Serrated polyps of the colorectum: histological classification and clinical significance

Janina Orłowska

Histopathology Laboratory of the Department of Gastroenterology and Hepatology, Medical Centre for Postgraduate Education, Oncology Centre, Warsaw

Serrated polyps of the colorectum are heterogeneous lesions, a subset of which is now regarded as the precursor of colorectal cancer with DNA microsatellite instability. The serrated pathway encompassing hyperplastic aberrant crypt foci, hyperplastic polyps, sessile serrated polyps (adenomas), mixed polyps, and traditional serrated adenomas, with a meticulous review of their up-to-date histological classifications, is presented. Some remarks concerning genetics of serrated polyps and the mechanism leading to carcinoma development are also included.

Key words: serrated polyps, hyperplastic polyp, sessile serrated polyp, serrated adenoma.

Colorectal cancer

Colorectal cancer (CRC) is recently the most frequent cancer in both genders in Europe [1]. It is also the second leading cause of cancer-related deaths in the United States [2]. Increased effort needs to be focused on secondary prevention of colorectal cancer, mainly by early detection and removal of pre-malignant and malignant lesions. Colonoscopy is the most valuable tool as a screening method allowing simultaneous removal of the majority of the lesions [3].

The development of about 80% of sporadic CRCs follows a sequence of histological steps from normal epithelium to adenoma, with subsequently increasing steps of dysplasia and eventually giving rise to invasive carcinoma, as was first described by Muto *et al*. in 1975 [4] and defined as the "**adenoma-carcinoma sequence**". Intensive studies addressing the genetic alterations confirmed this theory and proved them to be the most frequent molecular multi-step model pathway for CRCs which are characterized by chromosomal instability and mutation of the adenomatous polyposis coli (APC) tumour suppressor gene on chromosome 5q21 [5].

The main hallmark of conventional **adenoma** is the presence of **intraepithelial neoplasia (IEN)** [6], previously defined as **dysplasia** [7]. Intraepithelial neoplasia/dysplasia is classified as low-grade (LGD) or high-grade (HGD) according to Riddell *et al*. [7]. Independently of their architectural features (tubular, tubulo-villous, villous), conventional **adenomas** are characterized by closely spaced, round or oval glandular lumens with tubules or smooth villous contours covered by dysplastic epithelium composed of incompletely differentiated columnar cells. Cellular crowding with nuclear hyperchromatism and stratification of variable degree can be seen. Decreased mucous content of the cells, simultaneous with nuclear to cytoplasmic ratio alterations, is reflected in dark blue appearance of epithelium.

In 1983 a hypothesis on the relationship between hyperplastic polyps (HPs) and CRC was proposed by Jass [8], who continually developed a concept of serrated neoplasia pathway for microsatellite unstable CRC [9, 10], giving rise to the theory of **hyperplastic polyp-carcinoma sequence or serrated polyp-carcinoma sequence**. Approximately 15% of sporadic, or nonsyndromic CRCs, are proved to develop by this way. There is now strong evidence that HP might serve as the precursor of CRC with DNA methylation and deficient DNA mismatch repair. This novel pathway applies particularly to the subset of HP that occurs in the proximal colon [11].

Aberrant crypt focus

Aberrant crypt focus (ACF) is postulated to be the earliest preneoplastic lesion in the CRC pathogenesis. Formerly seen only by experimentalists, it has started to be recognized by pathologists in human material mostly since the colonoscopic screening programmes for CRC were introduced. Aberrant crypt focus is endoscopically defined by its gross features of slight bulging over the surface of surrounding mucosa. They vary from single altered glands to plaques of > 200 abnormal crypts [12]. Aberrant crypts are two to three times larger in diameter than normal and are slightly elevated above the mucosal surface. Their histology ranges from almost normal but elongated crypts, formerly described as transitional colonic mucosa, up to the hyperplastic and dysplastic (micro-adenomas) types mentioned in the **WHO** classification [13]. A mixed form of ACF composed both of hyperplastic and dysplastic crypts was also described [14]. Aberrant crypt focuses were found in 2.8% and 10.2% of colorectal surgical specimens, with diverticulosis and cancer, respectively (Fig. 1. A-D) [14].

Fairy tale of serrated polyps classification: what a mess!

Once upon a time, life used to be simple, when only two different colorectal epithelial polyp categories were considered, representing divergent patterns of epithelial growth and differentiation:

- hyperplastic polyps, characterized by a serrated gland pattern, considered to be an innocuous non-neoplastic lesions unrelated to the future development of carcinoma, contrary to
- adenomas, composed of round or oval glands covered by dysplastic epithelium, and acknowledged as neoplastic and an immediate precursor to colorectal cancer.

The historical background for epithelial polyps' developing nomenclature is presented in Table I.

Their nomenclature and histological classification started to be more difficult in 1981, when the concept of a **dangerous hyperplastic-like polyp** was introduced [15]. It was confirmed 15 years later, in 1996 [16] by Torlakovic and Snover, who first used the term **serrated polyps**, defining a group of "polyps with a saw-tooth crypt configuration originally diagnosed as hyperplastic polyps". After detailed histopathological analysis of all polyps previously diagnosed as hyperplastic removed from patients with **hyperplastic polyposis**, the authors suggested that these polyps were, in fact, **serrated adenomas**, and proposed to rename "hyperplastic polyposis" as "**serrated adenomatous polyposis**". However, some slides presented in the figures of this report are not only histologically identical to, but also labelled with the currently used term **sessile serrated polyp**. In a subsequent study of 289 **serrated polyps**, a distinct group of **serrated polyps with abnormal proliferation**, being difficult to distinguish from hyperplastic polyps, was identified [17].

Designations such as **traditional serrated adenoma** (TSA) or **serrated adenoma** (SA) were first used and described in 1990, as synonymous with **mixed hyperplastic adenomatous polyp** (MHAP) by Longacre and Fenoglio-Preiser [18].

It was thought that the third edition of the WHO classification of colorectal tumours, published in 2000 [13], would give the resolution to this long lasting discussion. Into the formerly known group of conventional adenomas (tubular, tubulo-villous and villous), a new entity was added, called **serrated adenoma**. This morphologically unique variant was included with adenomas in order to emphasize its neoplastic, dysplastic nature. According to this classification, **serrated adenomas** "are characterized by the saw-tooth configuration of a hyperplastic polyp on low power microscopy, but the epithelium lining the upper portion of the crypts and luminal surface is dysplastic. By contrast, **mixed hyperplastic polyp/adenoma** contains separate identifiable areas of each histopathological type" [13]. Unfortunately, both these subtypes were only described in the text but not mentioned as separate entities.

Alternative terms for **serrated adenoma** were proposed in the literature a little later, and included: **sessile serrated adenoma** (SSA), **sessile serrated polyp** (SSP) [19], and **serrated polyp with abnormal proliferation** (SPAP) [20].

Since then, it has become increasingly apparent that **serrated polyps** constitute a heterogeneous group of lesions. They encompass the majority of classical **hyperplastic polyps**, and a minority of more advanced or variant lesions such as sessile serrated polyps, traditional serrated adenomas, and mixed polyps [21]. The latter minority of **more advanced lesions** accounts for about 5% of the total number of polyps removed colonoscopically [22] and is associated with increased malignant potential.

Still being universally applied, the WHO classification published in 2000 raises continual problems with serrated polyps terminology deriving from misunderstanding and erroneously treating the majority of them as **serrated adenomas**, which, like all **adenomas**, ought to be dysplastic by definition [13].

Fortunately, great progress has been made during the last decade in understanding the nature of **serrated polyps**, and progression from one entity to another. Thanks to this, as in most fairy tales, there is going to be a happy ending.

Table I. Historical background to serrated polyps nomenclature and nature

Year	Author	Nomenclature and nature
1934	Westhues [66]	**Hyperplastic polyp**, essentially non-neoplastic nature
1962	Morson [67]	**Metaplastic polyp**, lack of any relationship to either adenoma or carcinoma
1981	Sumner [15]	Single polyp **hybrid between a hyperplastic and an adenomatous polyp** in the setting of hyperplastic polyposis The concept of a **dangerous hyperplastic-like polyp**
1984	Urbanski [68]	**Mixed hyperplastic adenomatous polyps**: an under-diagnosed entity
1990	Longacre and Fenoglio-Preiser [18]	Designations: **traditional serrated adenoma or serrated adenoma** first used as synonymous with **mixed hyperplastic adenomatous polyp** (MHAP)
1996	Torlacovic and Snover [16]	Introduced the term **serrated polyps**, defining a group of "polyps originally diagnosed as hyperplastic polyps, reappraisal of "**hyperplastic polyposis**" as "**serrated adenomatous polyposis**, some slides presented in the figures labelled as currently used term **sessile serrated polyp**
1996	Rubio and Jaramillo [69]	**Flat serrated adenoma** with low- and high-grade dysplasia
2000	WHO [13]	A new entity called serrated adenoma was added to classification, **Mixed hyperplastic polyp/adenoma** described in the text but not mentioned as separate entity
2003	Torlacovic *et al*. [17]	A distinct group of **serrated polyps with abnormal proliferation** was identified
2003	Jass [19]	Alternative terms for **serrated adenoma** have been proposed, such as: sessile serrated adenoma, sessile serrated polyp
2004	O'Brien *et al*. [20]	Serrated polyp with abnormal proliferation (SPAP)
2006	Goldstein [70]	Eight cases of small colonic **CRC** and/or **HGD** in **SSA**, with some slides presented in the figures characteristic for currently used term **sessile serrated polyp**
2008	Farris *et al*. [21]	**Serrated polyps** constitute a heterogeneous group encompassing the majority of classical **hyperplastic polyps**, and a minority of **more advanced or variant lesions** such as sessile serrated polyps, traditional serrated adenomas, and mixed polyps

Serrated polyps up-to-date histological classification

In 2009, two histological classifications of serrated polyps were published, clarifying most doubts. They are quoted and presented together in Table II [23, 24]. Only slight modification concerning the sequence of the lesions was introduced, to facilitate their comparison. The classification by Odze and Hornick [24] achieves essential order by dividing all serrated polyps into separate groups, according to whether dysplasia is present or not. It gives an important clue to understanding the meaning of terms. A summary of morphological features of serrated polyps in comparison with conventional adenomas is included in Table III.

I. NONDYSPLASTIC SERRATED POLYPS

They comprise two subgroups depending on whether architecture and proliferation are normal (A) or not (B). Those with normal features, i.e. hyperplastic polyps (A), were further divided into three kinds depending on the amount of mucus in epithelial cells, with similar terminology used in both classifications (Table II).

A. Normal architecture, normal proliferation

Hyperplastic polyp

Hyperplastic polyps (HPs), traditionally considered to be non-neoplastic lesions, have a prevalence of 10-12.5% in asymptomatic patients in large cohort studies [25, 26]. They comprise 80–90% of all serrated polyps and they may be found throughout the colon of adults but are especially common in the rectosigmoid area, where they are still considered to be innocuous lesions [22]. The prevalence rate increases with age. Endoscopically, most HPs are small, < 5 mm in diameter, sessile or slightly raised mucosal excrescences. Microscopically, HPs are characterized by elongated crypts lined by proliferative columnar absorptive epithelium with infolded epithelial tufts on the luminal surface, imparting a saw-tooth outline (Fig. 1 E-H, 6 B). It is a consequence of simultaneous increase of proliferation, as well as inhibition of programmed cellular apoptosis.

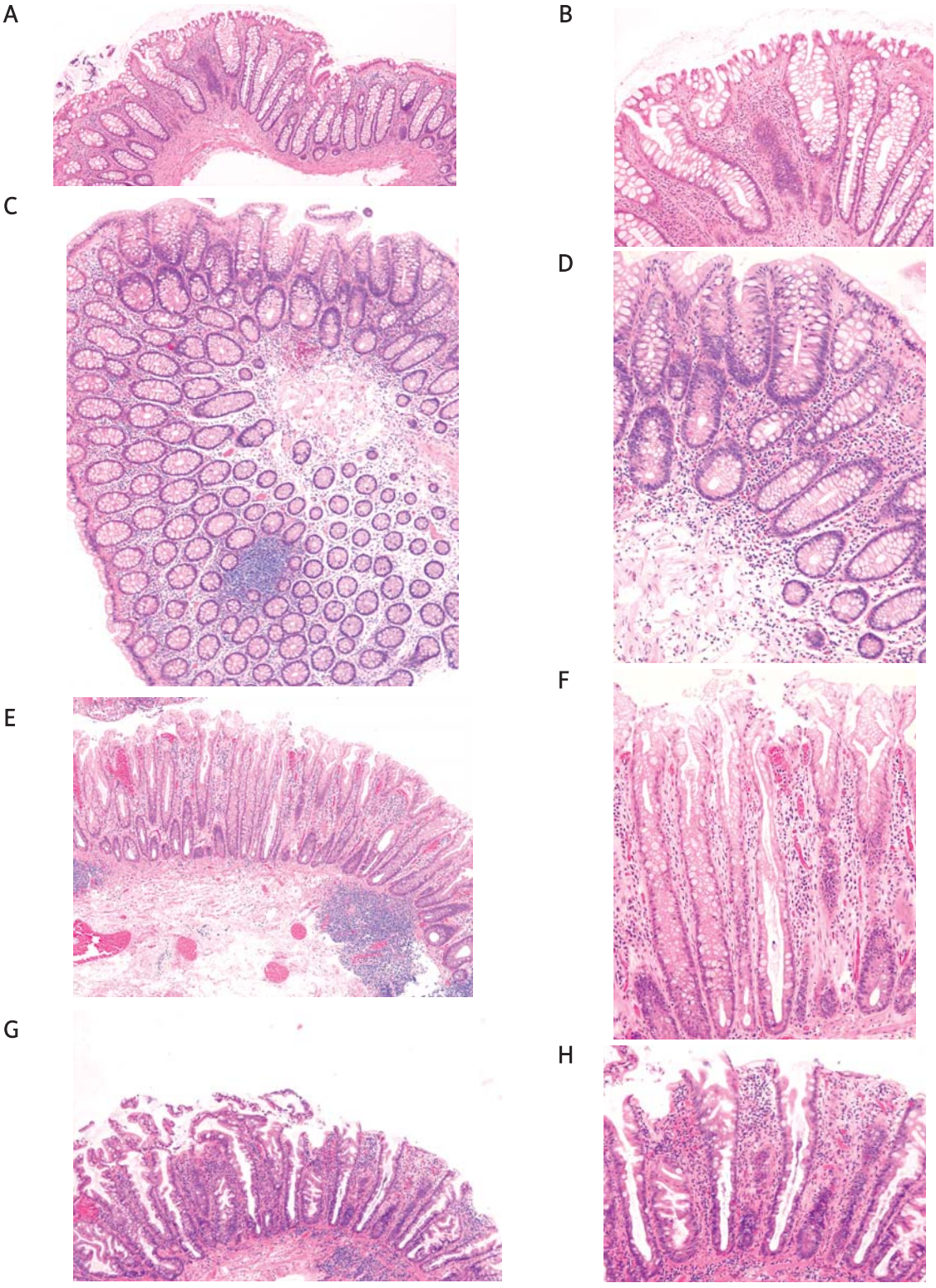

Fig. 1. Aberrant crypt foci and hyperplastic polyps
A, B: Hyperplastic ACF: crypts are larger or longer, sometimes showing apical branching. The luminal openings are serrated and slightly elevated from the surrounding normal mucosa, but without dysplasia. C, D: Dysplastic ACF: Broadened, dysplastic crypts in the upper part of the figure. Both crypts and cells have different degree abnormalities, with enlarged, elongated, sometimes stratified and depolarized nuclei. The number of goblet cells is decreased and mucin is depleted.
E, F, G, H: Hyperplastic polyps comprising glands with serrations limited mostly to the upper one-half of the crypts. Non-branching narrow crypts at the bases are similar in diameter and shape to those of normal colon. The narrow bases of the crypts are lined predominantly with undifferentiated cells.
(A, C, E, G: Low power view, B, D, F, H: High power view)

Table II. Comparison of two up-to-date classifications of serrated colonic polyps, 2009

ODZE RD AND HORNICK JL [24]	NOFFSINGER AE [23]
I. NONDYSPLASTIC SERRATED POLYPS	
A. Normal architecture, normal proliferation	
Hyperplastic polyps: • goblet cell hyperplastic polyp· • microvesicular hyperplastic polyp· • mucin-poor hyperplastic polyp	Hyperplastic polyps: • goblet cell-rich variant • microvesicular variant • mucin-poor variant
B. Abnormal architecture, abnormal proliferation	
Sessile serrated polyp	Sessile serrated polyp (sessile serrated adenoma)
II. DYSPLASTIC SERRATED POLYPS	
Serrated adenoma (traditional) Sessile serrated polyp with dysplasia (mixed polyp, advanced sessile serrated polyp) Conventional adenoma with serrated architecture	Serrated adenoma Mixed polyps • hyperplastic polyp with traditional adenoma • hyperplastic polyp with serrated adenoma Traditional adenoma with serration
III. UNCLASSIFIABLE SERRATED POLYP (either with or without dysplasia)	

Table III. Endoscopic and morphological features of hyperplastic polyp (HP), sessile serrated polyp (SSP), traditional serrated adenoma (TSA), and traditional adenomas (TA-TVA-VA*)

	HP	**SSP**	**TSA**	**TA-TVA-VA**
Location	Rectosigmoid	Right colon	Throughout, 60% left	Throughout, 60% left
Shape	Flat or pedunculated	Flat	Pedunculated	Pedunculated or protuberant
Size	< 5 mm	5-10 mm	> 10 mm	
Cytological dysplasia	Absent	Absent or minimal	Present	Present
Growth pattern	Bottom-up	Bottom-up	Bottom-up	Top-down
Serration	Present	Present	Present	Absent
Surface maturation	Present (hypermaturation)	Present	Present	Absent
Basal crypt dilatation	Absent	Present	Absent	May be present
Horizontal crypts	Absent	Present	Absent	May be present
Branched crypts	Absent	Present	Absent	May be present
Basal crypts serration	Absent	Present	Absent	Absent
Nuclear shape	Flat or low columnar	Round to oval	Tall columnar	Tall columnar
Cytoplasmic eosinophilia	Not prominent	Slightly eosinophilic	Eosinophilic	Basophilic

**TA indicates tubular adenoma, TVA, tubulo-villous adenoma, and VA, villous adenoma*
Modified after Li and Burgart [71]

They frequently exhibit mature, sometimes distended goblet cells. In classic HP, serrated crypt architecture is limited to the upper one-third to one-half of the crypt epithelium. The degree of serration varies from lesion to lesion. The collagen table underlying the surface epithelium is frequently thickened. The deeper parts of the crypts appear straight and tubular. The nuclei are small, regular, round, and located at the base of the cells adjoining the basement membrane. The proliferative zone is restricted to the lower third of the crypts.

Small left-sided hyperplastic polyps were subclassified by Torlacovic *et al.* [17] into three general subtypes, based on their morphological growth pattern, lack of proliferative or maturation abnormalities, and the mucin content of the epithelial cells, as follows:

The micro-vesicular variant, the most common, representing the typical HP found in the distal colon. Its epithelium is characterized by the presence of abundant micro-vesicular mucin-containing cells and a decreased number of goblet cells. Dystrophic

goblet cells and cells with round vesicular nuclei and prominent nucleoli are rare and, if present, are normally confined to the lower portions of the crypts.

Goblet cell-rich variant, typically sessile lesion ≤ 0.5 cm, more commonly localized in the left colon. It shows less serration than do other HP variants, which may be limited to the superficial one-third of the lesion or even to its surface. Its epithelium consists mostly of a huge number of typical goblet cells.

Mucin-poor HP, the least common variant containing small cells with micro-papillary architecture and scanty, mucin-depleted cytoplasm. Goblet cells are decreased or absent. Hyperchromatic nuclei may be prominent, but an influence of characteristic inflammatory infiltrate in *lamina propria* has to be taken into account.

There is abundant epidemiological evidence to suggest that hyperplastic polyps, at least the micro-vesicular type, may occasionally progress to carcinoma [27-29]. This is particularly true for lesions that are larger, right sided, and atypical in morphology, referred to as sessile serrated polyps [30, 31].

B. Abnormal architecture, abnormal proliferation

Sessile serrated polyp

Sessile serrated polyps (SSPs) are most likely to be misdiagnosed as HPs; clues to the correct diagnosis include right side location and large size. Nevertheless, although proximal anatomical location appears to be an important marker of "bad" hyperplastic polyps, "good" and "bad" hyperplastic polyps cannot necessarily be distinguished on the basis of anatomical site alone.

It is nowadays acknowledged that SSP may represent a different entity [24], formerly known as "sessile serrated **adenoma**" (SSA), with both names used synonymously (but with SSA in brackets) by Noffsinger [23], as well as in other recently published reports [29, 32]. One particularly confusing point is that SSAs do not display dysplasia, which is the hallmark of adenomatous polyps in general. Therefore, one has to be aware reading reports concerning serrated polyps which are still termed sessile serrated **adenomas**, though some of their descriptions and included histological figures are exact equivalents of sessile serrated **polyps** [33]. It is worth stressing once more that SSPs are included in the group of **nondysplastic serrated polyps** with only abnormal architecture and abnormal proliferation. Therefore, only the term "**sessile serrated polyp**" (SSP) will be used further in this review.

Sessile serrated polyps are considered as a large variant of HPs or possibly as an intermediary between HPs and serrated adenomas. The diagnosis of SSP is based mainly on architectural features that seem to emanate from the abnormal proliferation and/or decreased apoptosis (Fig. 2). They include pronounced budding and branching of crypts, basal dilatation of ≥ 10% of crypts, and a peculiar growth pattern in which the crypts seem to grow parallel to *muscularis mucosae*, often creating an inverted T- or L-shaped crypt. Preliminary diagnosis of SSP may be made even in a low-power microscopic field on condition that slides are prepared from a well oriented specimen enabling estimation of the longitudinally sectioned crypts. Serration is often seen at the base of the crypt. Increased crypt epithelium/stroma ratio, vesicular, round to oval, mixed with columnar nuclei with prominent (and eosinophilic) nucleoli, and mitoses in the upper half of crypts can also be of value [31]. Increased production of intracellular and/or luminal mucin and irregular distribution of goblet cells, sometimes abnormally located in the lower parts of the crypts, may be visible. Furthermore, one can find inverted crypts herniation subjacent to *muscularis mucosae*.

The summary of the most important histological features of SSP is as follows [34]:

1. **Abnormal proliferation/dysmaturation:**
   - Nuclear atypia in middle/upper crypts,
   - Oval nuclei in middle crypts,
   - Prominent nucleoli in middle/superficial crypts,
   - Dystrophic goblet cells,
   - Irregular distribution of goblet cells,
   - Mitoses in middle/upper crypts.
2. **Architectural abnormalities:**
   - Basal crypt dilatation,
   - Horizontal orientation of deep crypts,
   - Prominent serrations,
   - Serration to the base of the crypt,
   - Inverted crypts.
3. **Other features:**
   - Lack of thickened basement membrane.

II. DYSPLASTIC SERRATED POLYPS

Serrated adenoma (traditional)

Traditional serrated adenoma is the only serrated entity mentioned in the WHO 2000 classification [13]. It occurs at the mean age of 60 to 65 years, almost exclusively in the left colon, particularly in the sigmoid and rectum. It is an uncommon lesion, accounting for only 0.6–1.3% of colorectal polyps and 1.7% (52/3000) of adenomas [18, 35]. Endoscopically they are more often pedunculated than sessile [36], and even flat or carpet-like lesions have been described, being found amongst "flat" neoplastic colorectal lesions in 1.2%, to 12.2% [37, 38]. Protuberant lesions with a tubulovillous or villous component may be confused with traditional tubulovillous or villous adenomas. There is a predisposition of larger lesions, measuring >1 cm, to involve the right colon.

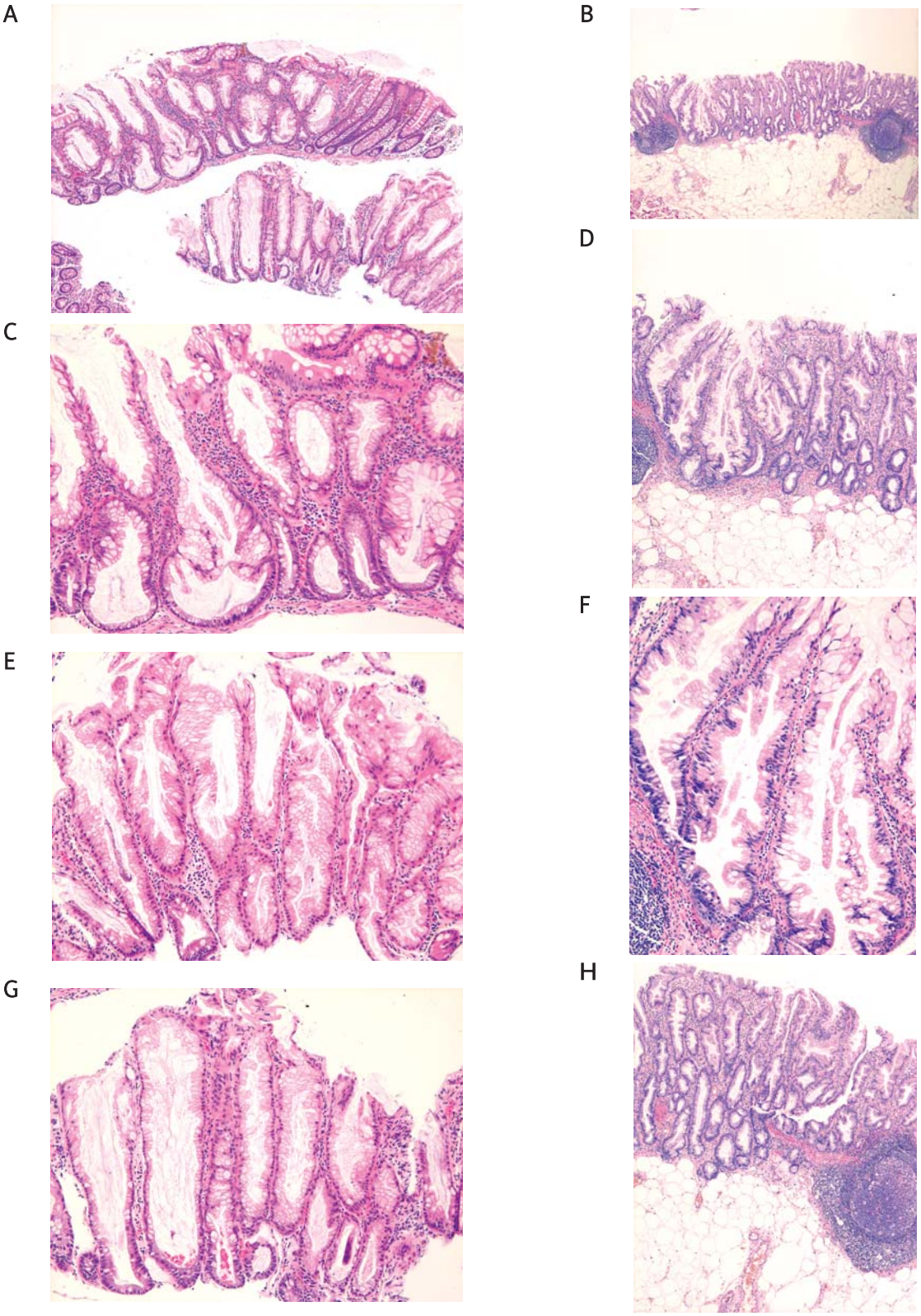

Fig. 2. Sessile serrated polyps: two SSP in the left column (A, C, E, G), and one in the right (B, D, F, H). A, B: Low power view of SSP. C – H: Higher power view of SSP. Serrated but distinct architecture with broadened and irregular shape of bottom part of the crypts, lacking the features of epithelial dysplasia. Prominent serration at all levels of the crypts, dilated and horizontally shaped crypts. C, D, F: The basal portions of the crypts are branched, horizontal and appear flask or T-shaped (C). At high power view, an irregular distribution of mature and dystrophic goblet cells abnormally located in the lower parts of the crypts is visible. H. Note that there are crypts that appear to be in the early stages of herniation through the muscularis mucosae, a phenomenon that leads to the appearance of "inverted hyperplastic polyp" in many SSPs.

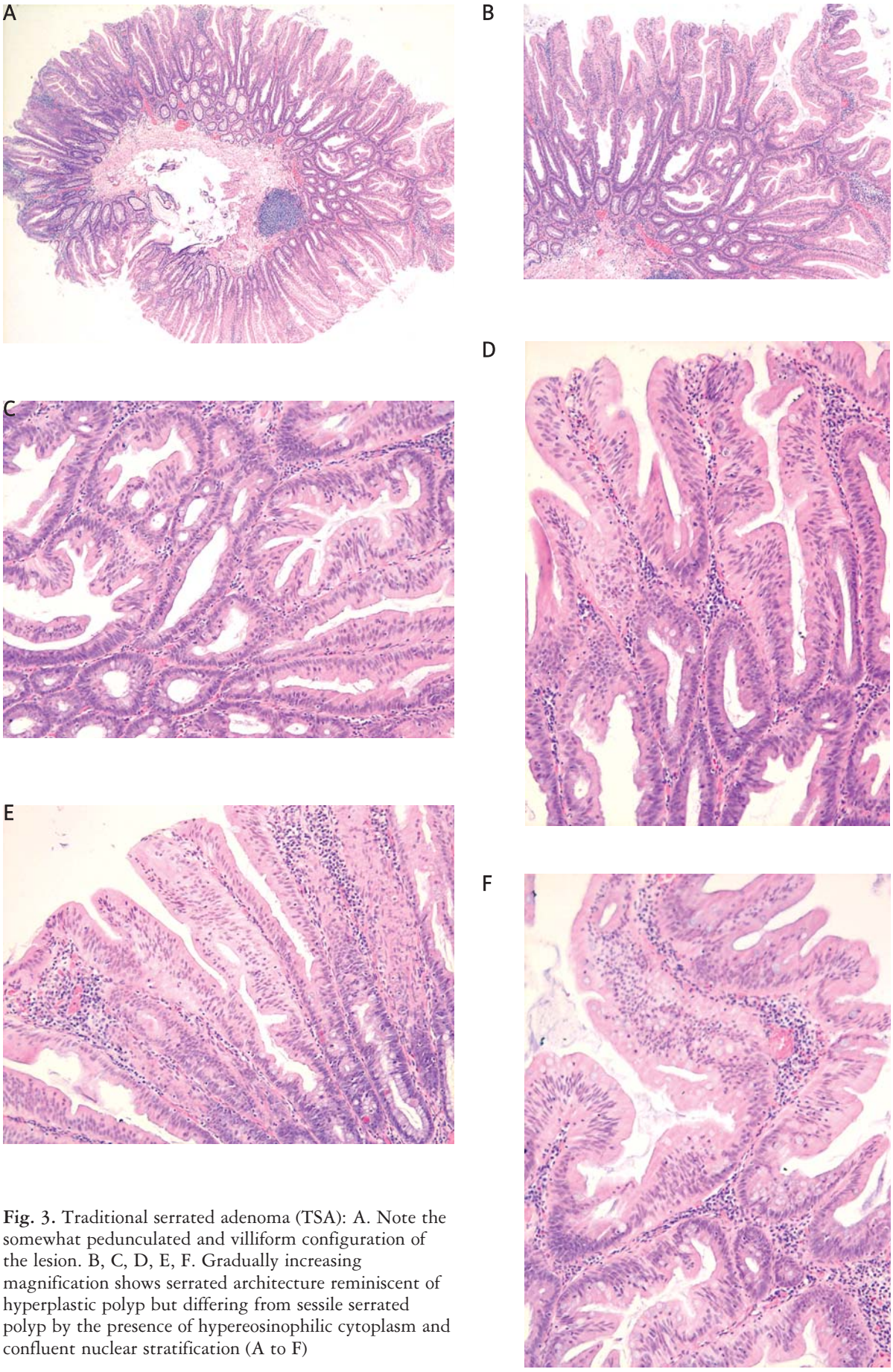

Fig. 3. Traditional serrated adenoma (TSA): A. Note the somewhat pedunculated and villiform configuration of the lesion. B, C, D, E, F. Gradually increasing magnification shows serrated architecture reminiscent of hyperplastic polyp but differing from sessile serrated polyp by the presence of hypereosinophilic cytoplasm and confluent nuclear stratification (A to F)

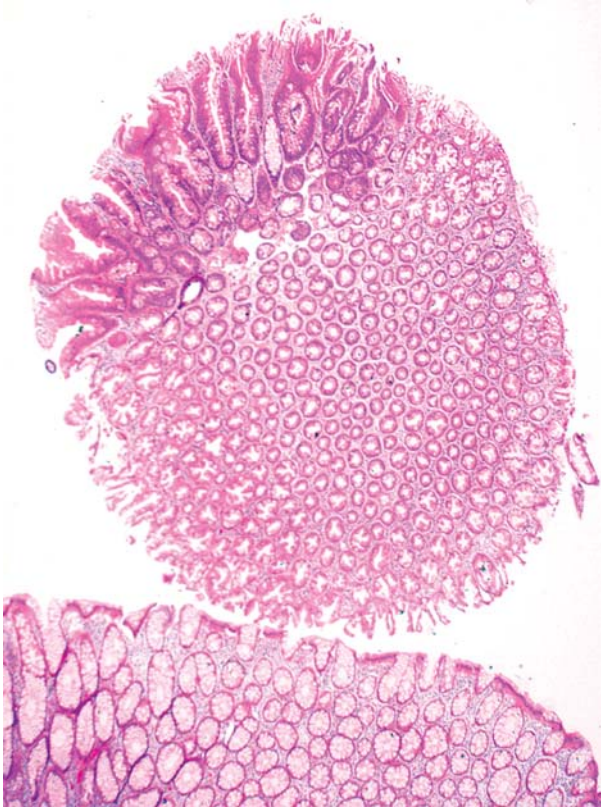

Fig. 4. Mixed hyperplastic/adenomatous polyp composed of nondysplastic hyperplastic part and dysplastic component with morphology resembling traditional serrated adenoma at the top of the lesion

Traditional serrated adenoma is characterised by the prominent serrated saw-tooth crypt configuration of the epithelium with phenotypic evidence of dysplasia at all levels of the polyp, including the surface epithelium [39]. There is increased architectural complexity with tubular and papillary or villiform growth pattern (Fig. 3). The number of goblet cells, uncommonly dystrophic, is variable. Both grades of epithelial dysplasia (LGD and HGD) may be encountered, with low-grade dysplasia being the most frequent. Some specific nuclear features, especially seen in the superficial crypt region, although typically round and vesicular, include their hyperchromasia, elongation (pencil-like nuclei), stratification and prominent nucleoli. HGD is characterized by increased cytological atypia with marked stratification of nuclei, and a back-to-back epithelial growth pattern. Mucin-depleted cytoplasm is relatively abundant and hypereosinophilic [40].

Some recent studies have suggested that the rate of malignant transformation is similar to that of conventional adenomas [35, 41] and is likely to be related to the size and location of the lesion [42]. Residual serrated adenomas were found in the neighbourhood of 27/466 (5.8%) CRCs [43]. Large TSAs in the proximal colon may progress at a more rapid rate than those in its distal part.

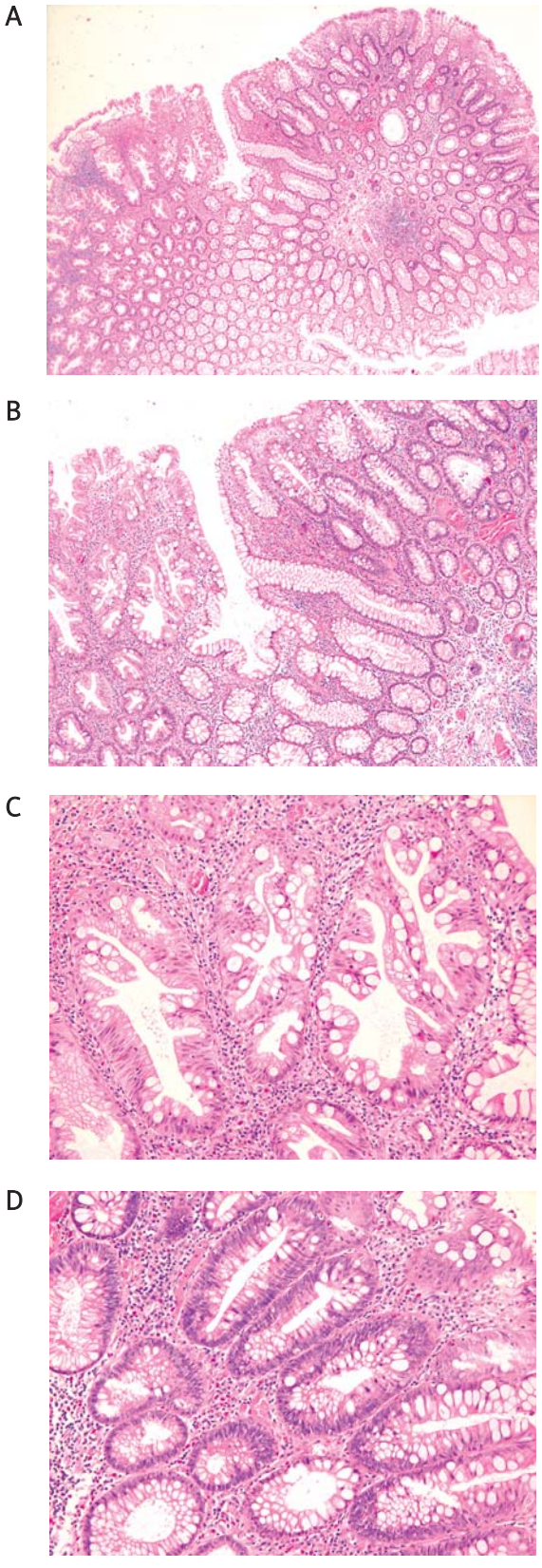

Fig. 5. Mixed hyperplastic/adenomatous polyp composed of nondysplastic hyperplastic part (left) and dysplastic component with morphology resembling conventional tubular adenoma on the right of the lesion (A, B). C, D. High power view of hyperplastic (C), and dysplastic (D) fragments

Sessile serrated polyp with dysplasia (mixed hyperplastic/adenomatous polyp) (mixed polyps)

Though HPs belong to nondysplastic serrated polyps, it is worth remembering that in large ones, especially those located in the proximal colon, adenomatous and even carcinomatous changes have been reported [44–48]. Such a situation is represented by **mixed hyperplastic adenomatous polyp**, which was first described by Urbanski *et al*. in 1984 [49]. Hyperplastic areas were revealed in as many as 96/1000 (9.6%) adenomas in the same year by Franzin *et al.* [50]. In 1990, Longacre & Fenoglio-Preiser selected 110 **mixed polyps** (MP) from the lesions previously identified either as a) hyperplastic, b) mixed hyperplastic/adenomatous or c) tubulovillous adenoma. According to the authors, mixed polyps accounted for only 0.6% of colorectal polyps. Foci of "significant dysplasia" were reported in 37% of these lesions, 11/110 (10%) contained "intramucosal adenocarcinoma", and in 1 polyp invasive carcinoma with lymph node metastases was found. As far as diagnosis of an "intramucosal adenocarcinoma" is concerned, these cases should be included in the HGD category regarding the modified Vienna classification [51].

Mixed polyps combine hyperplastic and dysplastic features, either with each component histologically distinct from the other or with various components intermingled with another (Fig. 4, 5 and 6 C). It is unclear whether the mixed polyps develop from pre-existing hyperplastic lesions or the dysplastic and hyperplastic features result from separate, independent processes. However, it has recently been proved to be more likely that these polyps occur as a result of focal dysplastic change within a sessile serrated polyp and may have varied histological components [52–54] as follows:

- a **serrated** component that is non-dysplastic and resembles either HP or SSP, and
- a **dysplastic** component that may resemble either TSA or conventional adenoma.

Conventional adenoma with serrated architecture

Conventional Adenoma with Serrated Architecture [24] or Traditional Adenoma with Serration [23] is very uncommon, but it is worth paying attention so as to avoid another pitfall in differentiation of serrated polyps from conventional tubular, tubulovillous, or villous adenomas. Sometimes conventional adenomas may show features of architectural serration, but the cytological features of cigar-shaped nuclei with clumped chromatin, and their stratification, as well as scanty cytoplasm gives the impression of dark blue epithelium (Fig. 6 F) which is a helpful hallmark distinguishing them from traditional serrated adenomas characterized by an abundant, pink eosinophilic cytoplasm (Fig. 6 E). In one study, these lesions accounted for only 2% of colorectal polyps [54]. Figure 6 includes a high power view of the glands typical of hyperplastic polyp (B), mixed hyperplastic–adenomatous polyp (C), conventional adenoma (D), traditional serrated adenoma (E), and conventional adenoma with serrated architecture (F) in comparison with normal mucosa (A).

III. UNCLASSIFIABLE SERRATED POLYPS

Most descriptions and illustrations of serrated polyps focus on lesions that are relatively easy to distinguish from both hyperplastic polyps and conventional adenomas. However, some may resemble and be difficult to distinguish from HPs. The reasons are various, but mostly due to overlapping features or processing artefacts, there may be difficulties with distinguishing hyperplastic and other serrated polyps from each other. For lesions like these, it is most important to determine whether the lesion has cytological evidence of dysplasia in order to include it in either the "nondysplastic" or "dysplastic" serrated polyp category. Thus, applying either the term unclassifiable serrated polyp **without dysplasia** or unclassifiable serrated polyp **with dysplasia** may be important for treatment modality.

Serrated polyp – carcinoma pathway

Serrated mucosal lesions of the colorectum have emerged as an important concept supporting the existence of an alternative **serrated polyp – carcinoma pathway** [11, 54, 55] (opposite to distinct classical adenoma – carcinoma pathway). It has been postulated that about 10–15% of sporadic CRCs would have their origin in serrated polyps that harbour a significant malignant potential. The most simplified sequence of events is as follows:

normal mucosa > hyperplastic ACF > hyperplastic polyp > sessile serrated polyp > mixed polyp > traditional serrated adenoma > carcinoma [56–60].

However, there may be two, slightly overlapping categories of "serrated carcinoma pathways", recently proposed by Noffsinger, depending on whether CRC arises from pre-existing SSP or TSA; they are included in Table IV [23].

1. SSP is likely to give rise to CRC predominantly located in the right colon, comprising 12% of all CRCs. SSP is characterised by CIMP-H, showing oncogenic BRAF mutations, and high-level DNA microsatellite instability (MSI-H). SSP is most likely the precursor to sporadic MSI-H CRC.

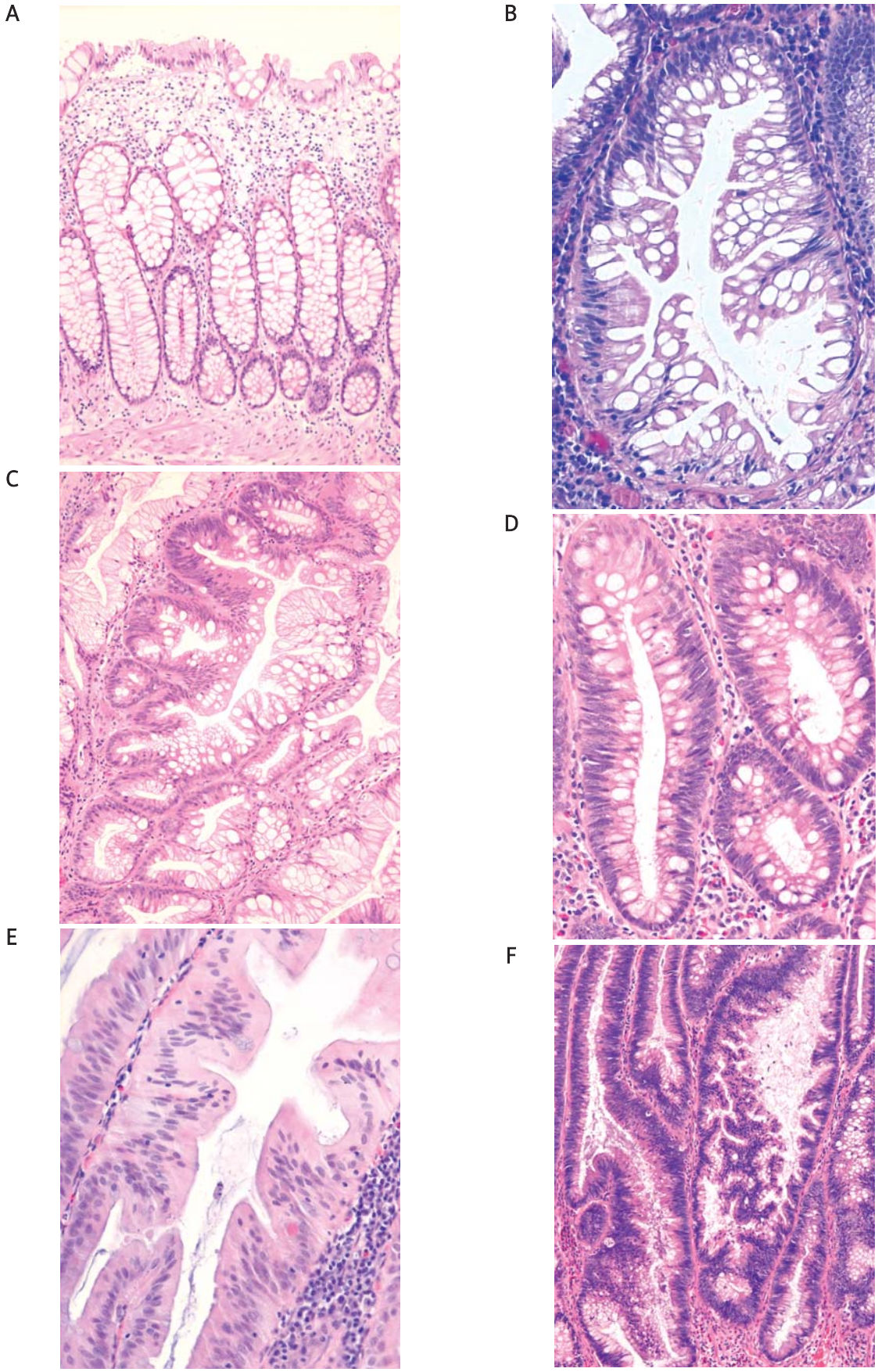

Fig. 6. High power view of the glands typical of hyperplastic polyp (B), mixed hyperplastic – adenomatous polyp (C), conventional adenoma (D), traditional serrated adenoma (E), and conventional adenoma with serrated architecture (F) in comparison with normal mucosa (A)

Table IV. Molecular classification of two serrated polyp-carcinoma pathways in comparison with classical adenoma-carcinoma pathway, modified according to the text and diagram [23]

	ADENOMA PATHWAY	SERRATED PATHWAY	
		Sessile Serrated Polyp	Traditional Serrated Adenoma
CIMP status	Negative	High	High
MSI status	MSS	MSI-H	MSI-L or MSS
Chromosomal instability	Present	Absent	Absent
KRAS mutation	+++	0–10%	Appr. 80%
BRAF mutation	Rare	75–82%	Appr. 20–30%
MLH1 status	Normal	Methylated	Partial methylation
MGMT methylation	– – –	+/–	+++

Abbreviations: CIMP – CpG island methylator phenotype; MGMT – O-6-methylguanine DNA methyltransferase; MSI – microsatellite instability; MSI-H – high-level microsatellite instability; MSI-L – low-level microsatellite instability; MSS – microsatellite stability.

Table V. Molecular features of different serrated polyps in comparison with adenomas. Frequency of KRAS and BRAF mutation and loss of expression of O-6-methylguanine DNA methyltransferase (MGMT) by polyp type [54*, 24**]

Type of polyp	KRAS mutation	BRAF mutation	MGMT loss
NONDYSPLASTIC SERRATED POLYPS			
Hyperplastic Polyp	2/49 (4%)	33/49 (67%)	6/42 (14%)
Goblet Cell	High	Low	Low
Microvesicular	Rare	High	Moderate
Mucin-poor	Rare	High	Moderate
Sessile Serrated Polyp	Low 1/31 (3%)	High 26/32 (81%)	High 7/31 (23%)
DYSPLASTIC SERRATED POLYPS			
Traditional Serrated Adenoma	Low 4/15 (27%)	Low 5/15 (33%)	Moderate 2/15 (13%)
Mixed Polyp	Moderate 5/10 (50%)	High 4/10 (40%)	High 7/9 (78%)
CONVENTIONAL ADENOMAS			
Tubular adenoma < 10 mm	7/38 (18%)	2/38 (5%)	8/36 (22%)
Tubular adenoma > 10 mm	4/23 (17%)	0/23 (0%)	11/20 (55%)
Adenoma with villosity	11/22 (50%)	2/22 (9%)	7/22 (32%)

**Numbers (%)*
***Rare, Low, Moderate, High*

2. TSAs probably give rise to often left-sided CRCs, constituting approximately 8% of cancers. TSAs are CIMP-H, chromosomally stable, MSI-L or MSS, and demonstrate MGMT methylation or partial methylation of MLH1. They more often contain KRAS rather than BRAF mutations. TSA may progress to MSI-L or MSS serrated CRC.

As far as KRAS and BRAF mutations in serrated polyps are concerned, nearly all studies have demonstrated that mutations in these two genes are mutually exclusive [27, 61].

Molecular features concerning the frequency of KRAS and BRAF mutations and loss of expression of O-6-methylguanine DNA methyltransferase (MGMT) by different serrated polyp types in comparison with adenomas are presented in Table V.

There are visible differences in some molecular results given in tables IV and V probably resulting from overlapping of different categories taken into account.

The recently described serrated adenocarcinoma, a distinct variant of CRC, is likely to develop as a consequence of serrated pathway, and accounts for

about 7.5% of all CRCs, and up to 17.5% of proximal CRCs [62].

Practical remarks

1. A **well oriented polyp** providing sufficient numbers of longitudinally sectioned crypts is mandatory for the exact evaluation of histological features of serrated polyps. Correct assessment of the deepest portions of the mucosa lying immediately above and beneath *muscularis mucosae* is of great value. Precise diagnosis is impossible when only superficially or tangentially cut slides are made [20, 53].
2. Until recently, small hyperplastic polyps were not believed to require definitive treatment, although they are typically removed in the process of endoscopy. However, careful diagnosis of all types of serrated polyps is of great importance. Pathological reports should always contain remarks as to whether their **removal** was **completed or not**, since they might have contained some focal features of more advanced lesions. It is specially obligatory for large lesions, particularly when located in the right colon, which should be removed in total [29].
3. So far, there have not been presented convincing data concerning the usefulness of dividing hyperplastic polyps into subtypes: goblet cell, microvesicular and mucin-poor variants. That is why their subclassification is not necessary in routine pathology diagnostic practice.

Treatment and screening

Despite there is being an ongoing debate regarding the classification of serrated polyps, as well as their biological and clinical significance [21, 29, 61], they are acknowledged to be precursor lesions having a risk of progression to adenocarcinoma, and as such they require complete eradication and enrolment of patients in a surveillance colonoscopy programme. Although rarely, even small sessile serrated polyps may contain dysplasia or eventually carcinoma. Regardless of the fact that in most cases it takes many years to progress, some recent studies suggest that the potential for malignant transformation of SSP is similar to that of conventional tubular adenomas. That is why standard conventional adenoma-type surveillance starting from SSP has definitely been recommended by the most recent colorectal cancer screening guidance published by the National Comprehensive Cancer Network (NCCN) in 2010 [62].

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Address for correspondence

Janina Orłowska MD
Histopathology Laboratory
Department of Gastroenterology and Hepatology,
Medical Centre for Postgraduate Education, Oncology Centre
Roentgena 5
02-781 Warsaw
phone +48 22 546 27 29
e-mail: jorlowska@coi.waw.pl