAF*-mutated CRCs with high CIMP and MSI, mainly located in right colon and characterized by specific histological features as medullary, mucinous and signet ring. They typically show a favorable prognosis. The second group of CRCs have *BRAF* mutation, high CIMP but they are MSS. The third group is characterized by *KRAS* mutations and MSS, although *KRAS* mutations are infrequent in serrated lesions.

Post-polypectomy endoscopic surveillance

The new European CRC screening Guidelines (ESGE) updated the necessity of endoscopic follow-up in patients with one or more polyps that were completely removed, on the basis of endoscopic and histological risk factors [29]. They recommend that patients with complete removal of 1 - 4 < 10 mm in size adenomas with low grade dysplasia, irrespective of villous components, or any serrated polyp < 10 mm without dysplasia, do not require endoscopic surveillance and should be returned to screening. If a scheduled screening program is not available, repetition of colonoscopy 10 years after the index procedure is recommended. Colonoscopy after 3 years is suggested for patients with complete removal of at least 1 adenoma ≥ 10 mm or with high grade dysplasia, or ≥ 5 adenomas, or any serrated polyp ≥ 10mm or with dysplasia. A 3 - 6-month early repeat colonoscopy is recommended following piecemeal endoscopic resection of polyps ≥ 20 mm.

Inflammatory bowel disease-associated dysplasia of the colorectum

General definition

Dysplasia arising in inflammatory bowel disease (IBD) is an unequivocal neoplastic alteration of the colorectal epithelium that remains confined within the basement membrane in which it originated [16]. Cancer risk in ulcerative colitis (UC) and Crohn disease is almost equivalent for patients with similar lengths of colon involved [30]. In population-based cohorts, UC increases the risk of CRC 2.4-fold. Male sex, young age at diagnosis, coexisting primary sclerosing cholangitis (PSC) and extensive colitis are adverse factors for developing CRC [31].

Clinical picture

No clinical sign or symptoms characterized the dysplasia in IBD; polypoid lesions may cause bleeding, but it is not an early symptom. Endoscopically, dysplasia is classified according to the SCENIC classification based on their appearance (visible or non-visible) [32]. Visible lesions are subdivided in polypoid (pedunculated or sessile) or non-polypoid (superficial, flat or depressed). Other essential parameters to report are the presence of ulceration and the features of the borders. Typically, dysplastic lesions may occur in different tracts of the colon simultaneously.

Histologic elementary lesions

Historically, dysplasia was histologically classified using the Vienna [33] or the Riddell [34] system. The latter is the most world-wise used and subdivided the lesions in indefinite, low-grade or high-grade dysplasia combining cytological and architectural atypia. The most common morphological phenotypes of IBD- related dysplasia are the intestinal (or conventional) and serrated types. In low-grade dysplasia the crypts are tubular and/or villous or serrated, only with mild crowding. Dysplastic cells usually involve both the crypt and the surface epithelium, but early cases and the indefinite for dysplasia type show only involvement of the crypts, taking the name of “crypt” or “pit” dysplasia. In high-grade dysplasia, the epithelium manifests marked cytonuclear atypia with loss of cell polarity and mitotic figures, while the architecture becomes more cribriform and packaged. There are less common types of dysplasia such as the: i) mucinous subtype; ii) the goblet cell deficient and the iii) terminal epithelial differentiation (also known as crypt cell dysplasia). Among these, the mucinous dysplasia was the most investigated shows tubulovillous/villous architecture with tall mucinous cells representing > 50% of the lesion. It typically shows low-grade dysplastic features

affecting the crypts with mild nuclear enlargement and hyperchromasia.

Molecular background

The inflammatory microenvironment is the major trigger in the IBD- associated neoplastic process. Tumorigenic transcriptional factors as NF-kB, the productions of cytokines as IL-1β, IL-6 and TNF-α and the actions of proteinases damage the cells, initiating neoplastic transformation. The frequent multifocality of the lesions reflects this diffuse pre-neoplastic field in which many factors cooperate in the development of dysplasia. The progression of oncogenic mutations that establish the inflammation-dysplasia-carcinoma cascade in IBD differs from the classic paradigm of the sporadic adenoma-carcinoma sequence. Mutations of *TP53* occur in 60-90% of IBD-associated CRCs and usually it is the first gene involved in process. Other genes involved are the *MYC* amplifications and *MLH1* and *RNF43* mutations. Almost 25% of IBD-related CRCs show high tumor mutation burden, correlated with MSI and occasionally with defects in *POLE* [35,36].

Genetic adenomatous syndromes of the colorectal tract

General definition

The study of familial cancer syndromes has identified key genes which are crucial not only for their role in genetic susceptibility to cancer, but also for the awareness they provide into the molecular pathogenesis and classification also in many sporadic cancers [16].

Lynch syndrome

Lynch syndrome (LS) is an autosomal dominant disease resulting from constitutional pathogenic mutations affecting the DNA mismatch repair genes most in *MLH1*, *MSH2*, *MSH6*, and *PMS2*.

LS is characterized by predisposition to a wide variety of cancers as tumors of the colorectum, endometrium, stomach, small bowel, ovary, gallbladder, hepatobiliary tract, pancreas, urinary tract kidney, brain, and prostate [37,38]. Sex, age, the involved gene, and history of cancer are the main factors that affect risk of LS patients.

In the Muir-Torre syndrome variant, the previously described internal cancers occur together with sebaceous skin tumor [39] Constitutional mismatch repair deficiency syndrome (CMMRD) is a recessive disease, characterized by biallelic mismatch repair gene mutations. The affected individuals develop multiple adenomas in the colorectal tract at a very young age and they are prone to develop CRC, brain tumors, leukemia, lymphoma, neurofibromatosis type 1, and a wide range of other alteration [40].

Because patients with LS do not develop large numbers of colorectal adenomas, initially the syndrome was called as “hereditary non-polyposis CRC”. Nowadays, this term is avoided and in the face of sometimes vague clinical criteria, diagnostics must be based on the germinal identification of the mismatch repair genes alterations.

CRC with MSI has typical histological features as the presence of tumor-infiltrating lymphocytes, Crohn-like peritumoral lymphocytic reaction, high histological grading, mucinous and signet-ring histotype and a medullary growth pattern [41]. Immunohistochemistry for the mismatch repair proteins (MLH1, PMS2, MSH2, and MSH6) is a common first step in the screening protocol CRCs for mismatch repair deficiency [42].

Familial adenomatous polyposis 1

Familial adenomatous polyposis (FAP) 1 is an autosomal dominant syndrome caused by pathogenic APC mutations. The disease is typically characterized by > 100 adenomatous polyps in the colorectum, other extracolonic alterations (including polyps) elsewhere in the gastrointestinal tract, and desmoid tumors [16].

The onset of colorectal adenomatous polyps usually occurs in the second decade of lite and patients have almost 100% risk of developing CRC by the age of 45 years. For this reason, total colectomy is recommended by that age. The prevalence is 1 in 8000-10,000 and accounts for < 1% of all CRCs [43].

The large bowel polyps are almost always conventional adenomas of different subtype (tubular, tubulovillous, or villous), grade (low or high), and size; with not important differences with sporadic adenomas. However, characteristic of FAP is the frequent presence of microadenomas identified as monocryptal or oligocryptal adenomas.

The fundamental molecular criterion is the presence of a pathogenic germline *APC* mutation -and this is the gold standard for FAP diagnosis, although a small number of cases have undetectable *APC* mutations and may be considered as presumed FAP if typical clinical features are present and molecular evidence of the other conditions is absent [16].

Other adenomatous polyposes

Other adenomatous polyposes are a heterogeneous group of generally, but not exclusively, inherited conditions characterized by multiple colorectal adenomatous polyps in which LS and FAP were excluded [16] as described recently by AIFEG consensus statement (exept for MUTYH associated) [44].

MUTYH-associated polyposis

MUTYH-associated polyposis (MAP) [45] is a constitutional DNA repair disorder caused by recessively inherited mutations in *MUTYH*, involved in base excision repair system. The prevalence is approximately 1 in 2000. Individuals with MAP develop multiple adenomatous polyps of colorectum during adulthood, usually in number of 10-100, but hundreds of lesions can develop [46]. Duodenal polyposis is observed in about 20% of cases, with a concomitant increased risk of duodenal adenocarcinoma.

NTHL 1-associated polyposis

NTHL 1-associated polyposis (NAP) [47] is a constitutional DNA repair disorder of base excision repair caused by recessively inherited mutations in *NTHL1*. NAP is thought to be rarer than MAP, although the exact prevalence is unknown.

Polymerase proofreading-associated polyposis

Polymerase proofreading-associaled polyposis (PPAP) is caused by dominantly inherited mutations in the exonuclease domains of *POLD1* and *POLE* [48]. These proofreading mutations cause a deficit in the correction of mispaired bases during DNA replication. This mistake leads to a hypermutant phenotype with exceedingly numerous point mutations. Colorectal adenomatous polyps occur during adulthood, generally by the age of 50 years. Adenomas and CRC are similar to sporadic tumors but they have a characteristic hypermutant somatic mutation genotype, rich in neoantigens that now appear to be good targets for PD1/PDL1 immune checkpoint inhibitor immunotherapy.

Hereditary mixed polyposis syndrome

Hereditary mixed polyposis syndrome is caused by a duplication that leads to increased and ectopic expression of the BMP antagonist GREM1. Patients develop a variety of colorectal polyps, including conventional adenomas, HPs, inflammatory polyps, prolapse-type polyps, and lymphoid aggregates, with a high risk of developing CRC.

Other less frequent syndromes as MSH3-associated polyposis, AXIN2-associated polyposis and immune deficiency-associated polyposis may cause hereditary adenomatous colorectal lesions.

Serrated polyposis syndrome

Serrated polyposis syndrome (SPS) is a recently described condition of largely unknown etiology, characterized by multiple serrated polyps in colorectum and it is frequently associated with an increased risk of CRC.

Most patients are diagnosed at 50-60 years of age, but the age range is wide. Updated WHO criteria for SPS include: at least 5 serrated lesions or polyps proximal to the rectum, all ≥ 5 mm, with 2 or more that are ≥ 10 mm, or more than 20 serrated lesions or polyps of any size distributed throughout the large bowel, with at least 5 proximal to the rectum.3 It is important to note that any serrated polyp subtype (HP, SSL, TSA, or serrated adenoma not classified) is included in the final polyp count, and that polyp count is cumulative over multiple colonoscopies.

A small proportion of patients with SPS have mutations in *RNF43*, which regulates the WNT pathway. However, most cases of SPS are not associated with any specific genetic variants [49].

Special dysplastic lesions of the appendix

Neoplastic lesions of the appendix, especially those with a mucinous phenotype, show peculiar clinical and histological characteristics that deserve a separate treatment.

Epidemiology of these lesions is not well established, mainly because of the lack of standardized classifications for appendiceal neoplasms.

In 2012 the Peritoneal Surface Oncology Group International (PSOGI) adopted a consensus on diagnostic terminology comprehending serrate polyp (with or without dysplasia), LAMN (low grade appendiceal mucinous neoplasm), HAMN (high grade appendiceal mucinous neoplasm), mucinous adenocarcinoma, mucinous adenocarcinoma with signet ring cells, mucinous signet ring cell carcinoma [50,51].

These lesions may present similarly, with acute appendicitis, evident cystic dilatation of appendix, evidence of abdominal or pelvic mass and, eventually, pseudomyxoma peritonei [16].

HPs and TSAs show the same histological features commons common to the lesions that develop in other parts of the large bowel, as previously described.

Low grade Appendiceal Mucinous Neoplasm (LAMN) is defined as a mucinous neoplasm with low grade cytologic dysplasia and: i) loss of the *lamina propria* and *muscularis mucosae*, ii) fibrosis of the submucosa, iii) "pushing" pattern of growth into the wall (expansile or diverticulum-like), iv) dissection of acellular mucin into the wall or v) mucin and/or neoplastic mucinous epithelial cells outside the wall of the appendix.

High grade Appendiceal Mucinous Neoplasm (HAMN) is a histological entity expected by PSOGI and is described as a mucinous neoplasm with the presence of high-grade cytological atypia and without infiltrative invasion. Nevertheless, primary appendiceal mucinous

neoplasms rarely show at the same time the presence of cytological atypia and the absence of metastatic disease presentation. In such cases comprehensive histologic evaluation of the appendix is recommended in order to exclude an association with invasive adenocarcinoma.
From a molecular point of view, mucinous appendiceal neoplasia show high prevalence of *KRAS* mutations. Mutations in *GNAS* and *RNF43* genes have been reported in some cases, even in association with those of *RAS*.

Advanced adenomas

This new term was included in the last WHO edition [16] and refers to all adenomas ≥ or = 10 mm in size, with tubulovillous or villous architecture, and/or high-grade dysplasia or intramucosal adenocarcinoma.
The endoscopic resection of these lesions represents the main activity of the screening program to prevent the CRC onset.
Crucial is the differentiation between pseudoinvasion and invasive cancer (or early pT1 CRC). Pseudoinvasion is a prolapse of the neoplastic epithelium into the polyp head or deeper, accompanied with traumatic phenomena as hemorrhage, hemosiderin deposit and extracellular mucin. This differential diagnosis requires an expert panel of gastrointestinal pathologists to ensure a correct interpretation of the morphological picture.
The recommended management of adenomas with high-grade dysplasia should be endoscopic resection alone, because these lesions have no risk of residual neoplasia in the bowel wall or lymph nodes after complete endoscopic resection.

Malignant polyp

General definition

The term “malignant polyp” refers to a cancerized colorectal lesion invading the submucosa. These lesions are classified as pT1 in the TNM classification system [52]. According to the Vienna classification system, a consensus between Western and Japanese pathologists for classifying gastrointestinal epithelial neoplasia, the malignant polyp falls under category 5.2 (submucosal carcinoma and beyond) [33]. The prevalence of cancer in colorectal polyps ranges from 0.2% to 5% [53]. The most important clinical goal is to understand if an endoscopically resected colorectal lesion with submucosal invasion requires surgical resection of the colorectal segment from which the lesion was removed [54]. This selection is important to minimize both the risk of residual cancer and the risk of surgery.

Clinical picture

Endoscopic assessment of colorectal polyps and lesions to predict the histologic class (i.e., adenoma vs serrated histotype) and determine the presence of features associated with submucosal invasion are important skills for the colonoscopist.
The main endoscopic classifications based on the surface pattern of the lesions are: i) Narrow Band Imaging (NBI) International Colorectal Endoscopic Classification (NICE), that classifies polyps as type 1 (serrated class), type 2 (conventional adenoma) and type 3, which includes lesions with disruption of the surface pattern and vessel structure, specific (although not sensitive) for submucosal invasive cancer [55]; ii) Japanese Narrow Band Imaging Expert Team Classification (JNET), a new NBI colorectal magnification classification in 2014, that maintains NICE types 1 and 3 but divides type 2 into JNET 2a and 2b, with 2b features associated with high-grade dysplasia and superficial submucosal invasion [56]; iii) Kudo Pit Pattern Classification, that evaluates colorectal polyps through characterization of the pits, which are openings for crypts, using a six-tier system. Type I and II are characteristic of normal, serrated or inflammatory polyps, whereas pit pattern classes III-V are considered to indicate dysplastic and malignant changes [57].
The most important endoscopic classification systems based on morphological features is the Paris classification which describes 3 major superficial morphologies with subtypes. Lesions are classified as polyps (type 0 I), which include both pedunculated (0-Ip) and sessile (0-Is) morphologies; or flat lesions (type 0 II), which consist of slightly elevated (0-IIa), flat (0-IIb), and slightly depressed (0-IIc) morphologies. Lesions with the third major morphology, excavated (0-III), are rarely seen in the colon [58].

Histologic elementary lesions

The traditional histological criteria applied in ranking the risk of synchronous nodal metastasis are variably applied and the establishment of reliable criteria for the identification of patients needing surgery is crucial. In addition to resection margin, vascular invasion, and tumor differentiation, several other histologic features have been proposed. The most promising are tumor budding (part of the tumour microenvironment and involved in epithelial-mesenchymal transition) and those measuring tumor microscopic extension (i.e. depth, width, and area of the submucosal invasion) (Fig. 2A). Number and type of tumor infiltrating

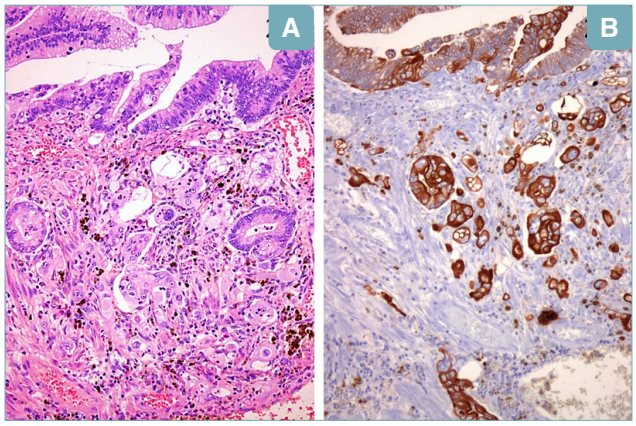

Figure 2. pT1 Adenocarcinoma. Invasive pT1 adenocarcinoma with micropapillary features originating from a tubulo-villous adenoma, magnification 200x (A). Immunohistochemical staining with anti-pancytokeratins antibody highlights a high degree of tumor budding, magnification 200x (B).

lymphocytes (TILs) in CRC have been reported to influence tumor behavior and patients' prognosis but also nodal metastasis risk in pT1 [59].

Depth of cancer invasion

Accurate measurement of the depth of invasion in malignant polyps requires specific handling of the specimen which enables the cut sections to be properly oriented for evaluation by the pathologist. For sessile malignant polyps, the Kikuchi classification describes the depth of invasion by dividing the submucosa into three levels (SM1-3). SM1, 2, and 3 denote invasion of cancer into the first one-third, second one-third, and the deepest one-third of the submucosa, respectively [60]. In non-polypoid lesions, the submucosa is almost never represented in its entirety in the resected specimens, the Kikuchi system has been largely replaced by measuring the depth of submucosal invasion with an optical micrometer. An invasion depth of < 1 mm is associated with a very low risk of lymph node metastasis (0-4%), provided that other adverse histologic features are absent. An invasion depth of ≥ 1 mm is associated with a substantial risk of residual disease in the bowel wall or lymph nodes metastasis (10-18%) and is generally an indication for adjuvant surgical resection [61].

Depth of invasion in malignant pedunculated polyps is usually classified using the Haggitt system in 4 levels [62], based on the invasive portion in the head, neck, and stalk of the pedunculated poly. In level 0, dysplastic elements are limited to the mucosa. Level 1 includes cancer invasion into the submucosa, but is limited to the head of the pedunculated polyp. Level 2 denotes cancer cells reaching the neck of the pedunculated polyp and, in level 3, cancer cells invade the stalk. Level 4 indicates cancer cells invading the submucosa below the stalk, but not the muscularis propria, and it is associated with high risk of lymph nodes metastasis [54]. All malignant nonpedunculated lesions that by definition have submucosal invasion are classified as Haggitt level 4. Because endoscopists transect pedunculated polyps through the stalk, it limits the clinical relevance of the Haggitt classification in assessment of malignant polyps resected endoscopically.

Width of infiltration

The objective approach introduced by Ueno et al. [63] in which depth and width beyond the muscularis mucosae are measured represents the most useful system to report histologically the dimension of malignant polyp. if, as previously mentioned, the depth of invasion is fundamental to predict the presence of lymph node metastases, studies on the extent of the carcinoma component are not univocal [64,65]. However, the main diagnostic protocols recognized worldwide its prognostic value.

Polypectomy resection margin

The width of any margin between the cancer and the resection margin at the polypectomy site is an important histologic risk factor for the presence of lymph node metastasis and recurrence for both pedunculated and nonpedunculated malignant polyps [66]. European guidelines define positive polypectomy margins of malignant polyps when malignant cells are detected < 1 mm of the margin [67].

Grade of tumor differentiation

It is well established that the risk of lymph-node metastasis is higher with high grade tumors vs low-grade ones.

Lymphovascular invasion

Lymphovascular invasion, defined as presence of tumor cells within endothelial-lined channels, in the endoscopic resection specimen is an independent risk factor for lymph node metastasis, although the definition used by pathologists varies and the inter-observer variability is high [68].

Tumor Budding

Tumour budding (TB), defined as a single cell or cluster up to four cells at the invasive front of colorectal cancer (CRC) [63], is proposed as an additional prog-

Table I. Histological report of pT1 colorectal carcinoma. Adenocarcinoma of the large intestine (low/high grade according to WHO 2019) infiltrating the submucosa, arising in tubular/tubulovillous/villous adenoma with low/high grade dysplasia of the glands/serrated lesion.

Histological features of the neoplasia		
Grading	@	Low-grade/High grade sec. WHO 2019
Lymphovascular invasion	@	Present/Absent
Budding	@	Present/Absent (Bd1; Bd2; Bd3 sec. ITBCC 2016)
	@	Count of buds
Adjacent adenomatous component	@	Present (conventional/serrated)/Absent
Haggitt Classification	@	0; 1;2; 3; 4
Kikuchi Classification	@	sm1; sm2; sm3
Depth of infiltration	@	Millimeter
Width of infiltration	@	Millimeter
Distance from the deep border of excision	@	Millimeter
Distance from the lateral border of excision	@	Millimeter

nostic factor in the 8th edition of the TNM classification published by the UICC [52]. The association of TB with tumor progression and with presence of local and distant metastases is supported by the biological features and pathogenetic aspects of tumor buds. Indeed, tumor buds are part of the tumor microenvironment and involved in epithelial-mesenchymal transition-type changes (Fig. 2B) [69]. Tumour buds are typically characterized by upregulation of biomarkers of migration, invasion and survival. In contrast, WNT signalling pathway is typically deregulated resulting in E-Cadherin under-expression [70]. Recently, recommendations of an International Tumor Budding Consensus Conference (ITBCC) established guidelines to evaluate TB in CRC, especially in the pT1 scenario but also in other CRC stages. In the histological report TB should be report as present/ absent, and in terms of number of buds for 0,785 mm2 field, and budding category (Bd 1 = 0-4 buds; Bd 2 = 5-9 buds; Bd 3 = 10 or more buds) [71,72]. The use of a standardized method helped in finding a strong support relationship between TB and lymph node metastases in pT1 CRC.
Despite improvements in stratification and novel guidelines, an intrinsic variability in pT1 CRC histological analyses still exists ascribed to the lack of standardization and inter-observer agreement in reporting the main risk factors. We propose a histological report to optimize diagnosis (Tab. I). Gastrointestinal pathology is known as a critical field with diagnostic discordances. Thus, a second opinion, especially from an expert gastrointestinal pathologists' panel has been proposed to minimize possible misdiagnosis [73].

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